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ISBN 978-92-4-006238-2 (electronic version)
ISBN 978-92-4-006239-9 (print version)
ISBN 978-92-4-006937-4 (ePub version)

Suggested citation. The WHO AWaRe (Access, Watch, Reserve) antibiotic book. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Design and layout by Interligar - Branding & Design

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Foreword

Antimicrobial resistance (AMR) is a threat to global health and development and is estimated to contribute to more than five million deaths globally each year. We need urgent global action, using a One Health approach, to keep our precious medicines working. One of the critical health targets of the 2030 Sustainable Development Goals is for access to safe, effective and affordable medicines for all. In the case of antibiotics and other antimicrobials, using them carefully is vital to maintaining their effectiveness.

The inappropriate use and overuse of antibiotics are driving a global increase in AMR and have a pernicious impact on the effectiveness of these critical medicines. It threatens to send us back to the pre-antibiotic era, when a routine infection could mean death. Through the Global Action Plan on AMR, WHO is working to improve the surveillance of antimicrobial resistance and reduce inappropriate antibiotic consumption.

The new AWaRe antibiotic book, produced as an adjunct to WHO's Essential Medicines List (EML), provides concise, evidence-based guidance for more than 30 of the most common clinical infections in children and adults in both primary health care and hospital settings. The EML has been a key strategic component of WHO's goal to improve the use of medicines since 1977. The latest version of the EML, published in 2021, includes 39 antibiotics out of 479 medicines, reflecting the vital role these medicines play in health care.

Given the urgency of the threat to human health from AMR, and the many clinical infections for which antibiotics play a lifesaving role, WHO took a pragmatic approach to developing simple, practical guidance on how they should be used. The AWaRe system groups the hundreds of different antibiotics used globally into three simple categories – Access, Watch and Reserve – based on their clinical importance and the risk of their use promoting resistance. The AWaRe antibiotic book provides clear guidance on the choice of antibiotic, formulation, dose and duration for essential antibiotics for hospital and primary health care settings, including guidance on when not to use antibiotics.

There is an urgent need to develop and implement clear, globally accepted indicators, building on the AWaRe system, to promote the appropriate use of antibiotics and reduce their inappropriate use. Many challenges remain, including how data should inform local policies, and how to change patterns of medicine use formed over decades, particularly in low- and middle-income countries.

The 2022 AWaRe book is an important step along the road towards the improved use of antibiotics in humans, the development of stronger AMR policy and better clinical care.

Dr Tedros Adhanom Ghebreyesus
WHO Director-General

Acknowledgements

The World Health Organization (WHO) gratefully acknowledges the contributions and collaborative efforts of all those involved in the development of this publication.

WHO Essential Medicines Team

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WHO is especially grateful to Professor Mike Sharland, who generously contributed his time and expertise in supporting the Essential Medicines Team in this project, and as Chair of the EML Antimicrobial Working Group.

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Expert reviewers

Additional thanks to the following experts who reviewed and provided feedback on early drafts of the book.

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Special thanks to the following WHO staff members for their valued input and support.

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Antimicrobial Resistance Division: Solange Carolino Alves, Anand Balachandran, Hanan Balkhy, Silvia Bertagnolio, Peter Beyer, Alessandro Cassini, Sergey Eremin, Martina Escher, Valeria Gigante, Haileyesus Getahun, Lianne Gonsalves, Verica Ivanovska, Thomas Joseph, Karen Mah, Arno Muller, Sarah Paulin-Deschenaux, Carmem Pessoa da Silva, Hatim Sati, Elizabeth Tayler, Deborah Tong, Kitty van Weezenbeek and Katherine Zingg

Communicable and Noncommunicable Diseases Department: Silvio Mariotti, Benoît Varenne and Teodora Wi

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WHO also acknowledges the contributions of Nicola Magrini, Italian Medicines Agency, Rome, Italy, former WHO staff and Secretary of the WHO Expert Committee on Selection and Use of Essential Medicines from 2014 to 2020.

Public consultation

WHO also acknowledges the individuals and organizations for the comments and feedback provided during the public consultation period.

Funding

Many thanks to the Fleming Fund, the government of Germany and GARDP for their financial support.

Acronyms and abbreviations

AMR	antimicrobial resistance
AmpC	ampicillinase C
AWaRe	Access, Watch and Reserve classification of antibiotics
CAP	community-acquired pneumonia
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CT	computed tomography
DALYs	disability-adjusted life years
EDL	WHO Model List of Essential In Vitro Diagnostics
EML	WHO Model List of Essential Medicines
EMLc	WHO Model List of Essential Medicines for Children
ESBL	extended-spectrum beta-lactamase
GLASS	Global Antimicrobial Resistance and Use Surveillance System
HAP	hospital-acquired pneumonia
HIV	human immunodeficiency virus
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
OXA-48	oxacillinase-48
SAGE-IVD	Strategic Advisory Group of Experts on In Vitro Diagnostics
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
STI	sexually transmitted infection
TB	tuberculosis
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
WHO	World Health Organization

Glossary

Antibiotic resistance

Antibiotic resistance is a subset of antimicrobial resistance that specifically refers to bacteria becoming resistant to antibiotics (medicines that act against bacteria).

Antimicrobial resistance (AMR)

AMR is the ability of bacteria, viruses, fungi and parasites to resist the effects of antimicrobial medicines that kill susceptible organisms or keep them from growing.

Antimicrobial resistance predates the use of antimicrobials in human medicine and many bacteria, viruses, fungi and parasites are intrinsically resistant to some antimicrobials. Microorganisms can also acquire resistance by being exposed to antimicrobials.

Infection with antimicrobial-resistant pathogens makes infections harder to treat and increases the risk of disease spread, severe illness and death.

Antiseptics

Antiseptics are antimicrobial products used to slow or stop the growth of microorganisms. They are usually used on the skin or mucous membranes, for example, the mouth. These include, for example, chlorhexidine. These products can be used as hand rubs, hand or mouth washes and skin preparations.

Access, Watch and Reserve (AWaRE) classification

AWaRe is the WHO classification of antibiotics introduced by WHO as part of the 2017 Model List of Essential Medicines.

In the AWaRe classification, there are three categories of antibiotics:

- Access antibiotics that have a narrow spectrum of activity and a good safety profile in terms of side-effects.
- Watch antibiotics that are broader-spectrum antibiotics and are recommended as first-choice options for patients with more severe clinical presentations or for infections where the causative pathogens are more likely to be resistant to Access antibiotics.
- Reserve antibiotics that are last-choice antibiotics used to treat multidrug-resistant infections.

This classification can be used to give an indirect indication of the appropriateness of antibiotic use. The World Health Organization (WHO) has defined a target that at least 60% of global antibiotic consumption at the national level should be from the Access group.

Carbapenemases

Carbapenemases are beta-lactamases, enzymes that can break the beta-lactam ring (an essential component of beta-lactam antibiotics) and make penicillins, cephalosporins, monobactams and carbapenems ineffective.

Coronavirus disease 2019 (COVID-19)

COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-2). The first human cases of COVID-19 were reported in December 2019.

C-reactive protein

C-reactive protein is a laboratory test used to detect inflammation as an indicator of various conditions, including bacterial infection, and to monitor response to treatment.

Disability-adjusted life years (DALYs)

DALYs are an indicator used to assess the overall burden of disease. It is a time-based measure that combines years of life lost due to premature mortality and years of healthy life lost due to disability. One DALY represents the loss of the equivalent of one year of full health.

Model List of Essential In Vitro Diagnostics

The WHO Model List of Essential In Vitro Diagnostics (or Essential Diagnostics List (EDL)) is a list of in vitro diagnostics that are recommended by WHO and that was first published in 2018. The EDL can be used as a reference for programme and laboratory managers, and procurement and reimbursement officers who are developing or updating their own national lists of essential diagnostics The list is updated every one to two years based on proposed additions and changes submitted to WHO by stakeholders and reviewed by the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE-IVD).

Enzyme immunoassay

An enzyme immunoassay is a laboratory test that uses enzyme-labelled antibodies and antigens to detect biologic molecules.

WHO Model List of Essential Medicines

The WHO Model List of Essential Medicines (or Essential Medicines List (EML)) is a list of those medicines that satisfy the priority health care needs of the population. The first EML was published in 1977. The EML includes the most efficacious, safe and cost-effective medicines for priority conditions, selected on the basis of current and estimated future public health relevance, evidence of effectiveness and safety, and cost–effectiveness. The EML is updated every 2 years based on proposed additions and changes submitted to WHO by stakeholders and reviewed by the WHO Expert Committee on the Selection and Use of Essential Medicines.

WHO Model List of Essential Medicines for Children

The WHO Model List of Essential Medicines for Children (or Essential Medicines List for Children (EMLc)) is a list of those medicines that satisfy the priority health care needs for children up to 12 years of age. The first EMLc was published in 2007. The EML includes the most efficacious, safe and cost-effective medicines for priority conditions in children, selected on the basis of current and estimated future public health relevance, evidence of effectiveness and safety, and cost–effectiveness. The EMLc is updated every 2 years based on proposed additions and changes submitted to WHO by stakeholders and reviewed by the WHO Expert Committee on the Selection and Use of Essential Medicines.

Extended-spectrum beta-lactamases (ESBLs)

ESBLs are a group of beta-lactamases, enzymes that can break the beta-lactam ring, which is an essential component of beta-lactam antibiotics, thus making penicillins, cephalosporins and monobactams (but not carbapenems) ineffective.

Genotypic resistance

Genotypic resistance is a type of resistance of an organism to an antibiotic or antibiotics due to genetic mutation and expression of resistance genes. It is determined by methods of antimicrobial susceptibility testing that detect resistance genes. This information may be important for choosing the correct antibiotic and for epidemiological and surveillance reasons.

Glutamate dehydrogenase

Glutamate dehydrogenase is a constitutive enzyme produced by all strains of *Clostridioides difficile* and it is easily detected in stool samples.

Global Antimicrobial Resistance and Use Surveillance System (GLASS)

The GLASS is the WHO surveillance system for antimicrobial resistance and use launched in 2015 to collect official national data in selected bacterial pathogens causing common infections in humans

Intramuscular

Route of administration of an injection to deliver a medication deep into the muscles.

Intravenous

Route of administration of an injection or infusion to deliver a medication into a vein.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

MRSA are strains of *Staphylococcus aureus* that are resistant to methicillin and other beta-lactam antibiotics due to the presence of the *mecA* (or sometimes *mecC*) gene which produces a different penicillin-binding protein with lower affinity for beta-lactam antibiotics.

Microbiota

Microbiota is a collective term for the microorganisms that live in or on the human body.

Nucleic acid amplification test

Nucleic acid amplification is a laboratory test used to detect a particular nucleic acid sequence to identify virus or bacteria in different biological samples. There are several ways of amplification, one of the most commonly used is the polymerase chain reaction.

Non-fermenters

Non-fermenters are bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

Phenotypic resistance

Phenotypic resistance is a type of resistance determined by methods of antimicrobial susceptibility testing such as disk diffusion, broth microdilution and agar dilution and considered the reference standard for detection of antibiotic resistance. Susceptibility/resistance is determined based on the ability of defined concentrations of antibiotics to inhibit growth. It can generally not determine the cause of the resistance (e.g. beta-lactamases versus efflux pumps), information that may be relevant for choosing the correct antibiotic.

Pharmacodynamics

Pharmacodynamics are the molecular, biochemical and physiological effects of medicines and their mechanisms of action – what the medicine does to the body.

Pharmacokinetics

Pharmacokinetics is the dynamics of absorption, distribution, metabolism and elimination of medicines by the body – what the body does to the medicine.

Rapid diagnostic tests

Rapid diagnostic tests are diagnostic assays designed for use at the point of care.

1. Introduction

There is a clear need for simple resources to improve the quality of antibiotic prescribing globally. The AWaRe book was designed as a tool to make the antibiotics section of the World Health Organization (WHO) Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) more helpful to prescribers and to update the 2001 *WHO model prescribing information (1)*.

Aim and scope

The aim of the AWaRe book is to provide short, clinical guidance on the management of common infections, including recommendations for empiric antibiotic treatment at the first clinical presentation and when a "no antibiotic" approach is appropriate. Guidance is given on the choice of antibiotics that should be used to treat the most likely bacterial pathogens causing each infection in adults and children, the dosage and the treatment duration.

The AWaRe book is intended for all health care workers who prescribe and dispense antibiotics in high-, middle- and low-income settings in both the primary health care and the facility/hospital setting. It aims to complement the *WHO policy guidance on integrated antimicrobial stewardship activities* and the toolkit for health care facilities in low- and middle-income countries *(2,3)*. The AWaRe book is not intended to replace existing local and national antibiotic prescribing guidelines and clinical judgment, but to provide simple guidance where currently none is available.

Methods

The antibiotic treatment recommendations outlined in the AWaRe book are based on reviews of the evidence undertaken for the 2017, 2019 and 2021 updates of the EML and EMLc. The EML and EMLc provide a list of safe and effective antibiotics that should be available and affordable for patients globally. The AWaRe book provides guidance on how to best use these antibiotics based on the principles of the Access, Watch and Reserve (AWaRe) framework (Box 1.1).

Box 1.1 – Principles of the AWaRe framework

- Maximizing clinical effectiveness
- Minimizing toxicity
- Minimizing unnecessary costs to patients and health care systems
- Reducing the emergence and spread of antibiotic resistance (i.e. prioritizing antibiotics that are less likely to lead to antibiotic resistance in an individual patient and the community)
- Parsimony (i.e. avoiding the inclusion of many similar antibiotics)
- Simplification (i.e. same Access antibiotic recommended for multiple indications)
- Alignment with existing WHO guidelines

The detailed reviews on the optimal choice of antibiotics to be used for each specific clinical infection were based on a standardized analysis of systematic reviews, meta-analyses and clinical practice guidelines by experts in evidence-based medicines from McMaster University (Hamilton, Canada).

Details of the evidence underlying the recommendations and the methodology can be found in the following publications:

- *The selection and use of essential medicines: report of the WHO Expert Committee, 2017*. WHO technical report series; 1006 *(4)*.
- *The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019*. WHO technical report series; 1021 *(5)*.
- *The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2021*. WHO technical report series; 1035 *(443)*.

The choice of antibiotics to use for each specific infection are formal recommendations based on the evaluation made by the EML Expert Committee on the evidence presented for the EML updates or derived from existing WHO guidelines where available. The AWaRe book also provides guidance on diagnosis, symptomatic treatment and treatment duration based on non-systematic reviews of the literature and expert opinion. Some factors to be considered when using the AWaRe book are outlined in Box 1.2.

Box 1.2 – General considerations about the use of the AWaRe book

As with any general guidance document, the individual circumstances of the patients need to be considered. Comorbidities (e.g. immunosuppression which changes the pathogens that need to be considered, or renal or hepatic insufficiency which may require dose adaption of antibiotics), concomitant medications (risk of interactions), pregnancy and breastfeeding status (some antibiotics may be contraindicated), allergies (see the chapter on allergies to antibiotics) and national regulations all may require an adaption of the guidance and **it is the responsibility of each prescriber to make sure that all these considerations are taken into account when prescribing an antibiotic**.

Patients should be informed about the most common side-effects of the antibiotic, how it should be stored and taken, how long to take it for and what to do if symptoms worsen or fail to improve and how leftover antibiotics should be properly disposed of.

Structure

There are separate chapters for 35 infections, divided for ease of use into primary health care and hospital facility sections fully acknowledging that there is overlap between these groups.

Each chapter on a clinical infection includes:

- **Background information**. The pathophysiology, epidemiology, global burden, most common pathogens and how to make the clinical diagnosis, including assessing disease severity.
- **Diagnostic tools**. As the availability of diagnostic tools varies considerably in different settings, the empiric antibiotic recommendations are based on clinical signs and symptoms. Relevant diagnostic tests (including imaging and laboratory tests) are suggested based on *WHO Model List of Essential In Vitro Diagnostics* (EDL) *(6)*. The list of tests provided for each infection is not based on a formal assessment of their predictive value, but as a general guide of tests that could be clinically helpful, where available.
- **Treatment**. Guidance is given where appropriate for "no antibiotic care" including symptomatic management for low-risk patients with minor infections that do not need antibiotic treatment. First- and second-choice antibiotic options are then given where relevant based on the EML, EMLc and AWaRe system as well as other WHO guidance documents.

- Guidance on which infections may benefit most from **targeted clinical microbiology surveillance** to help inform both local and national empiric antibiotic guidance.

Each chapter is complemented by an infographic containing a short summary of the most important information (e.g. clinical presentation, diagnostic tests, treatment) separately for children and adults that can be rapidly and easily consulted when needed.

General antibiotic stewardship principles have been included throughout all the AWaRe book. These include guidance on a risk-based prescribing approach with the no antibiotic care option, short standard durations across infections, rapid oral step down from intravenous antibiotics and standardized dosing to improve medicine purchasing and programme delivery.

The AWaRe book also includes chapters on the Reserve antibiotics listed in the 2021 EML and EMLc, the principles behind their selection and how these last-resort medicines should be used to preserve their effectiveness.

The AWaRe book is available both in print and electronic formats. Downloadable infographics with the key information for end-users are also provided for each infection (see Web Annex).

2. Improving the use of antibiotics with the AWaRe book

Background

About 90% of all antibiotics are taken by patients in the primary health care setting. It is estimated that around half of all antibiotic use is inappropriate in some way, such as: the use of an antibiotic when none is indicated; the choice of an antibiotic with unnecessarily broad spectrum (e.g. Watch instead of Access antibiotics; see the following section); and the wrong dose, duration of treatment, and delivery or formulation of the antibiotic *(7)*.

Note

The term antibiotic stewardship is preferred to antimicrobial stewardship and is used throughout the AWaRe book to acknowledge the fact that the book only provides guidance on antibiotic treatment.

AWaRe

The AWaRe book gives guidance on first- and second-choice antibiotics for common infections in line with the recommendations in the EML and EMLc *(8,9)*. WHO has classified antibiotics into four groups, Access, Watch, Reserve (AWaRe) and a fourth – Not Recommended – group. As well as the antibiotics in the EML and EMLc, more than 200 other antibiotics have now been classified into AWaRe groups to help inform local and national policy development and implementation *(10)*.

Access antibiotics have a narrow spectrum of activity, lower cost, a good safety profile and generally low resistance potential. They are often recommended as empiric first- or second-choice treatment options for common infections (see Box 2.1 for WHO's target for their use).

Watch antibiotics are broader-spectrum antibiotics, generally with higher costs and are recommended only as first-choice options for patients with more severe clinical presentations or for infections where the causative pathogens are more likely to be resistant to Access antibiotics, such as upper urinary tract infections (UTIs).

Reserve antibiotics are last-choice antibiotics used to treat multidrug-resistant infections (see chapter on Reserve antibiotics).

The AWaRe system is also represented as a traffic-light approach: Access = green, Watch = orange and Reserve = red. Simple graphics using the traffic light approach can be used to show the proportions of Access and Watch antibiotics used in settings such as a community clinic or pharmacy or as part of central monitoring of antibiotic consumption.

Countries, regions and districts are encouraged to use the AWaRe book as a basis for developing their own quality indicators and targets for safely reducing total levels of inappropriate antibiotic prescribing to improve patient safety and care, while reducing resistant infections and costs for patients and health systems (see Box 2.2 for goals of the AWaRe book).

Box 2.1 – WHO target for the use of Access antibiotics

To promote responsible use of antibiotics and slow the spread of antibiotic resistance, the WHO Global Programme of Work includes a target that at least "**60% of total antibiotic prescribing at the country level should be Access antibiotics by 2023**" *(11,12)*

Box 2.2 – Improving the use of antibiotics with the AWaRe book

- No antibiotic care – safely reducing antibiotic use
- Improving Access antibiotic use and reducing inappropriate use of oral and IV Watch antibiotics
- Reducing the use of Not Recommended antibiotics
- Improving AWaRe-ness!
- Improving appropriate antibiotic dosing and duration

No antibiotic care – safely reducing antibiotic use

☑ Key messages

- Most otherwise healthy patients with mild common infections **can be treated without antibiotics** as these infections are frequently self-limiting and the potential medicine-related adverse events outweigh the clinical benefits.
- The risks of taking antibiotics when they are not needed should always be considered, such as side-effects, allergic reactions, *Clostridioides difficile* infection and selection of resistant bacteria.
- Patients treated with symptomatic care only (no antibiotic care) should be clearly informed of what danger signs to monitor and what to do if they occur.

Management of low risk (mild) infections in primary health care

Most infections encountered in primary health care are not caused by bacteria (e.g. most respiratory tract infections have a viral cause) and therefore the patient will not benefit from antibiotic treatment (Table 2.1). Even when the cause of the infection is bacterial, many infections are frequently self-limiting, with a low risk of severe complications and the benefit of antibiotics is limited, shortening of the duration of symptoms by usually only around 1 or 2 days. Most otherwise healthy patients with mild infections may safely receive symptomatic treatment alone, such as anti-inflammatory medicines, pain killers or complementary medicines. Whenever appropriate, guidance on diagnosing mild infections that can be treated with *No Antibiotic Care* is given in the AWaRe book.

Table 2.1 – Common infections in primary health care where mild cases can be safely treated with No Antibiotic Care (i.e. symptomatic management only) – see individual chapters for more details

Infection (in alphabetical order)	Can it be safely treated without antibiotics?	Comment
Acute diarrhoea	Yes, in the great majority of cases (unless there is significant bloody diarrhoea)	Most cases do not require antibiotic treatment because the infection is of viral origin and the illness is usually self-limiting regardless of the causative pathogen. The cornerstone of treatment is rehydration and electrolyte replacement.
Bronchitis	Yes	Nearly all cases have a viral origin and there is no evidence that antibiotics are needed.
COPD exacerbations	Yes, in most mild cases	Most exacerbations of COPD are not triggered by bacterial infections; only certain cases will benefit from antibiotic treatment.
Dental infections	Yes, in most mild cases	Dental treatment rather than prescribing antibiotics is generally more appropriate in the management of dental infections.
Otitis media	Yes, in most mild cases	Most mild cases of acute otitis media can be managed symptomatically and do not require antibiotic treatment.
Pharyngitis	Yes, in most mild cases	Most cases do not require antibiotics because the infection is viral.[a]

continues

Table 2.1 *continued*

Infection (in alphabetical order)	Can it be safely treated without antibiotics?	Comment
Sinusitis	Yes, in most mild cases	Most cases do not require antibiotics as the infections is viral.
Skin and soft tissue infections (mild)	Only for certain conditions and in certain patients	In cases of wounds at low risk of becoming infected, antibiotic treatment is not needed. In cases of animal bites, only wounds in high-risk anatomical locations and patients with severe immunosuppression benefit from antibiotic treatment.
Urinary tract infection (lower)	Only in very select patients with no risk factors for complicated infections	In young women who are not pregnant, with mild symptoms and who may wish to avoid or delay antibiotic treatment, symptomatic treatment alone can be considered.

COPD: chronic obstructive pulmonary disease.

[a] Refer to the pharyngitis chapter for situations that require antibiotic treatment, for example, pharyngitis in settings where rheumatic fever is endemic.

Are antibiotics needed?

In 2006, WHO proposed that the percentage of patients attending a primary health care facility receiving an antibiotic should be less than 30% *(13)*. However, on average, around half of patients presenting with any infection in primary care still receive an antibiotic, thus contributing to the emergence and spread of antimicrobial resistance (AMR) *(14)*. It is therefore important that both health care professionals and patients consider the risks of taking antibiotics when they are not needed. These risks include the immediate risk of side-effects of the medicine, most commonly diarrhoea or allergic reactions (such as a rash; see chapter on allergy to antibiotics) and rarely more serious side-effects. Bacteria in patients prescribed an antibiotic for a respiratory infection or a UTI – as examples of infections for which antibiotics are often prescribed – commonly develop antibiotic resistance to the prescribed (and other) antibiotics. These patients are also more likely to transmit resistant bacteria to other people *(14)*. Patients with infections caused by antibiotic-resistant bacteria are more likely to have a delayed clinical recovery *(15)*. Furthermore, antibiotic treatment alters the patient's microbiota (i.e. all microorganisms that live in or on the human body), with potential long-term consequences and an increased risk of infection by *Clostridioides difficile*, a bacterium that can cause severe diarrhoea.

Think D8 – before prescribing!

Before prescribing antibiotics to patients, prescribers should consider the eight Ds (Box 2.3).

Box 2.3 – Points to always consider when prescribing

Diagnose – what is the clinical diagnosis? Is there evidence of a significant bacterial infection?

Decide – are antibiotics really needed? Do I need to take any cultures or other tests?

Drug (medicine) – which antibiotic to prescribe? Is it an Access or Watch or Reserve antibiotic? Are there any allergies, interactions or other contraindications?

Dose – what dose, how many times a day? Are any dose adjustments needed, for example, because of renal impairment?

Delivery – what formulation to use? Is this a good quality product? If intravenous treatment is needed, when is step down to oral delivery possible?

Duration – for how long? What is the stop date?

Discuss – inform the patient of the diagnosis, likely duration of symptoms, any likely medicine toxicity and what to do if not recovering.

Document – write down all decisions and the management plan.

Improving Access antibiotic use and reducing inappropriate use of oral Watch antibiotics

☑ Key messages

- The great majority of common infections in primary health care can be treated without any antibiotics or with Access antibiotics.
- Reducing the inappropriate use of Watch antibiotics is key to control antibiotic resistance.

The Sixty-eighth World Health Assembly in May 2015 endorsed a global action plan to tackle AMR (Box 2.4) *(16)*.

Box 2.4 – The five objectives of the global action plan

1. Improve awareness and understanding of antimicrobial resistance.
2. Strengthen surveillance and research.
3. Reduce the incidence of infection.
4. **Optimize the use of antimicrobial medicines**.
5. Ensure sustainable investment in countering antimicrobial resistance

The AWaRe book therefore aims to address one of the objectives of the WHO global action plan "Optimize the use of antimicrobial medicines" with a focus on antibacterial medicines or antibiotics (antimicrobials also include antifungal, antiviral and antiprotozoal medicines). The AWaRe book provides guidance on when not to prescribe antibiotics and, if indicated, which antibiotics to prescribe for the most common infections. The AWaRe book focusses on the optimal use of Access antibiotics as they remain the first-choice options for most infections.

The AWaRe book recommends that nine of the 10 most common infections seen in primary health care can be treated safely with either no antibiotics or Access antibiotics (Table 2.2). Only one infection, acute bloody diarrhoea (dysentery), requires the empiric treatment with antibiotics in the Watch category, such as ciprofloxacin or azithromycin.

The use of oral Watch antibiotics globally is increasing. They are now very commonly taken by patients in primary health care for minor infections (fever/cough/diarrhoea) in both high-income countries and low- and middle-income countries. Reducing the inappropriate use of both oral and intravenous Watch antibiotics is a critical strategy for the global control of antibiotic resistance, while ensuring vulnerable populations have continued or, where appropriate, improved access to Access antibiotics.

Table 2.2 – Common infections seen in primary health care settings and the antibiotic options recommended in the AWaRe book

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Infection	ACCESS / WATCH	First-choice antibiotic option (when an antibiotic is indicated[a])
Bronchitis	**No antibiotic**	No antibiotic
Community-acquired pneumonia (mild cases)	ACCESS	**Amoxicillin** **OR** **Phenoxymethylpenicillin**
Chronic obstructive pulmonary disease exacerbations	ACCESS	**Amoxicillin** (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Dental infections	ACCESS	**Amoxicillin** **OR** **Phenoxymethylpenicillin** (for most cases the first choice is a dental procedure and antibiotics are not necessary)
Infectious diarrhoea[b]	**No antibiotic or** WATCH	Most mild non-bloody diarrhoea is caused by viral infections and antibiotics are not necessary For acute severe bloody diarrhoea/ dysentery - **Ciprofloxacin**
Otitis media	ACCESS	**Amoxicillin** (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)

continues

Table 2.2 *continued*

Infection	ACCESS / WATCH	First-choice antibiotic option (when an antibiotic is indicated[a])
Pharyngitis	ACCESS	**Amoxicillin** **OR** **Phenoxymethylpenicillin** (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Sinusitis	ACCESS	**Amoxicillin** **OR** **Amoxicillin+clavulanic acid** (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Skin and soft tissue infection (mild cases)[c]	ACCESS	**Amoxicillin+clavulanic acid** **OR** **Cefalexin** **OR** **Cloxacillin**
Urinary tract infection, lower	ACCESS	**Amoxicillin+clavulanic acid** **OR** **Nitrofurantoin** **OR** **Sulfamethoxazole+trimethoprim** **OR** **Trimethoprim**

[a] The decision to treat is based on assessment of the patient and on a minimum set of criteria to start antibiotics described in the chapters for each infection.
[b] Only oral antibiotic options are reported here.
[c] Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these two antibiotics are the preferred options whenever possible (except for bite wounds).
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Reducing the use of Not Recommended antibiotics

☑ Key messages

- The wide use of fixed-dose combinations of antibiotics that are not compatible with the EML and not approved by the major regulatory agencies is of concern. Their use should be reduced as these combinations may result in increased toxicity and selection of resistance.
- WHO has developed a list of fixed-dose combinations of antibiotics whose use is strongly discouraged *(10)*.

In some countries, there is substantial use of fixed-dose combinations of antibiotics, which contain two or more agents in a single formulation. Recent data suggest that these combinations represent up to 20% of global antibiotic prescribing, especially in middle-income countries *(17)*. Some fixed-dose combinations of antibiotics are well established (e.g. sulfamethoxazole+trimethoprim) but other combinations often consisting of two or more broad-spectrum antibiotics, combined with antifungal and probiotic agents are of concern because they may contribute to the emergence and spread of AMR.

Improving AWaRe-ness!

☑ Key messages

- All prescribers and dispensers have a responsibility to improve the use of antibiotics.
- Patients also have responsibilities and efforts should be made to ensure they know basic principles of appropriate antibiotic use (e.g. taking antibiotics as prescribed and not using leftover antibiotics for a later illness) and symptomatic care.

All prescribers, dispensers and users of antibiotics, including both private and public providers, have a clear responsibility to ensure the best use of the medicines they give or take. Table 2.3 outlines some of the responsibilities of these various stakeholders. The aim is to provide a general framework of responsibility with broad examples that could lead into a programme of interventions.

Table 2.3 – Responsibilities of different stakeholders for improving the use of antibiotics

Group	Responsibility	Examples of practical actions
Health care policy-makers and relevant programme managers	• Discourage the unnecessary use of antibiotics. • Focus on promoting the use of Access antibiotics where appropriate. • Ensure local access to and availability of antibiotics in the national EML at the appropriate cost, quality and in the correct formulation[a]. • Make sure that the national EML is regularly updated and aligned with the WHO Model Lists where appropriate. • Undertake regular surveillance of antibiotic use at all levels, including by AWaRe group (e.g. Access/Watch ratio).	• Review national and local guidance documents and compare them with the AWaRe book. • Disseminate new guidance to all levels of the health care services. • Review provision of Access antibiotics, cost, quality[b], sustainability and barriers to use. • Develop a monitoring programme for antibiotic use across all levels of health care provision, including the Access/Watch antibiotics ratio. • Regularly review the national EML and align to the WHO Model Lists where synergies exist. • Disseminate data to providers on antibiotic use appropriately and regularly.
Physicians	• Be AWaRe of the AWaRe book and focus clinical care on D8! - Diagnosis – which infection - Decide – are antibiotics needed - Drug (medicine) – which antibiotic - Dose – at what dose - Delivery – what formulation - Duration – for how long - Discuss – with patient - Document – in the notes. • Know which infections could be managed with antibiotics in your setting. • Know which signs and symptoms would require hospital referral.	• Review national and local guidance documents and compare them with the AWaRe book. • Adapt or adopt EML guidance. • Assist with developing and implementing educational programmes. • Develop local tools for monitoring local patterns of antibiotic use and disseminate data appropriately and regularly to relevant stakeholders. • Act as local champions of the AWaRe book.

continues

Table 2.3 *continued*

Group	Responsibility	Examples of practical actions
Pharmacists	• Be AWaRe of the AWaRe book. • Do not provide antibiotics without a prescription. • Discourage self-medication with antibiotics. • Monitor relative use of Access and Watch antibiotics.	• Review, adapt or adopt the AWaRe book in line with local guidance documents. • Ensure in-pharmacy availability of the most common infection chapters of the AWaRe book and summaries of Access and Watch lists. • Monitor local patterns of antibiotic use such as Access/Watch ratios and disseminate data appropriately and regularly to relevant stakeholders.
Professional societies	• Be aware of AWaRe and the AWaRe book. • Contribute to awareness campaigns. • Educate health care workers about AWaRe.	• Disseminate new guidance to all levels of the health care services.
Nurses	• Be AWaRe of the AWaRe book and advise or prescribe accordingly.	• Review, adapt or adopt the AWaRe book in line with local guidance documents. • Review local availability of antibiotics. • Review practices and procedures that are non-compliant with the AWaRe book. • Monitor patterns of antibiotic use.
Community health workers	• Know which infections could be managed with antibiotics or with symptomatic treatment alone in your setting. • Know which signs and symptoms would require medical referral. • Be AWaRe of the AWaRe book.	

continues

Table 2.3 *continued*

Group	Responsibility	Examples of practical actions
Patients	• Be aware of AWaRe. • Avoid using leftover antibiotics. • Avoid asking for antibiotics over the counter in pharmacies and asking physicians to prescribe them. • Avoid stockpiling leftover antibiotics • Contribute to awareness campaigns (e.g. with family members and the community). • Return any expired, unwanted or unused antibiotic to a pharmacy or health centre for safe disposal.	• Act as champions for the better use of antibiotics. • Promote antibiotic-related educational activities for patients.

AWaRe: Access Watch and Reserve; EML: WHO Model Lists of Essential Medicines *(8)*.

[a] This includes discouraging the excessive use of fixed-dose combinations of antibiotics.

[b] This includes preventing and detecting the production and use of substandard and falsified medicinal antibiotics.

Substandard and falsified medicinal antibiotics

As antibiotics are the most common medicines used globally, the production and use of substandard and falsified medicinal antibiotics is a major problem. WHO estimates that up to one in 10 medical products in low- and middle-income country settings are substandard or falsified with antibiotics amongst the most commonly reported *(18)*. These products are typically found in informal market settings, which are a major source of antibiotics for patients globally, but also in less well-regulated pharmacies. All those involved in giving antibiotics to patients should take all reasonable steps to ensure that good quality medicinal products are provided, which are registered and licensed by the relevant national medicines regulatory authorities. Guidance on how to identify a possible problem of substandard and falsified medicinal antibiotics is provided in the WHO publication: *Substandard and falsified medical products (18)*.

Community health care workers

Community health care workers include informal health care providers, that is providers with no or limited formal training. In rural areas in low- and middle-income country settings,

they are often the first medical contact for many people in the community. Antibiotics are commonly prescribed by these informal providers, including the inappropriate prescription of broad-spectrum antibiotics or frequent prescription of antibiotics to treat upper respiratory tract infections that are often of viral origin *(19)*.

Improved antibiotic use could be helped by further education of this sector with a focus on the optimal use of Access antibiotics. Educational activities and training on how to manage common infections using the AWaRe book could be considered, for example, to decrease the use of oral Watch antibiotics and limit the use of antibiotics for severe infections only.

Appropriate antibiotic dosing and duration

Key messages

- Prescribers should always consult local and national dosing guidelines, where available.
- The dosing guidance provided in the AWaRe book is for the most common clinical infections in patients with normal kidney and liver function but the need for dose adjustments should always be considered.
- The guidance on duration of treatment is generally the shortest suggested duration for specific infections. More severe infections or patients with underlying conditions or immunosuppression may require longer courses of treatment than suggested in the AWaRe book.

Other relevant WHO resources (please check regularly for updates)

- WHO report on consensus guidance on paediatric dosing regimens for access antibiotics on the essential medicines list for children *(20)*.

For each infection discussed in the AWaRe book, guidance is given for both children and adults on the dose of antibiotic to be prescribed, how often the dose should be taken, the route of administration of the antibiotic and the duration of antibiotic treatment.

The guidance is based on: (i) existing WHO guidelines, (ii) a review of recent literature, (iii) a review of recent guidelines from different WHO regions and (iv) expert opinion (the EML Antimicrobial Working Group).

Users of the AWaRe book should be aware of the limited evidence underlying many antibiotic prescribing strategies, particularly the very poor evidence for dosing guidance for older antibiotics (when approval processes were less stringent and methods to determine

pharmacokinetic/pharmacodynamic target attainment less developed), which may explain some of the variation in international recommendations. The AWaRe book therefore does not provide formal recommendations for dosage, frequency of use, route of administration and duration, but rather provides general guidance on what would be considered appropriate dosing strategies and duration in most clinical cases.

Dosing

Wherever appropriate the same dose is given for each antibiotic for all infections to help local procurement and prescribing. In the hospital facility section, guidance is also given on when to consider **step down** from intravenous to oral antibiotics, encouraging the early discharge of patients from hospital when clinically appropriate.

Guidance on dose adjustments for abnormal kidney and liver function is not covered, and the summary of product characteristics should be consulted. In addition, detailed information on antibiotic administration, for example, the use of continuous or prolonged infusion times of beta-lactams in multidrug-resistant infections, is not covered as this is beyond the scope of the AWaRe book *(21,22)*.

Even though this dosing is not covered in the AWaRe book, higher doses or more frequent administration may be required in certain situations such as: patients with very severe infections (including sepsis / septic shock) or infections of certain body sites such as infections of the central nervous system; patients with significant underlying disease (e.g. severe immunosuppression); and overweight patients.

Dosing in children

For children, weight-based dosing was generally used for oral treatments based on WHO ranges. For children weighing more than 30 kg, adult dosing should be considered. The 2019 EML report on consensus guidance on paediatric dosing regimens was used as a reference but adapted by infection and severity of disease *(20)*.

Treatment duration

For treatment duration, where there was an acceptable range for the duration of therapy, the lowest number of days supported by the review of guidelines and expert opinion is used.

Strong evidence-based guidance on the most appropriate duration of treatment for many infections is limited. Therefore, duration is often individualized based on clinical response, on the success of surgical source control and, if available, changes in laboratory markers of infection. When an alternative diagnosis is established which does not require antibiotics, antibiotic treatment should be stopped. Shorter treatment where clinically appropriate is generally associated with less toxicity and a lower risk of selection and transmission of antibiotic resistance, with equivalent clinical outcomes.

Intravenous or oral antibiotics

Most non-severe infections can be safely treated with oral antibiotics and this approach is encouraged as it has several advantages, for example, less risk of line-associated infections and avoidance of hospitalizations. However, this is provided that there is no risk of poor enteral absorption (e.g. no vomiting) or need to treat pathogens for which effective oral options are not available, for example in the case of infections caused by certain multidrug-resistant pathogens.

When intravenous treatment is started (e.g. for severe infections), rapid oral step down should be considered as soon as this can be safely done.

3. Allergy to antibiotics

☑ Key messages

- True severe allergy to antibiotics is rare and allergies are often over-reported
- Beta-lactam antibiotics (penicillins and cephalosporins) of the Access group are among the most effective and safe medicines for many infections, and they should only be avoided when there is a high suspicion of true allergy.
- Cephalosporins and carbapenems can be safely used in most cases of non-severe penicillin allergy.
- All patients who are labelled as allergic should be carefully evaluated and their antibiotic allergy risk level should be determined.
- Routine skin testing before prescribing a beta-lactam antibiotic (e.g. penicillin or amoxicillin) is not needed, and direct oral challenge can be performed in carefully selected low-risk phenotypes.

The AWaRe book does not include alternative antibiotic options in cases of allergy to first-choice antibiotics. The reason for this is that a true allergy to antibiotics (true meaning an allergic reaction that is immune-mediated) is rare and the AWaRe book focuses on the empiric treatment options for most patients. Beta-lactam antibiotics of the Access group are among the most effective and safe medicines for many infections. Avoiding the use of this class, unless clearly justified because of severe allergy, exposes the patient to the risk of receiving suboptimal treatment for their infection.

This chapter on allergy describes general principles of the mechanisms of allergies to antibiotics and the implications for treatment. From the perspective of antibiotic stewardship, it is important to avoid over-diagnosing antibiotic allergies. Such over-diagnosis often occurs with antibiotics in the Access category (e.g. with penicillins) and can lead to the subsequent prescription of antibiotics in the Watch category, for example, macrolides that may be less effective and less safe. The detailed management of allergic reactions is beyond the scope of this chapter.

Definitions

- An **allergy** is a reaction of the immune system to a "non-self" substance.
- An **adverse reaction** is a response to a medicine which is harmful and unintended, and which occurs at the doses normally used *(23)*. Most adverse

reactions can be classified as type A or type B reactions (Table 3.1) depending on whether or not their effects are related to the primary mechanism of action of the medicine (type A, i.e. if they are predictable based on the mechanism of action or not) and also whether the immune system is involved (type B, i.e. hypersensitivity reactions) *(24)*. Most patients with type A adverse reactions (e.g. nausea, vomiting, headache and injection site reactions) should not be labelled as having a beta-lactam allergy, to prevent avoidance of beta-lactam antibiotics.

- A **hypersensitivity reaction** is any adverse reaction that is immunologically mediated. Hypersensitivity reactions are type B reactions and can be classified based on the timing of onset of symptoms after taking the antibiotic as well as on the underlying mechanism, that is, immediate reactions (potentially IgE-mediated) or delayed reactions (potentially T cell-mediated). Immediate reactions usually occur within 1–2 hours of taking the antibiotic and delayed reactions usually after more than 6–24 hours. Reactions occurring within 2–6 hours are often called accelerated.

Table 3.1 – Characteristics of adverse reactions to medicines

Type A (or on-target) adverse reaction[a]: characteristics	Type B (or off-target) adverse reaction[a]: characteristics
• Pharmacologically predictable • Dose/level dependent • Non-immune mediated • Less influenced by genetic factors Examples: antibiotic-associated diarrhoea and acute tubular necrosis due to aminoglycosides	• Pharmacologically unpredictable • Non-dose dependent • Often immunologically mediated hypersensitivity reactions[b] (IgE or T-cell mediated) Examples: skin exanthema, angioedema or anaphylaxis (immune-mediated)

[a] On-target (or augmented) means the effects are related to the primary mechanism of action of the medicine. Off-target means the effects are not related to the primary mechanism of action of the medicine.
[b] These reactions are immunologically mediated. They can be immediate (< 2 hours), accelerated (2–6 hours) or delayed (> 6 hours) reactions based on when symptoms appear after the administration of the antibiotic.

Epidemiology

Allergies to medicines are frequently self-reported, especially for antibiotics *(25)* with 5–15% of patients in high-income countries reporting a penicillin allergy *(24)*. However, in most cases (> 95%), these patients do not have a true immunologically mediated allergy and it is very likely that they can tolerate the antibiotic if re-exposed or challenged *(26)*.

Severe allergies to antibiotics (e.g. anaphylactic shock) are rare; nonetheless, antibiotics are the most common cause of life-threatening immunologically mediated reactions *(24)*.

Allergy to antibiotics is often over-diagnosed and patients are frequently labelled in health records as allergic to certain antibiotics (particularly to beta-lactams and sulfonamides) based on an unverified, vague, unknown or old (e.g. > 10 years) history of allergy reported by the patient, most often rashes. In most cases, these patients are unlikely to have a true allergy to the antibiotic and they will be able to safely tolerate it. Alternative explanations may exist for what the patients experienced previously, such as: (i) the antibiotic may have interacted with a concomitant infection, for example, antibiotic–infection interactions can occur in case of viral infections (e.g. the rash observed in patients with infectious mononucleosis caused by Epstein–Barr virus exposed to amoxicillin); or (ii) there may have been an "intolerance"/type A adverse reaction of the antibiotic manifested as, for example, nausea, vomiting, diarrhoea or headache; or (iii) a viral rash may have been confused with an allergic reaction. In addition, it is important to bear in mind that even true allergies are not always long-lasting and may decrease or disappear over time (> 10 years) *(26)*.

This over-diagnosis of allergy has important consequences because incorrectly labelling a patient as allergic to an antibiotic often results in the unnecessary use of alternative antibiotics. These alternatives may be less effective for the infection being treated and may expose the patient to other (sometimes more toxic) side-effects.

Unfortunately, most patients with a history of allergy to antibiotics are not evaluated to confirm the existence (or persistence) of the allergy.

Cross-reactivity

Antibiotic cross-reactivity refers to the development of an allergic reaction to different substances that have a closely related structure, for example, cross-reactivity can occur between penicillin and other beta-lactams (Table 3.2) *(26–28)*, which may be due to an immunological reaction to the beta-lactam ring shared by these antibiotics.

In patients with true allergy, cross-reactivity may occur and is generally predictable based on shared beta-lactam structures (e.g. R1 side chains), with the most frequently encountered example being aminopenicillins (e.g. amoxicillin, ampicillin) and aminocephalosporins such as cephalexin.

Table 3.2 – Cross-reactivity to antibiotics

Penicillins with other beta-lactams	% of cross-reactivity[a]	Safety of use
Penicillins and cephalosporins	< 2	Cephalosporins can be safely used in most cases of penicillin allergy and vice versa[b].

continues

Table 3.2 *continued*

Penicillins with other beta-lactams	% of cross-reactivity[a]	Safety of use
Penicillins and carbapenems	< 1	Carbapenems can be safely used in most cases of penicillin allergy and vice versa[b].
Penicillins and monobactams	0	Monobactams can be safely used in case of penicillin, cephalosporins (except ceftazidime) or carbapenem allergy[c].

[a] Percentage of patients allergic to penicillins that can develop an allergic reaction if exposed to a different beta-lactam (cephalosporins, carbapenems or monobactams).
[b] In cases of previous life-threatening reactions caused by the exposure to penicillins or other beta-lactams, any use of beta-lactams should be avoided, or an allergy specialist should be consulted.
[c] Monobactams can be safely used in cases of beta-lactam allergies except when there is an allergy to ceftazidime, a third-generation cephalosporin, because of similarities in the side chains of aztreonam and ceftazidime.

Clinical presentation

Signs and symptoms of antibiotic allergy can vary in severity, ranging from mild reactions that can be safely managed in an outpatient setting with or without need for symptomatic treatment (e.g. antihistamines) to severe reactions that require hospitalization and even admission to intensive care. Immediate and delayed reactions can be severe or non-severe.

Gastrointestinal symptoms and headache are not usually due to an allergic reaction but rather to an intolerance of the antibiotic that can vary in intensity from person to person or to *Clostridioides difficile* infection in case of diarrhoea.

Most cases of allergic reactions to antibiotics are not severe and often present as mild skin reactions (most commonly mild rash, hives and itching) with no systemic symptoms.

Severe reactions are rare but can become life-threatening. They can be immediate or delayed after administration of the antibiotic.

- Immediate severe reactions should be suspected if there is airway involvement, bronchospasm, wheezing, angioedema (swelling of the tissue under the skin with or without hives) or anaphylaxis. Usually, these reactions develop fewer than 4 hours after taking the antibiotic.
- Delayed severe reactions should be suspected in patients who have taken an antibiotic and present with severe skin symptoms (e.g. a painful blistering rash) and fever, joint pain or signs of organ involvement (e.g. hepatitis). Thrombocytopenia

(low platelet count), haemolytic anaemia (destruction of red blood cells) and signs and symptoms of hepatitis or nephritis in severe cases are suggestive of organ involvement. Usually, these reactions develop more than 24 hours after taking the antibiotic.

Allergy evaluation

All patients who are labelled as allergic should be carefully evaluated and their antibiotic allergy risk level should be determined. When evaluating a patient, a full history of their allergy should be taken from the patient with details of past reactions, including timing relative to antibiotic administration (immediate, intermediate, delayed or unknown) and treatment received (if any). Patients can be classified into three risk categories for allergy to antibiotics: low, moderate, and high risk; see Table 3.3 for examples but other assessment tools are also available *(29,30)*. Detailed documentation of all elements of the allergy is crucial. The patient should be educated about what types of antibiotics to avoid, if any, and should be provided, if possible, with written information such as a so-called allergy passport.

Table 3.3 – Antibiotic allergy risk levels based on the patient's allergy history

Allergy risk category	Examples
Low	• Patients with a history of isolated symptoms consistent with intolerance of an antibiotic, such as nausea, vomiting, diarrhoea or headache • Patients with a history of mild skin reactions especially if > 5 years before assessment • Patients with local injection site reactions • Patients with a history of unknown reactions a long time ago without features of immediate IgE-mediated reactions • Patients with a family history of antibiotic allergy
Moderate	• Patients with a history of acute onset urticaria • Patients with a history of reactions that look like IgE-mediated reactions but with no history of anaphylaxis
High	• Patients with a history of severe or life-threatening reaction (immediate or delayed) to an antibiotic (e.g. anaphylaxis, Stevens–Johnson syndrome or blistering or mucosal involvement rash) • Patients with a positive skin test • Patients with recurrent reactions or reactions to multiple antibiotics

Source: Shenoy ES, et al *(26)*.

Testing techniques for patients at low and moderate risk of antibiotic allergy include skin tests (this applies only to IgE-mediated reactions) and direct oral challenge tests. In direct oral challenge tests, a single therapeutic dose of the antibiotic is given orally to the patient under medical supervision with the ability to treat acute allergic responses. The patient should be kept under observation (usually at least 1-2 hours) to check for objective signs of an allergic reaction. A detailed description of different types of tests available is beyond the scope of this chapter. Routine skin testing before prescribing a beta-lactam antibiotic (e.g. penicillin and amoxicillin) is not needed in children or adults and should not be recommended in guidelines as this is an unnecessary barrier to the use of Access antibiotics.

In settings where allergy testing, specialist advice or treatment for anaphylaxis are not available, then pragmatic decisions should be based on a detailed history of any reported possible penicillin allergy. A rapid risk assessment needs to be done, including the medical importance of the infection the patient is presenting with (i.e. benefit–risk assessment in that patient and whether an antibiotic is really needed) and the availability of alternative antibiotics with similar effectiveness. Please see the relevant infection chapters and symptomatic non-antibiotic treatment of minor infections within chapters.

Patients with a definite history of immediate collapse, breathing difficulties or severe facial swelling within a few minutes to 1–2 hours of taking a penicillin class of antibiotic are likely to have had a true anaphylactic reaction. If any alternative antibiotics are available, they are preferred. Patients who have only had gastrointestinal symptoms or a rash appearing a few days after receiving an antibiotic of the penicillin group and who have shown no signs of becoming seriously unwell are generally less likely to develop severe anaphylaxis if they receive such antibiotics again in the future. Therefore, if one of these antibiotics is the most appropriate and available treatment option, they can be given and the patient advised to stop it if they develop a new skin rash, especially if the onset is rapid, the rash is raised and itchy and/or accompanying symptoms are present such as shortness of breath.

PRIMARY HEALTH CARE

4. Bronchitis

Key messages

- **Antibiotics are not needed** for most cases.
- Acute bronchitis usually presents as a persistent cough, with or without mild fever.
- Almost all cases are viral and self-limiting; patients should be informed that cough can last several weeks.
- Yellow/green colour of the sputum **does not** indicate bacterial infection and the need for antibiotics.
- Clinical presentation can differentiate bronchitis from pneumonia.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.
- Coronavirus disease (COVID-19) pandemic *(32)*.
- Living guidance for clinical management of COVID-19: living guidance, 23 November 2021 *(33)*.
- Therapeutics and COVID-19: living guideline, 16 September 2022 *(34)*.
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 *(35)*.
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013: Introduction *(36)*.
- Vaccines against influenza: WHO position paper – May 2022 *(37)*.

Definition

Acute bronchitis is a self-limiting inflammation of the trachea and bronchi characterized by persistent cough, with or without fever, usually caused by a viral infection *(38)*.

Bronchitis

Definition

A self-limiting inflammation of the trachea and bronchi characterized by persistent cough +/- fever (≥ 38.0 °C) usually caused by a viral infection

Diagnosis

Clinical Presentation

- Acute onset (<2 weeks) of cough lasting > 5 days +/- sputum production and shortness of breath (colour of the sputum does not indicate bacterial infection) +/- fever (≥ 38.0 °C)
- Generally a mild condition; cough usually lasts 10-20 days (can last longer)

Important: Symptoms can overlap with pneumonia and this can lead to inappropriate treatment with antibiotics. This should be avoided with a careful patient assessment
- **Bronchitis**: Less severe presentation, usually self-limiting (but cough may take weeks to resolve)
- **Pneumonia (see "Community-acquired pneumonia" infographic)**: More severe presentation with shortness of breath and systemic signs of infection (e.g. increased heart and respiratory rate)

Microbiology Tests

Usually not needed; consider testing for Influenza virus or SARS-CoV-2 (e.g. during influenza season or outbreaks based on local epidemiological risk/situation/protocols)

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Most Likely Pathogens

Respiratory viruses:
- Rhinovirus
- Influenza virus (A and B)
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Respiratory syncytial virus (RSV)
- Metapneumovirus
- Adenovirus
- Other respiratory viruses

Treatment

No Antibiotic Care

- Symptomatic treatment
- Bronchodilators (in case of wheezing), mucolytic or antitussive agents, can be considered based on local practices and patient preferences

Patients should be informed that:
- Great majority of cases are self-limiting and of viral origin
- Cough can persist for several weeks

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)
- **Hepatic impairment/cirrhosis**: Max 2 g/day

Antibiotic Treatment

Antibiotic treatment is **not recommended and should be avoided** as there is no evidence of a significant clinical benefit and there is a risk of side effects of antibiotics

Bronchitis

Definition

A self-limiting inflammation of the trachea and bronchi characterized by persistent cough +/- fever (≥ 38.0 °C) usually caused by a viral infection

Diagnosis

Clinical Presentation

- Acute onset of cough lasting > 5 days, usually with runny nose and mild fever, with no clinical signs of pneumonia
- Generally a mild condition, cough usually lasts 1-3 weeks

Important: Symptoms can overlap with pneumonia and this can lead to inappropriate treatment with antibiotics. This should be avoided with a careful patient assessment
- **Bronchitis**: Less severe presentation, usually self-limiting (but cough may take weeks to resolve)
- **Pneumonia (see "Community-acquired pneumonia" infographic)**: More severe presentation with shortness of breath and systemic signs of infection (e.g. increased heart and respiratory rate)

Microbiology Tests

Usually not needed; consider testing for Influenza virus or SARS-CoV-2 (e.g. during influenza season or outbreaks based on local epidemiological risk/situation/protocols)

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Most Likely Pathogens

Respiratory viruses:
- Rhinovirus
- Influenza virus (A and B)
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Respiratory syncytial virus (RSV)
- Metapneumovirus
- Adenovirus
- Other respiratory viruses

Treatment

No Antibiotic Care

- Symptomatic treatment
- Bronchodilators (in case of wheezing), mucolytic or antitussive agents, can be considered based on local practices and patient preferences

Patients/parents should be informed that:
- Great majority of cases are self-limiting and of viral origin
- Cough can persist for several weeks

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen (do not use if <3 months of age)
- **Pain control/antipyretic**: 5-10 mg/kg q6-8h
- **Oral weight bands**:

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen)
- **Pain control/antipyretic**: 10-15 mg/kg q6h
- **Oral weight bands**:

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q4-6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)

Antibiotic Treatment

Antibiotic treatment is **not recommended and should be avoided** as there is no evidence of a significant clinical benefit and there is a risk of side effects of antibiotics

Pathophysiology

Acute bronchitis is caused by tissue damage of the bronchial wall and inflammatory response triggered by the proliferation of microorganisms in the affected bronchi.

Epidemiology

Acute bronchitis is a very common condition that can affect people of all ages, mostly during the seasons when respiratory viruses are common. Smoking and exposure to air pollution are risk factors. Acute bronchitis is one of the most common reasons for consultations in the primary health care setting and it is associated with frequent unnecessary use of antibiotics both in children and adults *(39–41)*.

Most likely pathogens

A causative pathogen is not identified in most cases of acute bronchitis. Most cases of acute bronchitis are of viral origin (Table 4.1).

Table 4.1 – Pathogens most frequently associated with acute bronchitis (in descending order of frequency)

Respiratory viruses
Rhinovirus
Influenza virus (A and B)
Parainfluenza virus
Coronavirus (including SARS-CoV-2)
Respiratory syncytial virus
Metapneumovirus
Adenovirus
Other respiratory viruses

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
Note. Nearly all cases of acute bronchitis have a viral origin. Only in a very small proportion of cases, are atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*) involved. Atypical bacteria are intracellular and are colourless with Gram staining. They also have intrinsic resistance to beta-lactams either because they lack a cell wall (*Mycoplasma*) and / or are intracellular pathogens (*Chlamydia*).

Clinical presentation

Well-established clinical features of acute bronchitis include acute onset (less than 2 weeks) of cough lasting > 5 days with or without sputum production (of note yellow/green sputum

does not indicate a bacterial infection). Bronchitis is generally a mild condition with no tachycardia (i.e. no increased heart rate) or tachypnoea (i.e. no increased respiratory rate) and in most cases of acute bronchitis there is no fever. Cough usually persists for 10-20 days (around 1–3 weeks) but it can last longer.

Because the predominant symptoms are cough with or without fever, these symptoms can overlap with the clinical picture of pneumonia. As a result, patients can be incorrectly diagnosed as having pneumonia in the initial assessment and are often therefore inappropriately treated with antibiotics. This misdiagnosis can be avoided with careful patient assessment to clearly differentiate the two infections.

Usually, patients with pneumonia:

- are clinically unwell and with systemic signs of infection (e.g. fever, increased heart rate, increased respiratory rate or focal chest signs),
- are short of breath,
- have cough with sputum production.

Please refer to the chapter on community-acquired pneumonia (CAP) for the typical clinical presentation of patients with pneumonia.

In patients with pre-existing chronic obstructive pulmonary diseases (COPD), please refer to the chapter on this condition.

Laboratory tests

Patient microbiology tests

No microbiology test is usually required.

During the influenza season or in case of outbreaks, a nasopharyngeal swab to test for influenza could be considered. Local policies should be followed as to whether during the coronavirus disease 2019 (COVID-19) pandemic a nasopharyngeal swab or other sample (e.g. pharyngeal swab or saliva) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing (nucleic acid amplification test or rapid antigen test) should be obtained. Refer to the latest WHO guidelines for the management of patients with suspected SARS-CoV-2 infection.

Other tests

In the great majority of cases of bronchitis, laboratory tests are not needed.

In uncertain cases some experts advocate the use of biomarkers of infection (C-reactive protein, procalcitonin) to differentiate viral bronchitis from bacterial pneumonia, but these add costs and can also result in inappropriate prescribing due to the limited sensitivity and specificity of these tests.

Using microbiology surveillance data

As antibiotics are not recommended no routine microbiology surveillance is required.

Surveillance of circulating respiratory viruses can be useful to predict and follow epidemics and outbreaks, for example, SARS-CoV-2, influenza virus and respiratory syncytial virus.

Imaging

Imaging is usually not needed.

No antibiotic care

Patients or parents should be informed about the natural course of acute bronchitis. It should be explained that the cough can persist for several weeks, often at night, the great majority of cases are self-limiting (and of viral origin) and there is no benefit from a course of antibiotic treatment. For symptomatic care for cold or mild influenza symptoms refer to Table 4.2. There is no clear evidence to support the usefulness of bronchodilators (in case of wheezing), or mucolytic or antitussive agents, but their use could be considered based on local practices and patient preferences.

Table 4.2 – Medicines to consider for symptomatic treatment of acute bronchitis

Important

Medicines are listed in alphabetical order and they should all be considered equal treatment options.

Medicine	Formulation	Dose and frequency
Ibuprofen[a]	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	**Adults**: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) **Children**: • Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose
Paracetamol (acetaminophen)[b]	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	**Adults**: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)[c] **Children**: • Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours 3–< 6 kg: 60 mg given every 6 hours 6–< 10 kg: 100 mg given every 6 hours 10–< 15 kg: 150 mg given every 6 hours 15–< 20 kg: 200 mg given every 6 hours 20–< 30 kg: 300 mg given every 6 hours ≥ 30 kg: use adult dose

[a] Not for children < 3 months.
[b] Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.
[c] In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

Antibiotic treatment is **not recommended** for acute bronchitis and should be avoided. There is no evidence of a meaningful clinical benefit of antibiotics and their use is not supported by the available clinical evidence *(42)*.

5. Acute otitis media

Key messages

- **Antibiotics are not needed** for most cases.
- Symptomatic treatment alone (pain and fever control with close follow up) is appropriate in mild cases especially in children > 2 years.
- Antibiotic treatment could be considered in selected cases (e.g. severe symptoms, immunosuppression or bilateral otitis in children < 2 years).
- Amoxicillin has good activity against *Streptococcus pneumoniae*, the most common bacterial pathogen in acute otitis media.
- Higher doses of amoxicillin are effective against most resistant strains of *Streptococcus pneumoniae*.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019 *(35)*.
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013 *(36)*.
- Vaccines against influenza WHO position paper – May 2022 *(37)*.

Definition

Acute otitis media is an infection of the middle ear that occurs mostly in infants and children younger than 5 years, typically as a complication of a viral upper respiratory tract infection.

Acute otitis media

Definition

Infection of the middle ear that is rare in adults, often as a complication of a viral upper respiratory tract infection

Diagnosis

Clinical Presentation

Acute onset of ear pain (unilateral or bilateral), fever (≥38.0 °C), +/- ear discharge

Microbiology Tests

- Not needed unless a complication is suspected
- Cultures of pus from perforated ear drums should not be used to guide treatment

Other Laboratory Tests

Not needed unless a complication is suspected

Imaging

Not needed unless a complication (e.g. mastoiditis, brain abscess) is suspected

Otoscopy

Required for definitive diagnosis if available:
Bulging, inflamed/congested tympanic membrane (may be opaque/show decreased mobility)

Most Likely Pathogens

Respiratory viruses (most cases):
- Respiratory syncytial virus (RSV)
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Influenza virus (A and B)
- Other respiratory viruses

Bacteria (rarely bacterial superinfections can occur):
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Streptococcus pyogenes* (group A *Streptococcus*)

Prevention

Overlaps with prevention of upper respiratory tract infections; hand hygiene, vaccination against *S. pneumoniae*, influenza and SARS-CoV-2 viruses can be useful

Treatment

Clinical Considerations

Important: Most non-severe cases can be managed symptomatically with **no antibiotic treatment**
- Instruct patients to monitor symptoms and report back in case they worsen/persist after few days

Antibiotics should be considered if:
- Severe symptoms (e.g. systemically very unwell, ear pain despite analgesics, fever ≥39.0°C)

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)
- **Hepatic impairment/cirrhosis**: Max 2 g/day

Antibiotic Treatment Duration

5 days

Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)
All dosages are for normal renal function

First Choice

ACCESS Amoxicillin 500 mg q8h **ORAL**

Second Choice

ACCESS Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**

Acute otitis media

Definition

Infection of the middle ear that occurs mostly in children under 5 years of age, often as a complication of a viral upper respiratory tract infection

Most Likely Pathogens

Respiratory viruses:
- Respiratory syncytial virus (RSV)
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Influenza virus (A and B)
- Other respiratory viruses

Bacteria (rarely bacterial superinfections can occur):
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Streptococcus pyogenes* (group A *Streptococcus*)

Prevention

Overlaps with prevention of upper respiratory tract infections; hand hygiene, vaccination against *S. pneumoniae*, *H. influenzae* and influenza viruses can be useful

Diagnosis

Clinical Presentation

Acute onset of ear pain (unilateral or bilateral), fever (38.0 °C) +/- ear discharge

Microbiology Tests

- Not needed unless a complication is suspected
- Cultures of pus from perforated ear drums should not be used to guide treatment

Other Laboratory Tests

Not needed unless a complication is suspected

Imaging

Not needed unless a complication (e.g. mastoiditis, brain abscess) is suspected

Otoscopy

Required for definitive diagnosis if available:
Bulging, inflamed/congested tympanic membrane (may be opaque/show decreased mobility)

Acute otitis media

Treatment

Clinical Considerations

Important: Most non-severe cases can be managed symptomatically with no antibiotic treatment, especially in children >2 years of age

- Instruct caregivers to monitor symptoms and report back in case they worsen/persist after few days

Antibiotics should be considered if:
- Severe symptoms (e.g. systemically very unwell, ear pain despite analgesics, fever ≥39.0 °C)
- Immunocompromised children
- Bilateral acute otitis media in children <2 years

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen (do not use if <3 months of age)
- **Pain control/antipyretic**: 5-10 mg/kg q6-8h
- **Oral weight bands**:

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen)
- **Pain control/antipyretic**: 10-15 mg/kg q6h
- **Oral weight bands**:

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q4-6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)

Antibiotic Treatment Duration

5 days

Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)
All dosages are for normal renal function

First Choice

ACCESS

Amoxicillin 80-90 mg/kg/day **ORAL**
- **Oral weight bands**:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

Second Choice

ACCESS

Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**
- **Oral weight bands**:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin
Oral liquid must be refrigerated after reconstitution

Pathophysiology

Pathogens that infect the middle ear come from the nasopharynx through the Eustachian tube usually following a viral infection of the upper respiratory tract. Inflammation and oedema cause narrowing of the tube and accumulation of mucosal secretions which favours growth of pathogens in the middle ear. This sequence of events triggers the typical signs and symptoms of otitis media.

Epidemiology

Acute otitis media is very common in young children under 5 years of age with most experiencing at least one episode before the age of 3 years. Acute otitis media can complicate upper respiratory tract infections in up to a third of cases, especially in the first year of life *(43)*. The estimated global incidence of acute otitis media in 2017 was 317 million cases, for all ages and both sexes combined *(44)*. Children are more at risk of acute otitis media because their Eustachian tubes are narrower than those of an adult, which results in impaired drainage of fluids away from the middle ear. The incidence declines with age and adults are rarely affected. In countries where vaccination programmes against pneumococcal infection have been implemented, the incidence of acute otitis media among children has declined substantially *(45,46)*. In low- and middle-income countries, acute otitis media is still an important cause of hearing loss in children due to its progression into chronic suppurative otitis media when untreated *(47)*.

Most likely pathogens

Several bacterial and/or viral respiratory pathogens are associated with acute otitis media (Table 5.1) *(48)*. Most cases of otitis media are triggered by infections with respiratory viruses (respiratory syncytial virus, rhinovirus and coronavirus), which can be complicated by superinfection with bacteria.

Table 5.1 – Pathogens most frequently associated with acute otitis media (in descending order of frequency)

Respiratory viruses (most cases)	Bacteria (rarely)
Respiratory syncytial virus	*Streptococcus pneumoniae*
Rhinovirus	*Haemophilus influenzae*
Coronavirus (including SARS-CoV-2)	*Moraxella catarrhalis*
Influenza virus (A and B)	*Streptococcus pyogenes* (group A *Streptococcus*)
Other respiratory viruses	

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Otitis media caused by possible antibiotic-resistant pathogens

Amoxicillin has good activity against most isolates of *Streptococcus pneumoniae*. Local patterns of susceptibility and individual risk factors should be considered when evaluating the possibility of an infection caused by isolates likely to be resistant to amoxicillin. Resistance is more likely in the case of recent exposure to amoxicillin (less than 3 months) or recurrent episodes (more than four episodes a year) of acute otitis media. Higher doses of amoxicillin are still active against most resistant strains of *Streptococcus pneumoniae* and this antibiotic remains the treatment of choice.

Clinical presentation

Typical signs and symptoms of acute otitis media include recent onset of ear pain (unilateral or bilateral), fever (≥ 38.0 °C) and at times, ear discharge.

Laboratory tests

Patient microbiology tests

In uncomplicated cases, microbiological tests are usually not needed and cultures of pus from perforated ear drums should not be used to guide treatment.

Other tests

When acute otitis media is suspected clinically, blood tests are usually not needed (except in situations where complications such as mastoiditis are suspected).

Using microbiology surveillance data

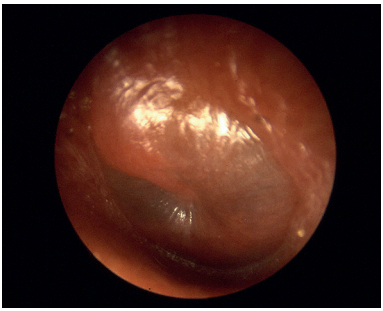
There is no role for routine surveillance for resistant pathogens.

Otoscopy

Otoscopy is required for a definitive diagnosis of acute otitis media. However, otoscopy or health care personnel with otoscopy skills may not be available in all settings.

In settings where otoscopy is available, classic findings include bulging, inflamed/congested tympanic membrane that may be opaque and show decreased mobility (Figure 5.1).

Figure 5.1 – Image of inflamed/congested tympanic membrane in otitis media



Source: © B. Welleschik, CC BY-SA 3.0, via Wikimedia Commons.

Imaging

In uncomplicated cases, no imaging study is needed. If available, imaging (e.g. computed tomography (CT) scan) may be indicated only in situations where complications such as mastoiditis are suspected.

No antibiotic care

Most non-severe cases of acute otitis media can be managed symptomatically and do not require antibiotic treatment, especially in children older than 2 years.

Non-severe cases usually have mild symptoms, often pain in one ear, and mild fever (< 39.0 °C), which improves with antipyretics. A watchful waiting approach with symptomatic management (i.e. analgesics and antipyretics) is appropriate (Table 5.2). Watchful waiting involves careful monitoring of the child by caregivers, with instructions to seek care in case of worsening of fever, pain or persistence of the symptoms.

The great majority of cases usually resolve spontaneously over a few days with no need for antibiotic treatment and the risk of complications (e.g. acute mastoiditis) is very low. Reassessment could be considered if symptoms do not improve over 3 days.

Table 5.2 – Medicines to consider for pain control of acute otitis media

Important

Medicines are listed in alphabetical order and they should all be considered equal treatment options.

Medicine	Formulation	Dose and frequency
Ibuprofen[a]	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	**Adults**: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) **Children**: • Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose
Paracetamol (acetaminophen)[b]	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	**Adults**: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)[c] **Children**: • Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours 3–< 6 kg: 60 mg given every 6 hours 6–< 10 kg: 100 mg given every 6 hours 10–< 15 kg: 150 mg given every 6 hours 15–< 20 kg: 200 mg given every 6 hours 20–< 30 kg: 300 mg given every 6 hours ≥ 30 kg: use adult dose

[a] Not for children < 3 months.
[b] Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.
[c] In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

Antibiotic treatment should be considered in specific cases (see Table 5.3 for choice of antibiotics):

- in cases with severe symptoms, for example, systemically very unwell, ear pain despite analgesics, fever ≥ 39.0 °C,
- in immunocompromised children because of the higher risk of complications, and
- in cases with bilateral acute otitis media in children under 2 years.

There is no clear consensus on offering antibiotic treatment in non-severe cases of recurrent acute otitis media (i.e. three or more episodes in the previous 6 months or four or more episodes in the previous year), in non-severe cases presenting with otorrhoea and in non-severe cases in neonates.

Table 5.3 – Empiric antibiotic treatment for acute bacterial otitis media

Important

Antibiotic treatment is not required in the great majority of cases (see Antibiotic treatment section)

	Adults	Children	Total treatment duration *(49–51)*
First choice	**Amoxicillin** (oral): 500 mg given every 8 hours	**Amoxicillin** (oral): 80–90 mg/kg/day Oral weight bands: 3–6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750 mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours	5 days

continues

Table 5.3 *continued*

	Adults	Children	Total treatment duration *(49–51)*
Second choice	Amoxicillin+ clavulanic acid (oral): 500 mg + 125 mg given every 8 hours	Amoxicillin+clavulanic acid [a] (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/ dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/ dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours	5 days

Note. All dosages are for normal renal and hepatic function.
[a] Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Prevention of acute otitis media is the same as prevention of upper respiratory tract infections. All strategies (e.g. hand hygiene) that help prevent upper respiratory tract infections can be useful in preventing otitis media, including vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b for all children *(35,36)*. For countries considering vaccination programmes for influenza, vaccination of high-risk groups could also be considered (e.g. young children) *(37)*.

6. Pharyngitis

Key messages

- **Antibiotics are not needed** for most cases since most cases are self-limiting and of viral origin.
- Pharyngitis (sore throat) is a very common condition and one of the main causes of antibiotic overuse in primary health care.
- In bacterial pharyngitis, antibiotic treatment only reduces sore throat pain for around 1 day.
- Cases caused by *Streptococcus pyogenes* (group A *Streptococcus*) can very rarely be complicated by, for example, rheumatic fever, rheumatic heart disease and acute glomerulonephritis.
- The only clear indication for antibiotic treatment of pharyngitis is to reduce the probability of developing rheumatic fever in endemic settings.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.
- Rheumatic heart disease – fact sheet *(52)*.
- Rheumatic fever and rheumatic heart disease: report of a WHO expert consultation, Geneva, 20 October–1 November 2001 *(53)*.
- Diphtheria vaccine: WHO position paper – August 2017 *(54)*.

Definition

Pharyngitis is commonly defined as an inflammation of the pharynx characterized by sore throat and painful swallowing.

Pharyngitis

Definition

Inflammation of the pharynx characterized by sore throat and painful swallowing

Most Likely Pathogens

Viruses (> 80% of cases):
- Respiratory viruses (most cases)
- Epstein Barr virus (rarely)

Bacteria:
- Group A *Streptococcus* (5-10% in adults)
- Streptococci (group C and G)

Other infectious causes:
- Acute HIV-infection and other sexually transmitted diseases (syphilis, gonorrhea)
- Acute toxoplasmosis
- Diphtheria

Non infectious (rare):
- Pollution
- Allergens
- Smoking

Diagnosis

Clinical Presentation

Sore throat and painful swallowing

- **Viral**: Symptoms are often the same as those of a viral upper respiratory tract infection (URTI) with cough, headache and myalgia
- **Bacterial**: More severe presentation, fever (≥38.0 °C), tender cervical lymph nodes and pharyngeal exudates (see "Centor Clinical Scoring System")

Microbiology Tests

Low likelihood of Group A *Streptococcus* (GAS) (Centor score 0-2):
- Tests usually not needed

Higher likelihood of GAS (Centor score 3-4):
- Rapid antigen test or throat culture could be considered, especially in countries where rheumatic fever (RF) and rheumatic heart disease are frequent
- Tests should only be performed if antibiotic treatment is considered following a positive test result

Other Laboratory Tests

Blood tests usually not needed

Imaging

Usually not needed unless a complication is suspected

Pharyngitis

Centor Clinical Scoring System

- This system can help indicate infection origin (bacterial or viral) and whether antibiotics are necessary
- However even with a score of 4, the probability of GAS infection is only 50% and this score has only been validated in high-income settings

Signs & Symptoms (1 point each)

- O Fever > 38.0 °C
- O No cough
- O Tender anterior cervical lymphadenitis
- O Tonsillar exudates

Score 0-2
- GAS pharyngitis unlikely
- **Symptomatic treatment only**

Score 3-4 - In case of low risk of RF (e.g. countries with **low** prevalence of RF)
- **Antibiotic treatment can be withheld** even in cases of likely GAS pharyngitis

Score 3-4 - In case of high risk of RF (e.g. countries with **med/high** prevalence of RF)
- Antibiotic treatment recommended

Treatment

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)
- **Hepatic impairment/cirrhosis**: Max 2 g/day

Antibiotic Treatment Duration

Depending on the local prevalence or previous history of rheumatic fever:
- Low Risk of RF: **5 days**
- High Risk of RF: **10 days**

Note: when clarithromycin or cefalexin are used treatment duration is always 5 days

Antibiotic Treatment

The only clear indication for antibiotic treatment is to reduce the probability of developing rheumatic fever in endemic settings (however, after 21 years of age the risk of RF is lower)

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

ACCESS Amoxicillin 500 mg q8h **ORAL**

OR

ACCESS Phenoxymethylpenicillin (as potassium) 500 mg (800 000 IU) q6h **ORAL**

Second Choice

ACCESS Cefalexin 500 mg q8h **ORAL**

OR

WATCH Clarithromycin 500 mg q12h **ORAL**

GAS remains universally susceptible to penicillin. However, resistance to macrolides is common in some communities

Pharyngitis

Definition

Inflammation of the pharynx characterized by sore throat and painful swallowing

Most Likely Pathogens

Viruses (> 80% of cases):
- Respiratory viruses (most cases)
- Epstein Barr virus

Bacteria:
- Group A *Streptococcus* (20-30% in children)
- Streptococci (group C and G)

Other infectious causes:
- Acute toxoplasmosis
- Diphtheria

Non infectious (rare):
- Pollution
- Allergens
- Smoking

Diagnosis

Clinical Presentation

Sore throat and painful swallowing

- **Viral**: Symptoms are often the same as those of a viral upper respiratory tract infection (URTI) with cough, headache and myalgia
- **Bacterial**: More severe presentation, fever (≥38.0 °C), tender cervical lymph nodes and pharyngeal exudates

Microbiology Tests

Lower likelihood to be caused by Group A *Streptococcus* (GAS) (Centor score 0-2):
- Tests usually not needed

Higher likelihood to be caused by GAS (Centor score 3-4):
- Rapid antigen test or throat culture could be considered, especially in countries where rheumatic fever (RF) and rheumatic heart disease are frequent
- Negative rapid antigen test could be confirmed with a throat culture if available

Other Laboratory Tests

Blood tests usually not needed

Imaging

Usually not needed unless a complication is suspected

Pharyngitis

Centor Clinical Scoring System

- This system can help indicate infection origin (bacterial or viral) and whether antibiotics are necessary
- However even with a score of 4, the probability of GAS infection is only 50% and this score has only been validated in high-income settings

Signs & Symptoms (1 point each)

- O Fever > 38.0 °C
- O No cough
- O Tender anterior cervical lymphadenitis
- O Tonsillar exudates

Score 0-2
- GAS pharyngitis unlikely
- **Symptomatic treatment only**

Score 3-4 - In case of low risk of RF (e.g. countries with **low** prevalence of RF)
- **Antibiotic treatment can be withheld** even in cases of likely GAS pharyngitis

Score 3-4 - In case of high risk of RF (e.g. countries with **med/high** prevalence of RF)
- Antibiotic treatment recommended

Treatment

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen (do not use if <3 months of age)
- **Pain control/antipyretic**: 5-10 mg/kg q6-8h
- **Oral weight bands**:

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen)
- **Pain control/antipyretic**: 10-15 mg/kg q6h
- **Oral weight bands**:

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q4-6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)

Antibiotic Treatment Duration

Depending on the local prevalence or previous history of rheumatic fever:
- Low Risk of RF: **5 days**
- High Risk of RF: **10 days**

Note: when clarithromycin or cefalexin are used treatment duration is always 5 days

Antibiotic Treatment

The only clear indication for antibiotic treatment is to reduce the probability of developing rheumatic fever in endemic settings

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

ACCESS

Amoxicillin 80-90 mg/kg/day **ORAL**
- **Oral weight bands**:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

OR

ACCESS

Phenoxymethylpenicillin (as potassium): 10-15 mg/kg/dose (16 000-24 000 IU/kg/dose) q6-8h **ORAL**

Second Choice

ACCESS

Cefalexin 25 mg/kg/dose q12h **ORAL**
- **Oral weight bands**:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR

WATCH

Clarithromycin 7.5 mg/kg/dose q12h **ORAL**

GAS remains universally susceptible to penicillin. However, resistance to macrolides is common in some communities

Pathophysiology

Viruses and bacteria responsible for pharyngitis gain access to the mucosal cells of the pharynx through different mechanisms and start replicating in these cells. Damage is caused to the cells where pathogens are replicating.

Epidemiology

Sore throat is one of the most common conditions in patients presenting to primary health care and remains a very frequent cause of inappropriate antibiotic prescribing. Up to 60% of patients with sore throat are given antibiotics in many high-income outpatient settings *(55,56)*.

Incidence and prevalence data on sore throat are unavailable for most low- and middle-income country settings. Most cases of pharyngitis are self-limiting and of viral origin. Cases of sore throat caused by bacteria (mostly *Streptococcus pyogenes*) are rare and were responsible for about 10% of cases among patients with sore throat of all ages in a meta-analysis, but severe complications can occur *(57)*. These complications are either due to invasion of the organism in the pharynx (e.g. suppurative complications such as quinsy) or to an abnormal immunological response (e.g. acute rheumatic fever) *(58,59)*. Suppurative complications occur in a very small number of cases, are difficult to predict and most can be readily treated *(60,61)*. For this reason, the prevention of suppurative complications should not be considered an indication for antibiotic treatment in sore throat.

Rheumatic fever is also a rare complication due to an autoimmune inflammatory reaction to untreated streptococcal pharyngitis; usually less than 3% of untreated cases of pharyngitis caused by *Streptococcus pyogenes* trigger rheumatic fever in settings where this condition is endemic *(53,62)*. The incidence of rheumatic fever peaks between 5 and 15 years of age and is rare in people older than 30 years.

When rheumatic fever develops, it usually presents (70–75% of cases) as an acute febrile illness with joint manifestations (e.g. pain or tenderness) and carditis. Less frequently, rheumatic fever can present as a predominantly neurological and/or behavioural disorder. Symptoms usually develop 2–3 weeks after the initial symptoms of pharyngitis are evident. Ultimately, rheumatic fever can result in damage to the heart valves (rheumatic heart disease). About 60% of people with rheumatic fever will develop rheumatic heart disease and the risk is two times higher for females than males.

Despite the lack of data from many countries, 30 million people worldwide are thought to be affected by rheumatic heart disease, with an estimated 320 000 deaths in 2015 *(63)*.

Cases of rheumatic fever are concentrated in the WHO African, South-East Asian and Western Pacific regions; these regions account for about 84% of cases. With 27% of all cases of rheumatic fever in 2015 India has the highest burden worldwide *(53)*.

Most likely pathogens

Most (> 80%) cases of pharyngitis are caused by a viral infection (respiratory viruses have been identified in 25–45% of cases; less frequently, the Epstein–Barr virus or other viruses of the herpesvirus family or SARS-CoV-2 are the cause). A minority of cases of pharyngitis are caused by bacteria, mainly *Streptococcus pyogenes* (group A *Streptococcus*). Other streptococci (group C and G) have also been implicated as causes of pharyngitis (Table 6.1). Other infectious causes that need to be considered are acute human immunodeficiency virus (HIV) infection and other sexually transmitted infections (STIs) such as syphilis and gonorrhoea, acute toxoplasmosis and diphtheria – consider diphtheria if fever and greyish-white membranes covering the tonsil(s) are present in a child not vaccinated against diphtheria. Rarely, the cause of pharyngitis is non-infectious, for example, exposure to pollution, allergens and smoking.

Table 6.1 – Pathogens most frequently associated with pharyngitis (in descending order of frequency)

Viruses (most cases)	Bacteria (rarely)
Respiratory syncytial virus	*Streptococcus pyogenes* (group A *Streptococcus*)
Rhinovirus	Group C *Streptococcus*
Coronavirus (including SARS-CoV-2)	Group G *Streptococcus*
Influenza virus (A and B)	*Treponema pallidum*
Other respiratory viruses	*Neisseria gonorrhoeae*
Other viruses (rarely)	
Epstein–Barr virus	
HIV	

HIV: human immunodeficiency virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Pharyngitis caused by antibiotic-resistant pathogens

Streptococcus pyogenes is still universally very susceptible to penicillin. Resistance to penicillin has never been reported and there is no evidence of increasing minimal inhibitory concentrations. However, resistance to macrolides is common in some settings.

Clinical presentation

Pharyngitis is characterized by sore throat and painful swallowing. Typical accompanying signs and symptoms can vary depending on the etiology. If the cause is viral, symptoms

match those of a viral upper respiratory tract infection, and cough, headache and myalgia are likely to be present. If the cause is bacterial, a more severe presentation is usually seen, with fever (≥ 38.0 °C), tender cervical lymph nodes and pharyngeal exudates. Several clinical scoring systems have been developed to identify patients with higher likelihood of pharyngitis being caused by *Streptococcus pyogenes* (see the next section).

Scoring symptoms of pharyngitis

The specific cause of pharyngitis may be difficult to recognize based on symptoms alone. Scoring systems can help differentiate a viral infection from one of bacterial origin. The rationale is to help health care workers standardize the therapeutic approach and decide whether antibiotic treatment could be given based on the most likely etiology. However, scoring systems have a low specificity (i.e. high risk of incorrectly identifying patients with viral pharyngitis as having a *Streptococcus pyogenes* infection) and can lead to unnecessary antibiotic treatment. Moreover, most systems have only been validated in high-income settings.

One of the most widely used systems in the adult population is the Centor clinical scoring system (Table 6.2). However, even with the highest score of 4, the probability of an infection caused by *Streptococcus pyogenes* is only 50% *(64)*.

In low- and middle-income countries, other scores could be considered that have been specifically validated in these settings *(65)*.

Table 6.2 – Centor score for the clinical assessment of pharyngitis

Relevant signs and symptoms	Points
Fever > 38.0 °C	1
No cough	1
Tender anterior cervical lymphadenitis	1
Tonsillar exudates	1
Total score	**Likelihood of *Streptococcus pyogenes* infection (%)**
0	1–2.5
1	5–10
2	11–17
3	28–35

continues

Table 6.2 *continued*

4	51–53
Centor score 0 – 1 – 2	• *Streptococcus pyogenes* pharyngitis unlikely • Give symptomatic treatment only
Centor score 3 – 4	• Score suggestive of *Streptococcus pyogenes* pharyngitis • In countries with a low prevalence of rheumatic fever, antibiotic treatment can be withheld even in cases of likely *Streptococcus pyogenes* pharyngitis • In countries with medium to high prevalence of rheumatic fever, antibiotic treatment is recommended as it reduces the likelihood of developing rheumatic fever by around two thirds.

Laboratory tests

Patient microbiology tests

The choice of whether microbiological tests are helpful and which to consider is based on the likelihood of *Streptococcus pyogenes* infection. In many settings no tests are routinely available. The rationale for identifying cases caused by *Streptococcus pyogenes* is that those are the cases that may benefit the most from antibiotic treatment in certain settings (mostly to prevent rheumatic fever). In general, most guidelines prefer rapid antigen tests to cultures because they give results more quickly. Table 6.3 summarizes the microbiology tests that could be considered to diagnose pharyngitis.

Table 6.3 – Microbiology tests that could be considered if available for the diagnosis of pharyngitis as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Group A *Streptococcus* antigen[a] (RDT)	To aid in the diagnosis of Group A streptococcal pharyngitis	Community settings and health facilities without laboratories[b]

continues

Table 6.3 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
Throat culture	First step in detection and identification of bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; RDT: rapid diagnostic test.
[a] Possible specimens include: throat swabs.
[b] Community and health settings without laboratories are settings such as health posts and centres, doctors' offices, outreach clinics, ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

In the case of a low likelihood of *Streptococcus pyogenes* as the causative pathogen (i.e. a Centor score of 0 to 2; see Table 6.2), rapid antigen test or throat culture are not usually needed.

In the case of a higher likelihood of *Streptococcus pyogenes* as the causative pathogen (i.e. Centor score 3–4), rapid antigen test or throat culture could be considered, especially in countries where rheumatic fever and rheumatic heart disease are important problems. (Note: WHO recommends the use of a rapid antigen test as part of the strategy for primary prevention of rheumatic fever through the effective treatment of streptococcal pharyngitis *(53)*).

In children and adolescents with a Centor score of 3 or 4, a negative rapid antigen test could be confirmed with a throat culture if available.

Other tests

When pharyngitis is suspected, blood tests are not usually needed unless a complication is thought to be present.

Using microbiology surveillance data

As amoxicillin or penicillin are the recommended first line treatment and *Streptococcus pyogenes* is still universally very susceptible to these antibiotics, there is no role for routine surveillance to inform empiric guidance.

Imaging

When pharyngitis is thought to be the cause of clinical symptoms, imaging is usually not required unless a complication is suspected.

No antibiotic care

Most cases of pharyngitis are of viral origin and do not benefit from antibiotics. In most cases, including those of bacterial origin, symptoms resolve within a week. Symptomatic treatment with oral analgesics and/or antipyretics, such as paracetamol and/or ibuprofen (Table 6.4) may be helpful.

Table 6.4 – Medicines to consider for pain control of pharyngitis

Important

Medicines are listed in alphabetical order and they should all be considered equal treatment options.

Medicine	Formulation	Dose and frequency
Ibuprofen[a]	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	**Adults**: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) **Children**: • Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose
Paracetamol (acetaminophen)[b]	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	**Adults**: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)[c] **Children**: • Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours 3–< 6 kg: 60 mg given every 6 hours 6–< 10 kg: 100 mg given every 6 hours 10–< 15 kg: 150 mg given every 6 hours 15–< 20 kg: 200 mg given every 6 hours 20–< 30 kg: 300 mg given every 6 hours ≥ 30 kg: use adult dose

[a] Not for children < 3 months.
[b] Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.
[c] In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

Most cases of pharyngitis are of viral origin and do not benefit from antibiotics.

When bacterial pharyngitis is suspected or proven, the decision to give antibiotic treatment is usually based on the likelihood of *Streptococcus pyogenes* infection and on the local prevalence or patient history of rheumatic fever. Options to consider are given in Table 6.5. Second choice options reported in Table 6.5 should only be considered in patients allergic to first-choice options. In the case of clarithromycin, the prevalence of macrolide resistance in the setting where the patient acquired the infection should be considered since macrolide resistance among *Streptococcus pyogenes* is high is certain countries.

In general, patients will fall into one of the following two categories.

- Patients treated in settings with a low prevalence of rheumatic fever. **Antibiotic treatment is not needed in most cases**. Antibiotics could be considered in some patients who have a high likelihood of pharyngitis caused by *Streptococcus pyogenes* (i.e. Centor score 3–4). However, even with a Centor score of 3 or 4, antibiotic treatment is not necessary in most cases. Antibiotic treatment reduces sore throat pain only by around 1 day and the pain can alternatively be managed by regular analgesia.

  Antibiotic treatment could be discussed with patients or their caregivers on a case-by-case basis, weighing the benefits (e.g. reduced transmission and slight reduction in duration of symptoms) and risks (e.g. side-effects of antibiotics, effect on the intestinal microbiota) *(66)*. Relief of symptoms or prevention of suppurative complications is not considered an indication for antibiotic treatment. The rationale is that most suppurative complications are not severe and can be readily recognized and treated.

- Patients treated in settings with a medium to high prevalence of rheumatic fever and rheumatic heart disease or patients with a history of rheumatic fever or rheumatic heart disease. Antibiotic treatment is usually given if the likelihood of *Streptococcus pyogenes* pharyngitis is high (i.e. Centor score 3–4). The rationale is to prevent rheumatic fever or its recurrence. However, after 21 years of age, the risk of rheumatic fever is usually lower.

Table 6.5 – Empiric antibiotic treatment in patients with a high likelihood of *Streptococcus pyogenes* pharyngitis

Note

The only clear indication for antibiotic treatment is to reduce the probability of developing rheumatic fever in endemic settings; however, after 21 years of age, the risk of rheumatic fever is lower.

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

	Adults	Children	Total treatment duration *(67,68)*
First choice	**Amoxicillin** (oral): 500 mg given every 8 hours **OR** **Phenoxymethylpenicillin** (oral): 500 mg (800 000 IU[a]) given every 6 hours	**Amoxicillin** (oral): 80–90 mg/kg/day Oral weight bands: 3–6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750 mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours **OR** **Phenoxymethylpenicillin** (oral): 10–15 mg/kg/dose (16 000–24 000 IU/kg/dose[a]) given every 6 to 8 hours	5[b] or 10[c] days depending on the local prevalence or previous history of rheumatic fever

continues

Table 6.5 *continued*

	Adults	Children	Total treatment duration *(67,68)*
Second choice	**Cefalexin** (oral): 500 mg given every 8 hours **OR** **Clarithromycin** [d] (oral): 500 mg given every 12 hours	**Cefalexin** (oral): 25 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 125 mg given every 12 hours 6–< 10 kg: 250 mg given every 12 hours 10–< 15 kg: 375 mg given every 12 hours 15–< 20 kg 500 mg given every 12 hours 20–< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose **OR** **Clarithromycin** [d] (oral): 7.5 mg/kg/dose given every 12 hours	5 days

IU: international units.
Note. All dosages are for normal renal and hepatic function.
[a] Units of the potassium salt.
[b] In settings with a low prevalence of rheumatic fever or in patients with no history of rheumatic fever or rheumatic heart disease.
[c] In settings with a high prevalence of rheumatic fever or in patients with a history of rheumatic fever or rheumatic heart disease and who are aged between 3 and 21 years.
[d] In settings with a high prevalence of macrolide resistance among *Streptococcus pyogenes*, clarithromycin should not be recommended for the empiric treatment of *Streptococcus pyogenes* pharyngitis. Azithromycin could be used as an alternative (e.g. when clarithromycin is not available) but there are increasing concerns about its potential for the emergence and spread of antibiotic resistance because of its long half-life.
ACCESS antibiotics are highlighted in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Streptococcus pyogenes pharyngitis, rheumatic fever and rheumatic heart disease

Currently, there is no licensed vaccine to prevent pharyngitis caused by *Streptococcus pyogenes*. Hand and respiratory hygiene are the best methods to limit transmission to

others. In countries where rheumatic fever is endemic, primary prevention of rheumatic fever relies on effective treatment of *Streptococcus pyogenes* pharyngitis.

In patients with a previous episode of rheumatic fever, long-term antibiotic prophylaxis with benzathine benzylpenicillin every 3–4 weeks is recommended in order to prevent subsequent episodes of *Streptococcus pyogenes* pharyngitis, which would carry a higher risk of a new episode of rheumatic fever and ultimately rheumatic heart disease *(53)*. The duration of prophylaxis should be decided on a case-by-case basis.

Of note, WHO is currently developing guidelines for the prevention and management of rheumatic fever and rheumatic heart disease *(52)*.

Other causes of bacterial pharyngitis: diphtheria

WHO recommends that all children worldwide be immunized against diphtheria and that people of any age who are unvaccinated or not fully vaccinated against diphtheria receive the doses necessary to complete their vaccination *(54)*.

7. Acute sinusitis

Key messages

- **Antibiotics are not needed** in the great majority of cases.
- Most cases of sinusitis occur as a complication of a viral upper respiratory tract infection and are self-limited.
- Symptoms can last for a long time (up to 4 weeks).
- Yellow/green coloured nasal discharge alone is not a sign of bacterial infection and not an indication for antibiotic treatment.
- If antibiotic treatment is required, amoxicillin has good activity against *Streptococcus pneumoniae*, the most common bacterial cause of acute bacterial sinusitis.

Other relevant WHO resources (please check regularly for updates)

- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 *(35)*.
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013: Introduction *(36)*.
- Vaccines against influenza WHO position paper – May 2022 *(37)*.

Definition

Acute sinusitis is a symptomatic inflammation of the paranasal sinuses and nasal cavity. Most cases occur as a complication of a viral upper respiratory tract infection (e.g. a common cold caused by respiratory viruses such as rhinovirus) and symptoms can last up to 4 weeks. Acute sinusitis can also be associated with asthma, allergic rhinitis, smoking or exposure to smoke. This guidance applies mainly to maxillary sinusitis as this is the most common clinical condition.

Acute sinusitis

Definition

A symptomatic inflammation of the paranasal sinuses and nasal cavity

Most Likely Pathogens

Respiratory viruses:
- Influenza virus (A and B)
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Respiratory syncytial virus (RSV)
- Other respiratory viruses

Bacteria (rarely):
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

Diagnosis

Clinical Presentation

- Diagnosis is made clinically; symptoms of bacterial and viral sinusitis overlap considerably
- Symptoms usually last 10-14 days and are self-limiting
- Main symptoms are nasal drainage, nasal obstruction or congestion, unilateral dental or facial pain, facial fullness or pressure, and sometimes cough
- Location of pain depends on involved sinuses
- Acute bacterial sinusitis suspected when:
  - Signs/symptoms persist ≥10 days without improvement

  OR
  - Significant worsening of symptoms after initial mild phase

Microbiology Tests

Usually not needed

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed unless a complication or an alternative diagnosis is suspected

Acute sinusitis

Treatment

No Antibiotic Care

- Treatment is to improve symptoms, but **antibiotics have minimal impact on symptom duration in most cases**
- Symptomatic treatment includes antipyretic and analgesic medications, nasal irrigation with a saline solution and topical intranasal glucocorticoids or decongestants
- Most guidelines recommend using disease severity (duration and intensity of symptoms) to direct treatment

Mild to Moderate Presentation (<10 days duration and improving):

- Watchful waiting approach with symptom relief and **no antibiotic treatment**

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)
- **Hepatic impairment/cirrhosis**: Max 2 g/day

Clinical Considerations

Antibiotics should be considered if:

- Severe onset of symptoms
  - Fever ≥39.0 °C & purulent nasal discharge or facial pain for at least 3-4 consecutive days
- Patients at increased risk of complications e.g. those with chronic underlying comorbid diseases (deciding on a case-by-case basis)
- "Red flag" signs/symptoms suggestive of complicated infection such as systemic toxicity, persistent fever ≥39.0°C, periorbital redness and swelling, severe headache, or altered mental status

Antibiotic Treatment Duration

5 days

Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

All dosages are for normal renal function
Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS Amoxicillin 1 g q8h **ORAL**

OR

ACCESS Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**

CHILDREN

Acute sinusitis

Definition

A symptomatic inflammation of the paranasal sinuses and nasal cavity. Much less common than in adults because sinuses are not fully developed.

Most Likely Pathogens

Respiratory viruses:
- Influenza virus (A and B)
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Respiratory syncytial virus (RSV)
- Other respiratory viruses

Bacteria (rarely):
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

Diagnosis

Clinical Presentation

- Diagnosis is made clinically; symptoms of bacterial and viral sinusitis overlap considerably
- Symptoms usually last 10-14 days and are self-limiting
- Main symptoms are nasal drainage, nasal obstruction or congestion, unilateral dental or facial pain, facial fullness or pressure, and cough
- Location of pain depends on involved sinuses
- Acute bacterial sinusitis suspected when:
  - Signs/symptoms persist ≥10 days without improvement

  OR
  - Significant worsening of symptoms after initial mild phase

Microbiology Tests

Usually not needed

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed unless a complication or an alternative diagnosis is suspected

Acute sinusitis

Treatment

No Antibiotic Care

- Treatment is to improve symptoms, but **antibiotics have minimal impact on symptom duration in most cases**
- Symptomatic treatment includes antipyretic and analgesic medications, nasal irrigation with a saline solution and topical intranasal glucocorticoids or decongestants
- Most guidelines recommend using disease severity (duration and intensity of symptoms) to direct treatment

Mild to Moderate Presentation (<10 days duration and improving trend of symptoms):

- Watchful waiting approach with symptom relief and **no antibiotic treatment**

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen (do not use if <3 months of age)
- **Pain control/antipyretic**: 5-10 mg/kg q6-8h
- **Oral weight bands**:

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen)
- **Pain control/antipyretic**: 10-15 mg/kg q6h
- **Oral weight bands**:

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q4-6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)

Clinical Considerations

Antibiotics should be considered if:

- Severe onset of symptoms
  - Fever ≥39.0 °C and purulent nasal discharge or facial pain for at least 3-4 consecutive days
- Patients at increased risk of complications e.g. those with chronic underlying comorbid diseases (deciding on a case-by-case basis)
- "Red flag" signs/symptoms suggestive of complicated infection such as systemic toxicity, persistent fever ≥39.0°C, periorbital redness and swelling, severe headache, or altered mental status

Antibiotic Treatment Duration

5 days

Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS

Amoxicillin 80-90 mg/kg/day **ORAL**
- **Oral weight bands**:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

OR

ACCESS

Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**
- **Oral weight bands**:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin
Oral liquid must be refrigerated after reconstitution

Pathophysiology

Nasal congestion, usually triggered by an infection of the upper respiratory tract, can lead to obstruction of the sinus ostia with consequent hypoxia of the sinuses and mucus retention. Mostly the maxillary and the anterior ethmoid sinuses are involved. The inflammatory response that develops produces the signs and symptoms of acute sinusitis.

Epidemiology

Upper respiratory tract infections are a common reason for consultations in an outpatient setting, both for children and adults. According to the 2017 Global Burden of Disease study, upper respiratory tract infections are one of the top three causes of new disease globally for all ages and both sexes combined – an estimated 17.1 billion cases are recorded a year *(44)*. Acute sinusitis accounts for 0.5% of all upper respiratory tract infections and is much more common in adults than in children whose sinuses are not fully developed.

Most available data are from high-income settings and show that antibiotics are frequently prescribed in cases of acute viral sinusitis *(7,41)*.

Most likely pathogens

Acute sinusitis is usually caused by respiratory viruses; only a small percentage (usually less than 2%) of cases are complicated by bacterial infection (Table 7.1).

Table 7.1 – Pathogens most frequently associated with acute sinusitis (in descending order of frequency)

Respiratory viruses (most cases)[a]	Bacteria
Influenza virus (A and B) Respiratory syncytial virus Parainfluenza virus Rhinovirus Coronavirus (including SARS-CoV-2) Other respiratory viruses	**Rarely** *Streptococcus pneumoniae* *Haemophilus influenzae* **Very rarely** *Moraxella catarrhalis* *Streptococcus pyogenes* (group A *Streptococcus*) *Staphylococcus aureus*

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
[a] About 98% of cases are caused by respiratory viruses.

Sinusitis caused by antibiotic-resistant pathogens

Amoxicillin has good clinical activity against the great majority of isolates of *Streptococcus pneumoniae*. However, since the introduction of anti-pneumococcal vaccines, there is concern about increasing incidence of acute sinusitis caused by *Haemophilus influenzae* and *Moraxella catarrhalis* and an increased incidence of beta-lactamase production among these strains that may result in amoxicillin resistance. Higher doses of amoxicillin are still active against most resistant strains of *Streptococcus pneumoniae* and this antibiotic remains the treatment of choice.

Local patterns of susceptibility and individual risk factors should be considered when evaluating the possibility of an infection caused by isolates likely to be resistant to amoxicillin.

Clinical presentation

The diagnosis of sinusitis is made based on clinical criteria and the time pattern; it is important to consider that symptoms of acute bacterial sinusitis and acute viral sinusitis overlap considerably. Symptoms usually last for 10–14 days and are self-limiting.

The main symptoms of acute sinusitis are purulent nasal drainage, nasal obstruction or congestion, unilateral dental or facial pain, and facial fullness or pressure. Cough may also be present.

The location of pain in sinusitis depends on which sinuses are affected. For example, pain can be localized on the forehead (frontal sinuses), over cheekbones/teeth/upper jaw (maxillary sinuses) or behind the nose (ethmoid and sphenoid sinuses).

Acute bacterial sinusitis should be suspected in two situations:

- signs and symptoms persist without improvement for more than 10 days
- symptoms become significantly worse after an initial mild phase.

Yellow/green colour of nasal discharge alone is not a sign of bacterial infection and is not an indication for antibiotic treatment.

Laboratory tests

Patient microbiology tests

When sinusitis is suspected clinically, nasal cultures or nucleic acid tests for respiratory viruses are not usually needed.

Other tests

When sinusitis is suspected clinically, blood tests are usually not needed.

Using microbiology surveillance data

As the great majority of cases have no positive bacterial cultures, there is no role for routine surveillance to inform empiric guidance.

Imaging

When sinusitis is suspected clinically, imaging is not usually needed unless a complication or an alternative diagnosis is suspected.

No antibiotic care

The goal of treatment is to improve symptoms. Antibiotics have only minimal effect on the duration of symptoms in most cases and current evidence suggests that even without antibiotic treatment, most cases in healthy patients resolve within 1–2 weeks *(69)*.

Most guidelines recommend using disease severity (i.e. duration and intensity of symptoms) to direct treatment.

In case of mild to moderate presentation (less than 10 days duration and improving symptoms), a watchful waiting approach with symptom relief and no antibiotic treatment is usually adequate. Symptoms should be managed with antipyretic and analgesic medications (Table 7.2). Nasal irrigation with a saline solution and topical intranasal glucocorticoids or decongestants may also be used to relieve symptoms, even though their effectiveness in relieving symptom is still uncertain *(70)*.

The rationale of a watchful waiting approach is that in uncomplicated cases in adults, antibiotics (compared to no treatment) can shorten the duration of symptoms and improve the course of infection (e.g. resolution of purulent nasal discharge) only in a small percentage of patients. However, these potential benefits must be balanced against the risk of adverse events from antibiotics (e.g. gastrointestinal side-effects, allergic reaction and rash) and of increasing bacterial resistance *(69)*.

Table 7.2 – Medicines to consider for symptomatic treatment of acute sinusitis

Important

Medicines are listed in alphabetical order and they should all be considered equal treatment options.

Medicine	Formulation	Dose and frequency
Ibuprofen[a]	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	**Adults**: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) **Children**: • Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose
Paracetamol (acetaminophen)[b]	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	**Adults**: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)[c] **Children**: • Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours 3–< 6 kg: 60 mg given every 6 hours 6–< 10 kg: 100 mg given every 6 hours 10–< 15 kg: 150 mg given every 6 hours 15–< 20 kg: 200 mg given every 6 hours 20–< 30 kg: 300 mg given every 6 hours ≥ 30 kg: use adult dose

[a] Not for children < 3 months.
[b] Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.
[c] In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

Antibiotic treatment is not required in the great majority of cases of sinusitis.

Antibiotic treatment could be considered in certain cases, such as severe onset of symptoms, patients with underlying comorbid diseases or in those at increased risk of

complications (see antibiotic options in Table 7.3). Severe onset is defined as fever ≥ 39.0 °C and purulent nasal discharge or facial pain for at least 3–4 consecutive days *(71)*. The decision to treat with antibiotics in patients with chronic comorbid diseases should always be made on a case-by-case basis. Relevant comorbid conditions to consider include chronic malignancies and immunodeficiency.

Antibiotic treatment could also be considered in cases with "red flag" signs and symptoms suggestive of a complicated infection, such as systemic toxicity, persistent fever ≥ 39.0 °C, periorbital redness and swelling, severe headache and altered mental status.

Prevention

Prevention of sinusitis is based on the prevention of upper respiratory tract infections. All strategies (e.g. hand and respiratory hygiene, influenza, pneumococcal and COVID-19 vaccines) that help prevent upper respiratory tract infections could be useful in preventing sinusitis, including vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b for all children worldwide *(35,36)*. For countries considering vaccination programmes for influenza, vaccination of high-risk groups could be considered, for example, children aged 6 months to 5 years *(37)*.

Table 7.3 – Empiric antibiotic treatment for bacterial sinusitis

Note

Antibiotic treatment is not required in the great majority of cases: see Antibiotic treatment section.

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Adults	Children	Total treatment duration *(72)*
Amoxicillin (oral): 1 g given every 8 hours **OR** Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours	Amoxicillin (oral): 80–90 mg/kg/day Oral weight bands: 3–< 6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750 mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours **OR** Amoxicillin+clavulanic acid [a] (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours	5 days

Note. All dosages are for normal renal and hepatic function.
[a] Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

8. Oral and dental infections

Note

Antibiotic prophylaxis before dental procedures is not addressed in this chapter. Local/national guidance documents should be consulted for this purpose.

Key messages

- Untreated tooth decay is the most common global health condition. Dental caries and periodontal disease are largely preventable.
- Key to prevention of dental infection is to maintain good oral health; this includes reducing sugar consumption, regular toothbrushing and interdental cleaning and stopping tobacco smoking.
- **Antibiotics are not needed for dental pain**, which can be treated with analgesics or a dental procedure if appropriate.
- Antibiotics should not be used before a dental procedure to decrease inflammation or to cure toothache.
- Antibiotics are not needed before most dental procedures to prevent surgical site infections.
- For people with a severe spreading dental infection, effective antibiotics and surgical management are vital. Sepsis and the spread of infection may block the upper airway or move to the brain and are life-threatening so should be managed promptly.

Other relevant WHO resources (please check regularly for updates)

- Guideline: sugars intake for adults and children, 2015 *(73)*.
- Oral health – fact sheet *(74)*.
- Ending childhood dental caries: WHO implementation manual, 2019 *(75)*.
- WHO monograph on tobacco cessation and oral health integration, 2017 *(76)*.
- Information brochure for early detection and management of noma, 2016 *(77)*.

Definition

Various dental conditions and terms are defined below. The anatomy of a healthy tooth is illustrated in Figure 8.1.

Abscess: localized collection of pus caused by a bacterial infection in the tooth, gingivae (gums) or alveolar bone supporting the tooth. Abscesses can be categorized as:

- apical abscess, when the infection at the apex of the dental root originates from within the dental pulp. This is the most common form of dental abscess and usually results from untreated dental caries.
- periodontal abscess, where there is a collection of pus between the root and alveolar bone usually resulting from serious gum diseases.

Alveolar bone: part of the jawbones which surrounds and supports the teeth.

Apical periodontitis: inflammation (associated with pain) within the alveolar bone around the apex of a tooth, often occurring as a consequence of a necrotic pulp following pulpitis, tooth fracture or trauma.

Dental caries: tooth decay.

Dental pulp: blood vessels and nerves within the inner part of the tooth.

Dry socket (alveolar osteitis): a recognized inflammatory complication of tooth extraction which may develop a few days after extraction, last for more than a week and is extremely painful.

Gingivae (gums): soft tissue covering the alveolar bone.

Necrotic pulp: An irreversible condition that occurs when the pulp within the tooth becomes non-vital (dies) and is often associated with apical periodontitis.

Noma (cancrum oris/gangrenous stomatitis): an acute necrotizing disease that destroys the soft tissues and bones of the mouth and face as it progresses from necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis), mostly in malnourished children living in extreme poverty and with weakened immune systems.

Pericoronitis: inflammation of the gingiva (gum) surrounding a partially erupted tooth, often a lower wisdom tooth, which may be associated with an infection.

Periodontal disease: a group of inflammatory diseases affecting the tissues that surround and support the teeth. This includes:

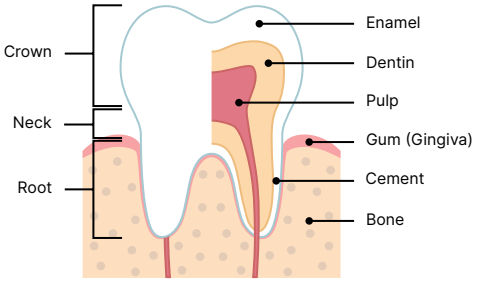
- **Gingivitis:** inflammation of the gingivae (gums).
- **Periodontitis:** chronic inflammatory disease of bacterial etiology that affects the soft and hard tissues which support the tooth, including alveolar bone.
- **Necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis):** a severe gum infection characterized by necrosis and ulcerations caused by a bacterial infection and often accompanied by severe pain and a strongly unpleasant smell.

Plaque: biofilm of microbes, mainly bacteria, which grows on surfaces within the mouth and contributes to oral diseases such as caries and periodontal disease.

Pulpitis: inflammation of the dental pulp causing pain. This condition often occurs as a result of the progression of dental caries and can lead to apical periodontitis which can then evolve into a dental abscess.

Spreading infection: development of sepsis or the spread of infection through the fascial spaces to vital structures of the head and neck (such as cellulitis) which can occur rapidly and become life-threatening.

Figure 8.1 – Anatomy of a healthy tooth



Healthy Tooth

Oral and dental infections

Definitions of Conditions That May Require Antibiotic Treatment

- **Abscess**: Localized collection of pus caused by a bacterial infection in the tooth, gums or alveolar bone supporting the tooth. Abscesses can be categorized as:
  - *Apical Abscess (more common):* Infection at the apex of the dental root that originates from within the dental pulp usually resulting from untreated dental caries
  - *Periodontal abscess:* Collection of pus between the root and alveolar bone usually resulting from serious gum diseases
- **Pericoronitis**: Inflammation of the gingiva (gum) surrounding a partially erupted tooth, often a lower wisdom tooth, which may be associated with an infection
- **Necrotizing periodontal disease**: A severe gum infection characterized by necrosis and ulcerations caused by a bacterial infection. Previously known as necrotizing ulcerative gingivitis
- **Noma**: An acute necrotizing disease that destroys the soft tissues and bones of the mouth and face as it progresses from necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis), rare in adults

Dental Terminology Definitions

- **Alveolar bone**: Part of the jawbones that surrounds and supports the teeth
- **Dental pulp**: Blood vessels and nerves within the inner part of the tooth
- **Gingivae (gums)**: Soft tissue covering the alveolar bone
- **Plaque**: Biofilm of microbes, mainly bacteria, which grows on surfaces within the mouth and contributes to oral diseases such as caries and periodontal disease

Only oral and dental infections where antibiotic treatment is usually required are reported

Common dental procedures are beyond the scope of this guidance

Most Likely Pathogens

Important: most dental infections are caused by conditions that favour the growth of pathogens in the mouth, including an abundance of sugars (e.g. sucrose) and reduced saliva flow (dry mouth)

Bacteria associated with caries:
- Acidogenic bacteria such as:
  - *Streptococcus* spp. (e.g. *S. mutans*)
  - *Lactobacillus* spp.
  - *Actinomyces* spp.

Bacteria associated with periodontal disease:
- Mostly anaerobes such as:
  - *Capnocytophaga* spp.
  - *Prevotella* spp.
  - *Aggregatibacter* spp.
  - *Porphyromonas* spp.

Prevention

- Minimize sugar consumption
- Prevent the accumulation of dental plaque with regular dental cleaning and good oral hygiene; fluoride is important because it strengthens the tooth enamel making it more resistant to caries
- Smoking cessation

Oral and dental infections

Diagnosis

Clinical Presentation

Dental abscess:

- Acute severe and persistent localized toothache that can radiate to the ear, jaw and neck
- Tooth tenderness (e.g. with chewing) and swelling of the cheek above the affected tooth are often present
- If left untreated, the infection can spread and present with signs of cellulitis around the eye or throat, fever (≥ 38.0 °C), tachycardia and lymphadenopathy

Pericoronitis:

- Inflamed, swollen gum tissue surrounding a partially erupted tooth
- Antibiotics are not normally required, although if infection is present, it should be carefully monitored as it can spread rapidly causing difficulty opening the mouth, swallowing or breathing
- Cellulitis of the neck (e.g. Ludwig angina) can be present and is a medical emergency

Necrotizing periodontal disease:

- Severe pain and inflamed ulcerated gums that bleed easily, necrosis of the interdental papillae, foul breath and a bad taste in the mouth
- It may also be accompanied by systemic symptoms, such as fever ≥ 38.0 °C, malaise and lymphadenopathy

Noma:

- It begins as necrotizing periodontal disease, it progresses rapidly destroying the soft tissues and bones of the mouth and further progressing to perforate the hard tissues and skin of the face
- If detected early, its progression can be rapidly halted, through basic oral hygiene rules, diet supplementation with proteins and nutrients and with antibiotics

Imaging

Dental radiographs should be undertaken wherever possible as part of the diagnosis to differentiate between the various causes of dental pain

Microbiology Tests

Mild cases: Usually not needed

Severe cases requiring hospitalization: Consider doing blood and/or pus aspirates cultures

Other Laboratory Tests

Mild cases: Usually not needed

Severe cases requiring hospitalization: White blood cell count, C-reactive protein and/or procalcitonin

Point-of-Care Tests and Investigations to Assist Diagnosis

Point-of-care tests can be done to establish the source of the dental pain/infection and make appropriate treatment decisions, for example:

- **Tapping the tooth to evaluate response to percussion**:
  - Tenderness indicates that the pain originates in the supporting bone and may be due to an abscess
- **Periodontal probing**
  - Can identify a periodontal abscess if pus exudes from a pocket greater than 3mm or necrotizing ulcerative disease if there is extremely tender gingival tissue and grey sloughing
- **Checking response to a cold stimulus**:
  - No response to cold may indicate a non-vital/necrotic pulp

Oral and dental infections

Treatment

Clinical Considerations

Important:

- Most dental infections and dental pain can be treated without antibiotic treatment by removal of the cause and drainage of the infection using a dental procedure (e.g. extraction of the tooth)
- Antibiotics do not prevent severe complications and cannot replace local surgical treatment
- Antibiotics should not be used before a dental procedure to "decrease inflammation" or to cure toothache. Antibiotics should not be used prior to most dental procedures to prevent surgical site infections

- Regular use of mouthwashes with an antiseptic product (e.g. chlorhexidine) is not necessary for the control of dental infections; rinsing with salty water is usually adequate

Antibiotic treatment is not needed in most cases but can be considered (always complementary to dental procedures):

- In patients with severe, spreading infections with systemic signs (e.g. facial swelling, inability to open the mouth, fever ≥ 38.0 °C, tachycardia)
- In severely immunocompromised patients and patients with uncontrolled diabetes (higher risk of complications)

Antibiotic Treatment Duration

If adequate source control achieved: **3 days**

If adequate source control **not** achieved: **5 days**

Note: patients should be reassessed before the end of treatment to check the resolution of the infection

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen 200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen) 500 mg-1 g q4-6h (max 4 g/day)
- **Hepatic impairment/cirrhosis**: Max 2 g/day

Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

For the treatment of infections of dental soft tissues (e.g. pericoronitis or necrotizing periodontal disease), metronidazole is an option

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS Amoxicillin 500 mg q8h **ORAL**

OR

ACCESS Phenoxymethylpenicillin (as potassium) 500 mg (800 000 IU) q6h **ORAL**

Oral and dental infections

Definitions of Conditions That May Require Antibiotic Treatment

- **Abscess:** Localized collection of pus caused by a bacterial infection in the tooth, gums or alveolar bone supporting the tooth. Abscesses can be categorized as:
  - *Apical Abscess (more common):* Infection at the apex of the dental root that originates from within the dental pulp usually resulting from untreated dental caries
  - *Periodontal abscess:* Collection of pus between the root and alveolar bone usually resulting from serious gum diseases
- **Pericoronitis**: Inflammation of the gingiva (gum) surrounding a partially erupted tooth, often a lower wisdom tooth, which may be associated with an infection
- **Necrotizing periodontal disease**: A severe gum infection characterized by necrosis and ulcerations caused by a bacterial infection. Previously known as necrotizing ulcerative gingivitis
- **Noma**: An acute necrotizing disease that destroys the soft tissues and bones of the mouth and face as it progresses from necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis), mostly in malnourished children living in extreme poverty and with weakened immune systems

Dental Terminology Definitions

- **Alveolar bone**: Part of the jawbones that surrounds and supports the teeth
- **Dental pulp**: Blood vessels and nerves within the inner part of the tooth
- **Gingivae (gums)**: Soft tissue covering the alveolar bone
- **Plaque**: Biofilm of microbes, mainly bacteria, which grows on surfaces within the mouth and contributes to oral diseases such as caries and periodontal disease

Only oral and dental infections where antibiotic treatment is usually required are reported

Common dental procedures are beyond the scope of this guidance

Most Likely Pathogens

Important: most dental infections are caused by conditions that favour the growth of pathogens in the mouth, including an abundance of sugars (e.g. sucrose) and reduced saliva flow (dry mouth)

Bacteria associated with caries:
- Acidogenic bacteria such as:
  - *Streptococcus* spp. (e.g. *S. mutans*)
  - *Lactobacillus* spp.
  - *Actinomyces* spp.

Bacteria associated with periodontal disease:
- Mostly anaerobes such as:
  - *Capnocytophaga* spp.
  - *Prevotella* spp.
  - *Aggregatibacter* spp.
  - *Porphyromonas* spp.

Prevention

- Minimize sugar consumption
- Prevent the accumulation of dental plaque with regular dental cleaning and good oral hygiene; fluoride is important because it strengthens the tooth enamel making it more resistant to caries
- Promote smoking cessation

Oral and dental infections

Diagnosis

Clinical Presentation

Dental abscess:

- Acute severe and persistent localized toothache that can radiate to the ear, jaw and neck
- Tooth tenderness (e.g. with chewing) and swelling of the cheek above the affected tooth are often present
- If left untreated, the infection can spread and present with signs of cellulitis around the eye or throat, fever (≥ 38.0 °C), tachycardia and lymphadenopathy

Pericoronitis:

- Inflamed, swollen gum tissue surrounding a partially erupted tooth
- Antibiotics are not normally required, although if infection is present, it should be carefully monitored as it can spread rapidly causing difficulty opening the mouth, swallowing or breathing
- Cellulitis of the neck (e.g. Ludwig angina) can be present and is a medical emergency

Necrotizing periodontal disease:

- Characterized by severe pain and inflamed ulcerated gums that bleed easily, necrosis of the interdental papillae, foul breath and a bad taste in the mouth
- It may also be accompanied by systemic symptoms, such as fever ≥ 38.0 °C, malaise and lymphadenopathy

Noma:

- It begins as necrotizing periodontal disease, it progresses rapidly destroying the soft tissues and bones of the mouth and further progressing to perforate the hard tissues and skin of the face
- If detected early, its progression can be rapidly halted, through basic oral hygiene rules, diet supplementation with proteins and nutrients and with antibiotics

Imaging

Dental radiographs should be undertaken wherever possible as part of the diagnosis to differentiate between the various causes of dental pain

Microbiology Tests

Mild cases: Usually not needed

Severe cases requiring hospitalization: Consider doing blood and/or pus aspirates cultures

Other Laboratory Tests

Mild cases: Usually not needed

Severe cases requiring hospitalization: White blood cell count, C-reactive protein and/or procalcitonin

Point-of-Care Tests and Investigations to Assist Diagnosis

Point-of-care tests can be done to establish the source of the dental pain/infection and make appropriate treatment decisions, for example:

- **Tapping the tooth to evaluate response to percussion**:
  - Tenderness indicates that the pain originates in the supporting bone and may be due to an abscess
- **Periodontal probing**
  - Can identify a periodontal abscess if pus exudes from a pocket greater than 3mm or necrotizing ulcerative disease if there is extremely tender gingival tissue and grey sloughing
- **Checking response to a cold stimulus**:
  - No response to cold may indicate a non-vital/necrotic pulp

Oral and dental infections

Treatment

Clinical Considerations

Important:

- Most dental infections and dental pain can be treated without antibiotic treatment by removal of the cause and drainage of the infection using a dental procedure (e.g. extraction of the tooth)
- Antibiotics do not prevent severe complications and cannot replace local surgical treatment
- Antibiotics should not be used before a dental procedure to "decrease inflammation" or to cure toothache. Antibiotics should not be used prior to most dental procedures to prevent surgical site infections

- Regular use of mouthwashes with an antiseptic product (e.g. chlorhexidine) is not necessary for the control of dental infections; rinsing with salty water is usually adequate

Antibiotic treatment is not needed in most cases but can be considered (always complementary to dental procedures):

- In patients with severe, spreading infections with systemic signs (e.g. facial swelling, inability to open the mouth, fever ≥ 38.0 °C, tachycardia)
- In severely immunocompromised patients and patients with uncontrolled diabetes (higher risk of complications)

Antibiotic Treatment Duration

If adequate source control achieved: **3 days**

If adequate source control **not** achieved: **5 days**

Note: patients should be reassessed before the end of treatment to check the resolution of the infection

Symptomatic Treatment

Medicines are listed in alphabetical order and should be considered equal treatment options

Ibuprofen (do not use if <3 months of age)
- **Pain control/antipyretic**: 5-10 mg/kg q6-8h
- **Oral weight bands**:

6-<10 kg	50 mg q8h
10-<15 kg	100 mg q8h
15-<20 kg	150 mg q8h
20-<30 kg	200 mg q8h
≥30 kg	200-400 mg q6-8h (Max 2.4 g/day)

OR

Paracetamol (acetaminophen)
- **Pain control/antipyretic**: 10-15 mg/kg q6h
- **Oral weight bands**:

3-<6 kg	60 mg q6h
6-<10 kg	100 mg q6h
10-<15 kg	150 mg q6h
15-<20 kg	200 mg q6h
20-<30 kg	300 mg q6h
≥30 kg	500 mg-1 g q4-6h (Max 4 g/day or 2 g/day if hepatic impairment/cirrhosis)

Antibiotic Treatment

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

For the treatment of infections of dental soft tissues (e.g. pericoronitis or necrotizing periodontal disease), metronidazole is an option

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS

Amoxicillin 80-90 mg/kg/day **ORAL**
- **Oral weight bands**:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

OR

ACCESS

Phenoxymethylpenicillin (as potassium): 10-15 mg/kg/dose (16 000-24 000 IU/kg/dose) q6-8h **ORAL**

Pathophysiology

Most dental conditions relate to the oral microbiota in dental plaque and do not require antibiotic treatment. Dental plaque is a microbe rich biofilm that sticks to surfaces within the mouth, including teeth, dentures and orthodontic appliances. In the presence of free sugars, especially sucrose from the diet, plaque bacteria can create an environment that favours tooth decay (dental caries). Acid produced by plaque bacteria in the presence of sugar causes this destruction, which is reversible only when confined to the outer enamel layer. Unless it is removed, the progression of caries is hard to stop once it enters the deeper parts of the tooth.

If dental caries progresses to reach the pulp, inflammatory pain (pulpitis) occurs which can eventually lead to pulpal necrosis and the tooth becoming non-vital. When this occurs, a tooth may initially be pain free or become tender to touch (apical periodontitis). If left to progress further, a localized accumulation of pus (periapical abscess) may form or an infection of the tooth, gums or alveolar bone supporting the tooth may spread to adjacent vital structures in the head and neck (e.g. cellulitis) or through the bloodstream (e.g. sepsis).

Accumulation of dental plaque around the gingival margin of teeth (at the gumline) and in periodontal pockets (below the gumline) can stimulate an inflammatory response. In some people this can lead to immune-mediated destruction of the periodontal structures (e.g. gums or alveolar bone) which support the teeth. Progressive destruction of these periodontal tissues may lead to teeth becoming mobile and eventually to tooth loss.

Some protective mechanisms to reduce plaque accumulation include saliva and the cleansing action of the tongue. Regular removal of plaque through oral hygiene practices, such as toothbrushing and interdental cleaning, is essential to prevent and manage dental caries and periodontal disease.

Epidemiology

Despite being largely preventable, oral disease (including dental caries and periodontal disease) is common and an important public health problem *(78)*.

Untreated dental caries affect almost half of the world's population (42% in 2015) making it the most prevalent of the oral conditions reported in the Global Burden of Disease Study *(78)*.

The prevalence of untreated caries in permanent teeth was highest in young people aged 15–19 years. Periodontal disease is less common than dental caries, with an overall yearly prevalence of around 7%. As periodontal disease may progress through life, it is highest in older people aged 55–59 years *(78)*.

Common risk factors for dental infections include diets high in free sugars and poor oral hygiene leading to dental caries. Poor oral hygiene, smoking or chewing tobacco, stress, malnutrition and being immunocompromised are risk factors for periodontal diseases,

including necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis). Poor oral hygiene and severe malnutrition are also risk factors for noma, a necrotizing disease most commonly seen in children living in low-income countries and with a 90% fatality rate if left untreated.

Most likely pathogens

The normal oral microbiota is richly diverse, including both aerobic and anaerobic bacteria, together with fungi, especially *Candida* spp.. Most dental infections are caused by conditions in the oral environment which favour the growth of pathogens. For example, an abundance of free sugars, such as sucrose, favours cariogenic bacteria (e.g. *Streptococcus mutans*) resulting in tooth decay. Reduced saliva flow makes patients with a dry mouth at increased risk of dental caries as there is less natural protection from the saliva. Furthermore, a recent course of antibiotics is a common cause for oral candidiasis (thrush). While the precise composition of an individual's oral microbiota will differ between parts of the mouth and will change over time and between individuals, Table 8.1 shows a typical mix of the bacteria that are part of the oral microbiota in health and disease. The oral microbiota and associated disease can be significantly different depending on the precise location. For example, enamel caries is more often associated with *Streptococcus mutans* whereas *Actinomyces* spp. predominate in root caries.

Table 8.1 – Normal resident oral microbiota and pathogens most frequently associated with dental infections (in descending order of frequency)

Normal resident oral microbiota[a]	Bacteria associated with caries[b]	Bacteria associated with periodontal disease
Streptococcus spp.	*Streptococcus* spp. (e.g. *Streptococcus mutans*)	Anaerobes (most cases), e.g.:
Actinomyces spp.	*Lactobacillus* spp.	*Prevotella* spp.
Prevotella spp.	*Actinomyces* spp.	*Capnocytophaga* spp.
Veillonella spp.		*Aggregatibacter* spp.
		Porphyromonas spp.

[a] A richly diverse group of pathogens, including both aerobic bacteria and anaerobes.
[b] Mostly acidogenic bacteria

Clinical presentation

Typical signs and symptoms of selected oral conditions are described in the following two sections. Dental pain is often due to inflammation rather than infection and careful diagnosis is required to ensure optimal treatment is provided and antibiotic use minimized.

The severity of signs and symptoms may range from mild diseases (most cases) that can be safely managed in an outpatient setting to severe infections of dental origin (including sepsis) that require hospitalization and intravenous antibiotic treatment. Oral and dental infections commonly involve the lymph nodes and can also spread through the fascial spaces of the head and neck to block the airway, move into the brain through the periorbital area and can present as osteomyelitis. Please refer to the chapters on sepsis, lymphadenitis and osteomyelitis if these sequelae are suspected.

Conditions that may require antibiotic treatment

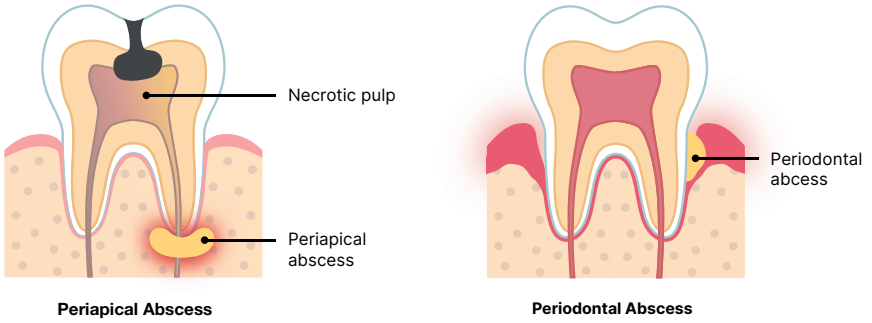
Abscess

An apical abscess (Figure 8.2) is the most common type of dental abscess. It is often, but not always, painful and characterized by persistent localized pain that can radiate to the ear, jaw and neck. Tooth tenderness (stimulated by chewing or food trapping) is common as well as swelling of the soft tissues adjacent to the affected tooth.

If an apical abscess is left untreated, there is a high risk of spread to vital structures of the head and neck or systemic spread of the infection that can then lead to sepsis. Signs that the infection has spread include cellulitis around the eye or throat (causing difficulties swallowing or breathing, e.g. Ludwig angina), fever (≥ 38.0 °C), malaise, tachycardia (increased heart rate) and lymphadenopathy. This must be treated as a medical emergency.

A periodontal abscess (Figure 8.2) is less common than an apical abscess. It is usually a localized accumulation of pus in the periodontal tissues (gums and alveolar bone supporting the tooth) which can be readily drained by professional cleaning of the periodontal pocket or by extraction of the tooth without the need for antibiotics.

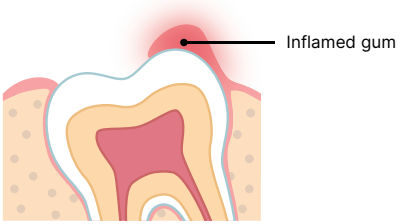
Figure 8.2 – Periapical and periodontal abscess



Pericoronitis

Pericoronitis is inflammation and sometimes infection of the gum around a partially erupted tooth, often a lower wisdom tooth (Figure 8.3). It usually occurs in late adolescence and early adult life and can be treated by professional cleaning, saline (hot salty water) mouthwash and, if necessary, by draining the infection. Antibiotics are not normally required, although if infection is present, it should be carefully monitored as it can spread rapidly causing difficulty opening the mouth, swallowing or breathing. Cellulitis of the neck (e.g. Ludwig angina) is a medical emergency as it can quickly become life-threatening.

Figure 8.3 – Pericoronitis

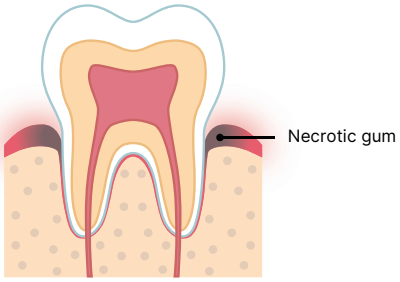


Pericoronitis

Necrotizing periodontal disease

Necrotizing periodontal disease (Figure 8.4), which was previously known as necrotizing ulcerative gingivitis, is characterized by the following: severe pain and inflamed ulcerated gums that bleed easily; necrosis of the interdental papillae; foul breath; and a bad taste in the mouth. It may also be accompanied by systemic symptoms, such as fever ≥ 38.0 °C, malaise and lymphadenopathy.

Figure 8.4 – Necrotizing periodontal disease



Necrotizing Periodontal Disease

Noma

Noma is a necrotizing disease that destroys the mouth and face. It begins as necrotizing periodontal disease that progresses rapidly, destroying the soft tissues and bones of the mouth and further progressing to perforate the hard tissues and skin of the face. It mostly affects young children between the ages of 2 and 6 years suffering from severe malnutrition, living in extreme poverty and with weakened immune systems. Its prevalence is highest in sub-Saharan Africa. Noma is fatal for 90% of the children affected. If detected early, its progression can be rapidly halted, through basic oral hygiene rules, diet supplementation with proteins and nutrients and with antibiotics. Early detection helps to prevent suffering, disability and death. Please also refer to the WHO information brochure for early detection and management of noma for more information about this topic *(77)*.

Conditions that do not require antibiotic treatment

Dental caries progression to pulpal disease

Dental caries is the localized destruction of dental hard tissue (enamel or dentine) by acid-producing plaque bacteria in the presence of dietary sugar. This process can be reversible in early lesions. Caries can sometimes lead to the formation of cavities (i.e. holes in the tooth) which are often hidden in the space between the teeth. Diagnosis is based on response of the tooth to cold/hot stimulus and radiographic imaging. Cavities and devitalized teeth may appear dark in colour compared to other teeth.

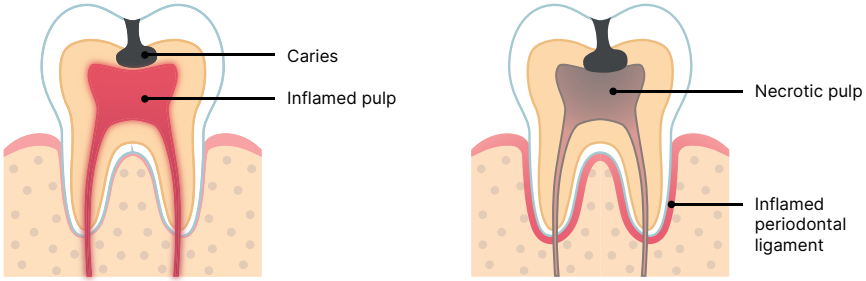
Caries develops slowly and can be pain free in the initial phase. However, if left untreated, the lesion can extend to the dental pulp causing pulpitis to begin with, then pulpal necrosis and ultimately dental abscess. Severe disease or necrosis of the dental pulp as a consequence of dental caries can be associated with systemic infections.

Reversible pulpitis is characterized by acute pain or discomfort initially caused by drinking hot or cold beverages. It is possible to treat the problem at this stage with a simple restoration.

If caries progresses, irreversible pulpitis (Figure 8.5) develops causing constant severe pain which characteristically keeps the patient awake at night. This pain may stop suddenly when progression of the disease leads to necrosis of the dental pulp.

If left untreated, apical periodontitis (Figure 8.5) often develops, characterized by dull throbbing in the surrounding area (mouth and jaw) and soreness while biting. The pain may be eased by cold and made worse by heat (e.g. hot and cold beverages). Progression of the condition may lead to an apical abscess, and this is the most common cause of dental abscess.

Figure 8.5 – Irreversible pulpitis and apical periodontitis



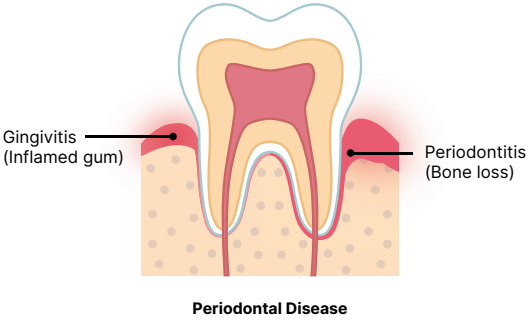
Dry socket / alveolar osteitis

Dry socket (alveolar osteitis) is a recognized inflammatory complication of tooth extraction. It occurs 2–3 days after extraction and can last for up to 10 days. Severe pain develops a few days after the dental procedure, associated with slow healing of the socket; it may be accompanied by an unpleasant taste. Appropriate pain control is necessary as pain may last for many days. Antibiotics are not appropriate for the prophylaxis or treatment of dry socket unless osteomyelitis is suspected; please refer to the chapter on osteomyelitis if this is suspected.

Periodontal disease

Periodontal disease (Figure 8.6) is the term used to describe a range of conditions affecting the tissues that surround and support the teeth, including gingivitis and periodontitis. As these are generally immune-mediated diseases, it is usually inappropriate to use antibiotics for their treatment.

Figure 8.6 – Periodontal disease



Gingivitis

Gingivitis is characterized by redness and swelling of the gums due to the build up of food debris and microbial biofilm. It is usually painless, but bleeding when toothbrushing is common. Halitosis may be present. In its early stages, gingivitis is reversible with good oral hygiene. Severe forms of gingivitis are known but are rare.

Periodontitis

Periodontitis is an inflammatory disease characterized by the progressive destruction of the alveolar bone which supports the teeth. It is often a hidden disease as it is generally painless and progresses below the gums. Halitosis may be present. In case of periapical periodontitis, soreness, while biting can occur due to a devitalized (dead) tooth.

The disease process of periodontitis occurs over time (usually years) and people often only become aware of it when their teeth start to move or fall out; a more aggressive destruction of the bone may sometimes be seen. Oral health professionals use special probes when carrying out periodontal screening to enable early diagnosis and treatment of periodontitis. Addressing risk factors, including effective cleaning of the periodontal tissues (under the gums), smoking cessation and good diabetes control are essential. Antibiotics are only appropriate for the treatment of aggressively destructive conditions; antibiotics are not appropriate for chronic periodontitis.

Laboratory tests

Patient microbiology tests

Routine microbiology tests are not required in most cases of dental infection but can be considered in severe cases requiring hospitalization, when culture and sensitivity testing (e.g. blood and/or pus aspirates for culture) can help in the selection of an appropriate antibiotic, for example, if cellulitis (e.g. Ludwig angina) is spreading to vital structures or if sepsis is suspected. Please also refer to the chapter on sepsis, if suspected.

Other tests

Most dental infections are bacterial, except for oral thrush (a fungal infection usually caused by *Candida* spp.) and cold sores (a viral infection) which are easily recognizable clinically.

Acute dental conditions are routinely diagnosed using point-of-care tests and investigations (see point-of-care tests and investigations in the following section).

Routine laboratory tests are not required in most cases of dental infections but may be considered in severe cases requiring hospitalization.

Using microbiology surveillance data

Routine microbiology surveillance of oral microbiota does not generally take place, so such data are unavailable for clinical guidance.

Point-of-care tests and investigations to assist diagnosis

Establishing the source of the dental pain/infection is an important element of accurate diagnosis and is essential to make appropriate treatment decisions. Sensitivity of the tooth to a cold stimulus indicates a vital pulp; depending on the intensity and duration of the stimulated pain, this may indicate pulpitis.

No response to cold may indicate a non-vital/necrotic pulp and tenderness to percussion (tapping the tooth) indicates that the pain originates in the supporting bone and may be due to an abscess. Periodontal probing can identify a periodontal abscess if pus exudes from a pocket greater than 3 mm or necrotizing ulcerative disease if there is extremely tender gingival tissue and grey sloughing.

Imaging

If a dental infection is suspected, imaging using dental radiographs (X-rays) should be done wherever possible as part of the diagnosis. Radiographs are important for differentiating between the various causes of dental pain, including how far caries (decay) has progressed and where tenderness to percussion is associated with a radiolucency (i.e. black area on radiographic image) in the alveolar bone suggesting an abscess. Location of the radiolucency relative to the tooth helps differentiate between an apical or periodontal abscess.

Treatment

Dental bacterial infections are rarely self-limiting and may rapidly become life-threatening if left untreated. Most dental infection and pain are amenable to treatment by removal of the cause and drainage of the infection using a dental procedure, such as extraction of the tooth. Removal of the cause of the infection using a dental procedure is usually the quickest and safest way of resolving the problem, and is essential to avoid the risk of rapidly spreading and potentially life-threatening infection. Antibiotics are normally only required for the treatment of spreading infections.

No antibiotic care

Most dental infections are characterized by some level of dental pain and, while adequate pain control should always be offered, the prescription of medications alone is not usually appropriate.

Caries, pulpal disease and dental abscesses are best treated with a dental procedure to remove the source of the problem; using painkillers alone is suboptimal as the condition can progress to a life-threatening spreading infection.

Dry socket (alveolar osteitis) is an extremely painful and common occurrence following dental extraction. It occurs 2–3 days after extraction and can last for up to 10 days. This condition requires optimum pain management but no antibiotics are needed unless osteomyelitis is suspected; please refer to the chapter on osteomyelitis if this is suspected.

Ibuprofen and paracetamol are first choice painkillers for dental pain (Table 8.2). In the case of severe pain, ibuprofen and paracetamol may work better when taken in combination.

Caution should be exercised as the incidence of paracetamol (acetaminophen) overdose in relation to dental pain is relatively high. Opioid painkillers should be avoided as they offer no benefit for this sort of pain and are associated with the risk of substance misuse.

Table 8.2 – Medicines to control acute dental pain

Important

Medicines are listed in alphabetical order and they should all be considered equal treatment options.

Medicine	Formulation	Dose and frequency
Ibuprofen[a]	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	**Adults**: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) **Children**: • Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose

continues

Table 8.2 *continued*

Medicine	Formulation	Dose and frequency
Paracetamol (acetaminophen)[b]	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	**Adults**: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)[c] **Children**: • Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours 3–< 6 kg: 60 mg given every 6 hours 6–< 10 kg: 100 mg given every 6 hours 10–< 15 kg: 150 mg given every 6 hours 15–< 20 kg: 200 mg given every 6 hours 20–< 30 kg: 300 mg given every 6 hours ≥ 30 kg: use adult dose

[a] Not for children < 3 months, or for people with hypersensitivity to aspirin or any other NSAID (non-steroidal anti-inflammatory drug), or for people with a history of gastrointestinal bleeding or ulceration.
[b] Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect. Warning: overdose is relatively common among people with severe dental pain.
[c] In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Oral antiseptics

Regular use of mouthwashes with an antiseptic product (e.g. chlorhexidine) is not required for the control of dental infections. Such products could be considered in case of acute exacerbations of periodontal disease. Of note, no formulation of oral antiseptics is currently included in the EML and EMLc and rinsing with saline (salty water) is usually adequate as well as being cheaper and more readily available. Caution should be exercised with the use of chlorhexidine mouthwash in patients following extractions or treatment of alveolar osteitis (dry socket following dental extraction) as it has been associated with anaphylaxis.

Dental procedures

Dental procedures are usually the quickest and safest solutions for dental pain and infection.

Commonly performed dental procedures are briefly described in Table 8.3. Detailed information on these procedures is beyond the scope of this chapter.

Table 8.3 – Commonly performed procedures for certain dental diseases

Dental disease	Procedure
Abscess	1. Apical abscess Source control through: • Tooth extraction • Pulp extirpation (drainage of pus and removal of necrotic pulp tissue by drilling through the tooth into the pulp) followed by root canal treatment **OR** • Soft tissue incision and drainage followed by tooth extraction or root canal treatment. 2. Periodontal abscess Source control through: • Tooth extraction **OR** • Drainage of any pus collection by professional cleaning of the periodontal tissues.
Apical periodontitis/ pulpal necrosis	Source control through: • Tooth extraction **OR** • Pulp extirpation (drainage of pus and removal of necrotic pulp tissue by drilling through the tooth into the pulp) followed by root canal treatment
Dental caries (decay)/reversible pulpitis	Removal of caries and restorative filling Where access to dental care is not readily available or for people who are unable to accept a dental procedure (e.g. due to dental phobia), silver diamine fluoride may be appropriate to stop progression of the caries.
Dry socket (alveolar osteitis)	Reassurance that this is a common yet painful outcome Irrigation of the socket with saline
Pericoronitis	Source control through: • Tooth extraction **OR** • Drainage of any pus collection by irrigation under the operculum (flap of gum over the erupting tooth) with saline

continues

Table 8.3 *continued*

Dental disease	Procedure
Pulpitis (when irreversible)	Source control through: • Tooth extraction **OR** • Pulp extirpation (removal of the inflamed pulp and treatment of the root canal)
Necrotizing periodontal disease (previously known as necrotizing ulcerative gingivitis)[a]	• Regular toothbrushing with a fluoride-containing toothpaste and use of an interdental brush or dental floss to remove plaque • Professional cleaning around the teeth and periodontal tissues to remove the mineralized material known as scale, tartar or calculus • Smoking cessation advice
Noma	• Please refer to the WHO guidance for early detection and management of noma *(77)*

[a] Necrotizing periodontal disease can often be resolved by procedures alone – antibiotics are often not required.

Antibiotic treatment

Up to 10% of antibiotic prescribing in the outpatient setting can be by dentists for the treatment of oral and dental infections or prophylaxis of surgical procedures, of which a large proportion have been shown to be unnecessary or inappropriate *(79)*. Efforts should be made to restrict the use of antibiotics only to situations when their use is strictly necessary *(79,80)*.

Antibiotic treatment is required only for few dental conditions.

Antibiotics are not appropriate for inflammatory conditions (including periodontitis, irreversible pulpitis and dry socket treatment) because they do not prevent the development of severe complications and cannot replace local surgical or non-surgical treatment.

Antibiotics should not be used before a dental procedure to: calm an infection; decrease inflammation; cure toothache (pain relief is best achieved by a dental procedure not a dental prescription); or prevent surgical site infections.

Effective antibiotic treatment (along with a procedure for source control) is essential in patients with severe, spreading dental infections. Severe cases include those with systemic signs of infection, for example, facial swelling, inability to open the mouth, fever ≥ 38.0 °C and tachycardia. Even when necessary, antibiotics should only be used to complement surgical source control, for example, drainage of the abscess or tooth extraction. Antibiotic use could

also be considered in severely immunocompromised patients (including patients with uncontrolled diabetes) because they have a higher risk of complications. When antibiotic treatment is considered necessary, empiric use of amoxicillin or phenoxymethylpenicillin as indicated in Table 8.4 is considered appropriate. Using two antibiotics (e.g. amoxicillin and metronidazole) as adjunctive treatment is not necessary in the vast majority of cases and noma is usually the only indication for dual antibiotic therapy (using two antibiotics such as amoxicillin and metronidazole).

The AWaRe book does not include alternative antibiotic options in cases of allergy to first-choice antibiotics. For dental infections, only penicillin options are recommended by the AWaRe book, which may be considered problematic by some prescribers. However, even though allergies to antibiotics (particularly to beta-lactams) are frequently self-reported or indicated in health records, in most cases (> 95%), these patients do not have a true immunologically mediated allergy and it is very likely that they can safely tolerate the medicine if re-exposed to it. Please refer to the chapter on allergies to antibiotics for more information about this aspect.

Prevention

Dental caries does not occur without sugar, thus minimizing dietary free sugars is key to avoiding dental pain and infections caused by dental caries. Further information on dietary sugar can be found in the WHO guidance document on sugar intake for adults and children *(73)*.

As the progression of dental caries and periodontal disease may continue slowly from childhood to adulthood, the negative health effects of oral disease are cumulative. Even a small reduction in the risk factors early in life confers significant benefit in later life.

Stopping tobacco use, whether smoked or smokeless, should also be promoted for the prevention of periodontal disease and oral cancer.

Preventing the accumulation of dental plaque is important for preventing dental diseases such as dental caries or periodontal disease.

Where people are unable to perform adequate oral hygiene themselves, regular professional dental cleaning may be necessary to maintain oral health.

Fluoride plays an important role in improving oral health by strengthening the tooth enamel and making it more resistant to dental caries. Further information on fluoride and oral health can be found on the WHO website *(74)*. For prevention of dental caries in children, refer to the WHO guidance document *(75)*.

Table 8.4 – Empiric antibiotic treatment for selected cases of severe dental infections

Note

Antibiotic treatment is not required for most dental conditions. Dental procedures (e.g. drainage of an abscess and tooth extraction) are the main treatment.

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Adults	Children	Total treatment duration
Amoxicillin [a] (oral): 500 mg given every 8 hours **OR** Phenoxymethylpenicillin [a] (oral): 500 mg (800 000 IU[b]) given every 6 hours	Amoxicillin [a] (oral): 80–90 mg/kg/day Oral weight bands: 3–< 6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours **OR** Phenoxymethylpenicillin [a] (oral): 10–15 mg/kg/dose (16 000–24 000 IU/kg/dose[b]) given every 6 to 8 hours ≥ 30 kg: use adult dose	3 days, if adequate source control is achieved; otherwise 5 days[c] Patients should be reassessed before the end of treatment to check the resolution of the infection.

IU: international units.
Note. All dosages are for normal renal and hepatic function.
[a] For the treatment of infections of the dental soft tissues (e.g. pericoronitis or necrotizing periodontal disease), metronidazole is an option.
[b] Units of the potassium salt.
[c] If source control is not achieved or in cases where operative dental treatment is not available, often because of the unavailability of dentists in many low resource settings.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

9. Localized acute bacterial lymphadenitis

This chapter does not include severe or generalized infections or infections caused by viral, fungal or parasitic pathogens.

☑ Key messages

- **Antibiotics are not needed** for the great majority of cases of enlarged lymph nodes as they are caused by viral infections.
- A watchful waiting approach is reasonable when the patient is not severely ill and bacterial lymphadenitis or a malignancy is not suspected, because the condition is usually self-limiting.
- Human immunodeficiency virus (HIV) infection, tuberculosis and spreading dental infection should always be considered in the differential diagnosis.
- If bacterial lymphadenitis is suspected, empiric antibiotic treatment should cover *Staphylococcus aureus* and *Streptococcus pyogenes* with Access group antibiotics.

Definition

Lymphadenitis is the inflammation and enlargement (> 1–2 cm) of one or several lymph nodes. It can be classified as localized (most cases) where only one lymph node region is affected or generalized when multiple lymph node regions are affected. Lymphadenitis can also be classified based on the anatomical site of the lymph node region affected (e.g. cervical or axillary) and on the depth of the lymph node affected, either superficial or deep lymph nodes. Lymphadenitis has several infectious and non-infectious causes, including skin infections, dental infections, cancer or lymphoproliferative disorders. The term lymphadenitis (i.e. enlargement of a lymph node with inflammatory signs) and lymphadenopathy (i.e. disease of a lymph node in which they are abnormal in size and/or consistency) are often used interchangeably, although in lymphadenitis the inflammatory component (redness, warmth and pain) is more pronounced. Infection in the lymph nodes can be caused by bacteria, viruses, fungi or parasites. This chapter focuses on localized acute bacterial lymphadenitis, although most enlarged lymph nodes are caused by viral infections.

Localized acute bacterial lymphadenitis

This guidance excludes management of severe or generalized infections or those caused by viral, fungal or parasitic pathogens

Definition

Lymphadenitis refers to the inflammation and acute enlargement (>1-2 cm) of one or several lymph nodes

Classification based on:

- Number of lymph node regions affected:
  - *Localized* (most cases): 1 lymph node region affected
  - *Generalized*: >1 lymph node region affected
- Location of the affected lymph node (e.g. cervical, axillary)
- Depth of the affected lymph node (superficial or deep)

Most Likely Pathogens

Viruses (most cases):

- Epstein-Barr virus, Cytomegalovirus (both viruses can cause infectious mononucleosis)
- Respiratory viruses

Bacteria (more rarely):

- *Staphylococcus aureus* (including MRSA)
- *Streptococcus pyogenes* (group A *Streptococcus)*

Consider in specific situations (based on history and physical examination):

- Sexually transmitted infections (e.g. HIV)
- Zoonoses (e.g. brucellosis, tularemia, bartonellosis - the latter mostly following cat bites or scratches)
- Mycobacterial infections (including nontuberculous)

Diagnosis

Clinical Presentation

- Acute onset of a palpable, painful red and inflamed enlarged lymph node (>1-2 cm) +/- fever (≥ 38.0 °C), and other signs/symptoms of systemic disease & cellulitis
- Bacterial cause more probable if unilateral involvement, fluctuance and skin drainage of the lymph node

Microbiology Tests

Usually not needed; consider testing for HIV and tuberculosis if these are suspected

Other Laboratory Tests

Usually not needed but may be considered in selected cases

Biopsy

Consider when a malignancy is suspected

Imaging

- Usually not needed
- Ultrasound can be considered to confirm lymph node involvement, to quantify the enlargement and to detect the presence of an abscess; it is not reliable to rule out malignancies (biopsy should be performed)

Localized acute bacterial lymphadenitis

Treatment

Clinical Considerations

Important:

- The great majority of cases of enlarged lymph nodes are caused by viral infections and antibiotics are **not needed**
- A watchful waiting approach with follow up is appropriate (except if malignancy is suspected)

If symptoms are consistent with a bacterial infection, empiric treatment against *S. aureus* and *Streptococcus pyogenes* (group A *Streptococcus*) is indicated

Antibiotic Treatment Duration

5 days

Antibiotic Treatment

Note: history is key in order to adapt treatment if necessary

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL** OR 1 g+200 mg q8h **IV**

OR

ACCESS Cefalexin 500 mg q8h **ORAL**

OR

ACCESS Cloxacillin 500 mg q6h **ORAL** OR 2 g q6h **IV**

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible

If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability

Localized acute bacterial lymphadenitis

This guidance excludes management of severe or generalized infections or those caused by viral, fungal or parasitic pathogens

Definition

- Lymphadenitis refers to the inflammation and enlargement (>1-2 cm) of one or several lymph nodes
- Lymphadenopathy is another term often used

Classification based on:

- Number of lymph node regions affected:
  - *Localized* (most cases): 1 lymph node region affected
  - *Generalized*: >1 lymph node region affected
- Location of the affected lymph node (e.g. cervical, axillary)
- Depth of the affected lymph node (superficial or deep)

Most Likely Pathogens

Viruses (most cases):

- Epstein-Barr virus (can cause infectious mononucleosis)
- Cytomegalovirus (can cause infectious mononucleosis)
- Respiratory viruses

Bacteria (more rarely):

- *Staphylococcus aureus* (including MRSA)
- *Streptococcus pyogenes* (group A *Streptococcus)*

Consider in specific situations (based on history and physical examination):

- Sexually transmitted infections (e.g. HIV)
- Zoonoses (e.g. brucellosis, tularemia, bartonellosis - the latter mostly following cat bites or scratches)
- Mycobacterial infections (including nontuberculous)

Diagnosis

Clinical Presentation

- Acute onset of a palpable, painful red and inflamed enlarged lymph node (>1-2 cm) +/- fever (≥ 38.0 °C), and other signs/symptoms of systemic disease & cellulitis
- Bacterial cause more probable if unilateral involvement, fluctuance and skin drainage of the lymph node

Microbiology Tests

Usually not needed; consider testing for HIV and tuberculosis if these are suspected

Other Laboratory Tests

Usually not needed but may be considered in selected cases

Biopsy

Consider when a malignancy is suspected

Imaging

- Usually not needed
- Ultrasound can be considered to confirm lymph node involvement, to quantify the enlargement and to detect the presence of an abscess; it is not reliable to rule out malignancies (biopsy should be performed)

Localized acute bacterial lymphadenitis

Treatment

Clinical Considerations

Important:

- The great majority of cases of enlarged lymph nodes are caused by viral infections and antibiotics are **not needed**
- A watchful waiting approach with follow up is appropriate (except if malignancy is suspected)

If symptoms are consistent with a bacterial infection, empiric treatment against *S. aureus* and *Streptococcus pyogenes* (group A *Streptococcus*) is indicated

Antibiotic Treatment Duration

5 days

Antibiotic Treatment

Note: history is key in order to adapt treatment if necessary

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS

Amoxicillin+clavulanic acid
IV:
- 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
- > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h

ORAL: 80-90 mg/kg/day of amoxicillin component
- **Oral weight bands**:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin
Oral liquid must be refrigerated after reconstitution

OR

ACCESS

Cefalexin 25 mg/kg/dose q12h **ORAL**
- **Oral weight bands**:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR

ACCESS

Cloxacillin **IV**
- Neonates: 25-50 mg/kg/dose q12h
- Children: 25 mg/kg/dose q6h
- **ORAL**: 15 mg/kg/dose q6h
- **Oral weight bands**:

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible

If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability

Pathophysiology

Lymph nodes are an important part of the immune system which act as filters of lymph fluid. Lymphadenitis from an infectious cause is due to the immune system's response to localized or generalized inflammation and to the pathogen spreading to one or more lymph node regions.

Epidemiology

Lymphadenitis is a common condition worldwide and can occur at all ages; for example, cervical lymphadenitis occurs very frequently in healthy children. Lymphadenitis is usually associated with benign conditions (e.g. most infectious causes); however, it can also be a sign of malignancy (e.g. lymphoma).

Since lymphadenitis has many different causes, the epidemiology of the disease will reflect the specific etiology. For example, in Africa, tuberculous lymphadenitis (the most frequent cause of extrapulmonary tuberculosis (TB)) is still an important cause of persistent lymphadenitis, and chronic lymphadenopathy may be a sign of HIV infection *(81)*.

Most likely pathogens

Pathogens that can cause lymphadenitis are listed in Table 9.1.

Table 9.1 – Pathogens most frequently associated with acute lymphadenitis (in descending order of frequency)

Viruses	Bacteria
Most cases	**Most cases**
Epstein–Barr virus	*Staphylococcus aureus* (including MRSA)
Cytomegalovirus	*Streptococcus pyogenes* (group A *Streptococcus*)
Respiratory viruses	**More rarely**[a]
More rarely	Anaerobes
HIV	*Bartonella henselae* (mostly following cat bites or scratches)
	Chlamydia trachomatis (serovars L_1, L_2 and L_3 which cause lymphogranuloma venereum)
	Corynebacterium diphtheriae
	Francisella tularensis
	Haemophilus ducreyi
	Neisseria gonorrhoeae
	Rickettsia spp.
	Yersinia pestis

MRSA: methicillin-resistant *Staphylococcus aureus*.
Note. Pathogens associated with chronic lymphadenitis such as mycobacteria (including non-tuberculous) are not included in the table.
[a] This is not a full list but aims to show the variety of bacteria associated with localized lymphadenitis. The bacteria are listed in alphabetical order. Sexually transmitted infections and zoonoses need to be considered in the differential diagnosis.

Clinical presentation

Lymphadenitis is a noticeable enlargement (> 1–2 cm) of a lymph node. Acute onset, unilateral involvement, fluctuance and fluid that drains from the lymph node to the skin suggest a bacterial cause. Tenderness and inflammation are frequently associated with infectious causes. Fever (≥ 38.0 °C) and other signs and symptoms of systemic disease may be present, accompanied by cellulitis. Viral respiratory infections, infectious mononucleosis (caused by Epstein–Barr virus or cytomegalovirus), (acute) HIV infection and mycobacterial infections (mostly TB) always need to be considered when diagnosing the cause of acute lymphadenitis based on clinical history and findings. As the first step, it is important to identify the cause of the enlargement. Location of the enlarged lymph node and accompanying signs and symptoms of infection (e.g. symptoms of a dental infection, skin lesions, pharyngitis and signs and symptoms of an STI) can help establish the diagnosis. History and physical examination (including palpation of lymph nodes) usually help in the diagnosis and guide the investigation and treatment.

Laboratory tests

Patient microbiology tests

Routine microbiology testing is usually not needed because in most cases with an infectious cause, identifying the etiologic agent will not change the initial management. However, HIV infection and tuberculosis should be considered in the differential diagnosis and adequate testing should be done when these diseases are suspected.

Other tests

Routine laboratory testing is usually not needed. However, it may be considered in certain cases, for example, persistent lymph node enlargement for more than 4 weeks or the presence of warning signs such as important weight loss.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Biopsy

An excisional biopsy of the lymph node could be considered if a malignancy is suspected. An alternative technique that can be used is fine needle aspiration, another type of biopsy technique where a very thin needle is inserted into the mass under examination for sampling of cells/tissue.

Imaging

Routine imaging is usually not needed to begin with. An ultrasound can be considered to confirm lymph node involvement, to measure the size of the enlargement and to detect the presence of an abscess. However, ultrasound cannot reliably rule out malignancies; in suspected cases an excisional biopsy should be performed.

Antibiotic treatment

In certain cases, a watchful waiting approach without antibiotics is indicated when follow-up is feasible and the patient is not severely ill or a malignancy is not suspected. This approach is reasonable because the condition is frequently self-limiting – for example, mild cervical lymphadenitis is usually caused by a viral infection of the upper respiratory tract, especially in children but could also be associated with a dental infection.

If symptoms are consistent with a bacterial infection (e.g. fever, and painful, tender and inflamed lymph node), empiric treatment against *Staphylococcus aureus* and *Streptococcus pyogenes* is indicated. Antibiotic options are given in Table 9.2.

Table 9.2 – Empiric antibiotic treatment for bacterial lymphadenitis[a]

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Note

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid and have good efficacy in mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these two antibiotics are the preferred options whenever possible.

Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid IV: 1 g + 200 mg given every 8 hours Oral: 500 mg + 125 mg given every 8 hours **OR** **Cefalexin** (oral): 500 mg given every 8 hours **OR** **Cloxacillin**[b] IV: 2 g given every 6 hours Oral: 500 mg given every 6 hours	**Amoxicillin+clavulanic acid**[c] (IV/oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours **OR**	5 days

continues

Table 9.2 *continued*

Adults	Children	Total treatment duration
	Cefalexin (oral): 25 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 125 mg given every 12 hours 6–< 10 kg: 250 mg given every 12 hours 10–< 15 kg: 375 mg given every 12 hours 15–< 20 kg: 500 mg given every 12 hours 20–< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose **OR** Cloxacillin [b] IV: • Neonates: 25–50 mg/kg/dose given every 12 hours • Children: 25 mg/kg/dose given every 6 hours Oral: 15 mg/kg/dose given every 6 hours Oral weight bands: 3–< 6 kg: 62.5 mg given every 6 hours 6–< 10 kg: 125 mg given every 6 hours 10–< 15 kg: 250 mg given every 6 hours 15–< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours	

IV: intravenous.
Note. All dosages are for normal renal and hepatic function.
[a] Patient history is key in order to adapt treatment if necessary; for example, lymphadenitis in the context of cat scratch fever caused by *Bartonella henselae* would require a different antibiotic treatment.
[b] If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration, dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability.
[c] Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

10. Bacterial eye infections (excluding trachoma)

Note

See separate chapter on trachoma.

Key messages

- **Conjunctivitis** is mostly self-limiting and of viral origin. Allergies and toxic irritants should be included in the differential diagnosis. Topical antibiotics can be considered if a bacterial infection is suspected. Sexually transmitted infections should be included in the differential diagnosis in sexually active people and in newborns of infected mothers.
- **Keratitis** is mostly caused by bacteria and viruses in high-income countries and fungi predominate in low- and middle-income countries. Risk factors include eye trauma and prolonged contact lens use; in the latter case, *Acanthamoeba*, a parasite, or *Pseudomonas aeruginosa* should be considered as potential causes of the infection. Topical antibiotics are indicated as infectious keratitis is a potentially blinding condition.
- **Endophthalmitis** mostly occurs after a penetrating eye trauma (including eye surgery) or dissemination to the eye of a distant infection (e.g. endocarditis). It can be caused by bacteria or fungi. Treatment ideally requires both intravitreal and intravenous antibiotics as it is a potentially blinding condition.
- **Periorbital (or preseptal) cellulitis** is usually a mild condition more common in children. It can be treated with oral antibiotics active against Gram-positive pathogens from the skin (e.g. *Staphylococcus aureus*). It is very important to distinguish periorbital (or preseptal) from orbital cellulitis (deeper more severe infection) because the management is different.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.

Definition

Pathogens can infect most ocular structures and present with many combinations of signs and symptoms. It is important to determine which anatomical part is infected (Figure 10.1)

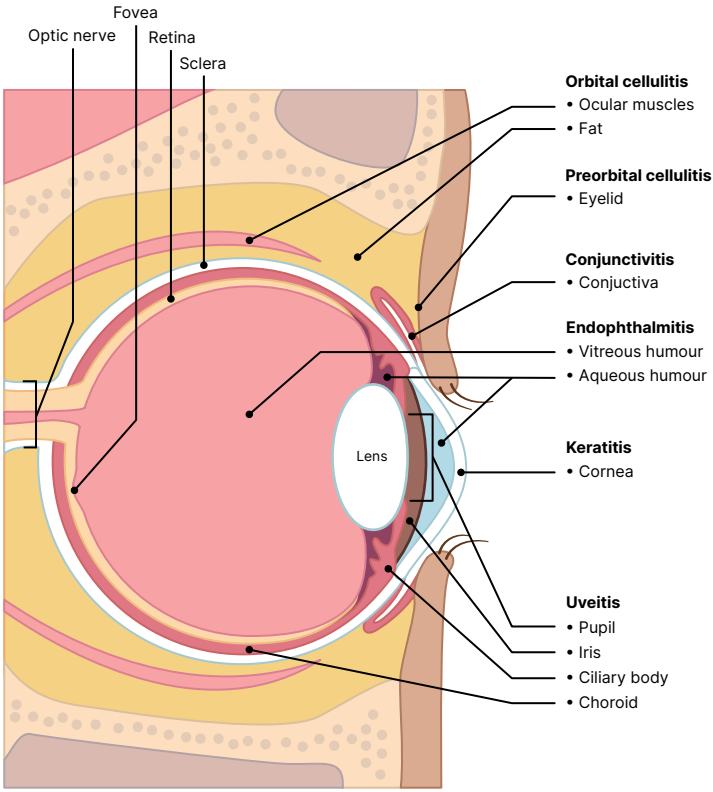
because the most probable causative pathogens may differ, with implications for treatment. In addition, eye infections can be acquired in different ways (e.g. exogenous or endogenous, see the pathophysiology section for more information on transmission) and this also has implications for treatment and helps determine the most likely causative pathogens.

It should be noted that many conditions presented in this chapter could also be of non-infectious origin (e.g. systemic inflammatory diseases affecting other parts of the body or, in the case of conjunctivitis, allergies or toxic irritants), but non-infectious eye conditions are beyond the scope of this chapter.

This chapter focuses on eye infections of bacterial origin presented in alphabetical order.

Infections not addressed in the AWaRe book (because they are rare) include: canaliculitis (infection of the lacrimal canaliculi) and dacryocystis (infection of the lacrimal sac).

Figure 10.1 – Eye anatomy and locations of common eye infections



Conjunctivitis

Bacterial eye infection

Definition

Infection of the conjunctiva (i.e. the mucosa that covers the inside part of the eyelids and the sclera, which is the white part of the eye)

Diagnosis

Clinical Presentation

- **Most cases are mild and self-limiting**
- Usually the eye is red, watery and itchy and patients have a feeling of "sand in the eye"
- Vision is normal and there is no pain (if pain is present consider corneal involvement)
- Thick purulent eye discharge can be present in bacterial infection

Hyperacute Bacterial Conjunctivitis:

- Severe infection that presents with decreased vision, purulent eye discharge, eyelid swelling, pain on palpation and preauricular adenopathy
- Consider urgent referral to an ophthalmologist due to risk for rapid progression to corneal perforation

Microbiology Tests

Usually not needed unless *Neisseria gonorrhoeae* or *Chlamydia trachomatis* are suspected

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Most Likely Pathogens

- Most cases are of viral origin
- Bacterial cases are less common than viruses
  - Consider *Chlamydia trachomatis* (serovars D to K) and *Neisseria gonorrhoeae* in the context of sexually transmitted infections (STI) see "*STI – Chlamydia urogenital infections and gonococcal infection*"
- Hyperacute bacterial conjunctivitis is mostly caused by *Neisseria gonorrhoeae*

Important: non-infectious causes (mostly allergies) should always be considered

Treatment

Clinical Considerations

- Most cases resolve without treatment in 7-10 days
- Antibiotics can be considered in case of suspected bacterial conjunctivitis or conjunctivitis in the context of a sexually transmitted infection

Antibiotic Treatment Duration

Since treatment duration varies, please refer to the corresponding treatment section

Bacterial Conjunctivitis

ACCESS
Gentamicin 0.3% **EYE DROPS**
1 drop in the affected eye q6h
Treatment duration: 5 days

OR

WATCH
Ofloxacin 0.3% **EYE DROPS**
1 drop in the affected eye q6h
Treatment duration: 5 days

OR

ACCESS
Tetracycline 1% **EYE OINTMENT**
1 cm in the affected eye q6h
Treatment duration: 5 days

Gonococcal Conjunctivitis

All dosages are for normal renal function

WATCH
Ceftriaxone 250 mg **IM**
Treatment duration: Single dose

COMBINED WITH

WATCH
Azithromycin 1 g **ORAL**
Treatment duration: Single dose

Conjunctivitis

Bacterial eye infection • Page 1 of 2

Definition

Infection of the conjunctiva (i.e. the mucosa that covers the inside part of the eyelids and the sclera, which is the white part of the eye)

Most Likely Pathogens

- Most cases are of viral origin
- Bacterial cases can occur in children more frequently than in adults (although less common than viruses)
- Consider *Chlamydia trachomatis* (serovars D-K) and *Neisseria gonorrhoeae* in neonates after vaginal delivery from infected mothers

Important: non-infectious causes (mostly allergies) should always be considered

Diagnosis

Clinical Presentation

- **Most cases are mild and self-limiting**
- Usually the eye is red, watery and itchy and patients have a feeling of "sand in the eye"
- Vision is normal and there is no pain (if pain is present consider corneal involvement)
- Thick purulent eye discharge can be present in bacterial infection

Hyperacute Bacterial Conjunctivitis:

- Severe infection that presents with decreased vision, purulent eye discharge, eyelid swelling, pain on palpation and preauricular adenopathy
- Consider urgent referral to an ophthalmologist due to risk for rapid progression to corneal perforation

Microbiology Tests

Usually not needed unless *Neisseria gonorrhoeae* or *Chlamydia trachomatis* are suspected

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Conjunctivitis

Bacterial eye infection • Page 2 of 2

Treatment

Clinical Considerations

- **Most cases resolve without treatment** in 7-10 days
- Antibiotics can be considered in case of suspected bacterial conjunctivitis

Antibiotic Treatment Duration

Since treatment duration varies, please refer to the corresponding treatment section

Bacterial Conjunctivitis

ACCESS
Gentamicin 0.3% **EYE DROPS**
• 1 drop in the affected eye q6h
Treatment duration: 5 days

OR

WATCH
Ofloxacin 0.3% **EYE DROPS**
• 1 drop in the affected eye q6h
Treatment duration: 5 days

OR

ACCESS
Tetracycline 1% **EYE OINTMENT**
• 1 cm in the affected eye q6h
Treatment duration: 5 days

Gonococcal Ophthalmia Neonatorum

All dosages are for normal renal function

WATCH
Ceftriaxone 50 mg/kg **IM**
Treatment duration: Single dose

Do not administer ceftriaxone in neonates receiving calcium-containing IV fluids and avoid in infants with hyperbilirubinaemia

Chlamydial Ophthalmia Neonatorum

Topical therapy alone is not effective

All dosages are for normal renal function

WATCH
Azithromycin 20 mg/kg q24h **ORAL**
Treatment duration: 3 days

Prevention of both Chlamydial and Gonococcal Ophthalmia Neonatorum

WATCH
Erythromycin 0.5% **EYE OINTMENT**
• To be applied to both eyes soon after birth

OR

ACCESS
Tetracycline 1% **EYE OINTMENT**
• To be applied to both eyes soon after birth

Endophthalmitis

Bacterial eye infection

Definition

- Infection of the intraocular fluids (vitreous and aqueous humor) and the retina
- Most cases occur as a result of penetrating eye trauma, after eye surgery or as a complication of keratitis
- Rare cases are due to bacteremia or fungemia from distant sites of infection (e.g. endocarditis, liver abscess)

Diagnosis

Clinical Presentation

- Usually painful red eye, blurred vision and trouble looking at bright light
- In cases where pathogens reach the eye through the bloodstream from other sites of infection, signs and symptoms of bacteremia/fungemia can be present although usually ocular symptoms occur first

Microbiology Tests

- Consider microscopy and culture of a sample of aqueous or vitreous humour aspirate
- Consider blood cultures if a distant source of infection is suspected (i.e. endogenous endophthalmitis)

Other Laboratory Tests

Consider tests to detect organ dysfunction

Imaging

Usually not needed

Most Likely Pathogens

Exogenous (Most Cases):

- **Bacteria**:
  - Mostly coagulase-negative Staphylococci, less frequently *Staphylococcus aureus*
  - *Streptococcus* spp.
  - *Klebsiella* spp. (more frequent in Asia)
  - *Bacillus cereus* (mostly in case of penetrating trauma)
- **Fungi**:
  - *Fusarium* spp.
  - *Aspergillus* spp.

Endogenous (Rare):

- **Bacteria**:
  - Mostly coagulase-negative Staphylococci, less frequently *Staphylococcus aureus*
  - *Streptococcus* spp.
  - *Klebsiella* spp. (more frequent in Asia)
  - *Bacillus cereus* (mostly in case of penetrating trauma)
- **Fungi**:
  - Mostly *Candida albicans*

Treatment

Clinical Considerations

- Endophthalmitis is an ocular emergency because it is a potentially blinding condition
- Systemic antibiotics (in combination with intravitreal antibiotics) should be considered given the severity of this condition, especially when referral to an ophthalmologist is not rapidly available

The cornerstone of treatment is intravitreal injection of antibiotics. Two common approaches to administer intravitreal antibiotics:

1. "Tap and inject": first a sample of vitreous humour is collected for culture (through vitreous aspiration), then antibiotics are injected into the vitreous
2. Vitrectomy is performed (i.e. eye surgery to remove some or all the inflamed vitreous from the eye as a form of source control) and during the procedure, the antibiotic is injected into the vitreous

Antibiotic Treatment Duration

Intravitreal: **Single dose**
- If no clinical improvement after 48 hours, the injection can be repeated

Systemic: Depends on underlying source of bacteremia

Bacterial Endophthalmitis

All dosages are for normal renal function

WATCH Vancomycin 1 mg **INTRAVITREAL INJECTION**

---------- **COMBINED WITH** ----------

WATCH Ceftazidime 2.25 mg **INTRAVITREAL INJECTION**

IF ENDOGENOUS INFECTION, **ADD**

WATCH Ceftriaxone 2 g q24h **IV**

---------- **COMBINED WITH** ----------

WATCH Vancomycin 15-20 mg/kg q12h **IV**

Endophthalmitis

Bacterial eye infection

Definition

- Infection of the intraocular fluids (vitreous and aqueous humor) and the retina
- Most cases occur as a result of penetrating eye trauma, after eye surgery or as a complication of keratitis
- Rare cases are due to bacteremia or fungemia from distant sites of infection (e.g. endocarditis, liver abscess)

Diagnosis

Clinical Presentation

- Usually painful red eye, blurred vision and trouble looking at bright light
- In cases where pathogens reach the eye through the bloodstream from other sites of infection, signs and symptoms of bacteremia/fungemia can be present although usually ocular symptoms occur first

Microbiology Tests

- Consider microscopy and culture of a sample of aqueous or vitreous humour aspirate
- Consider blood cultures if a distant source of infection is suspected (i.e. endogenous endophthalmitis)

Other Laboratory Tests

Consider tests to detect organ dysfunction

Imaging

Usually not needed

Most Likely Pathogens

Exogenous (Most Cases):

- **Bacteria**:
  - Mostly coagulase-negative Staphylococci, less frequently *Staphylococcus aureus*
  - *Streptococcus* spp.
  - *Klebsiella* spp. (more frequent in Asia)
  - *Bacillus cereus* (mostly in case of penetrating trauma)
- **Fungi**:
  - *Fusarium* spp.
  - *Aspergillus* spp.

Endogenous (Rare):

- **Bacteria**:
  - Mostly coagulase-negative Staphylococci, less frequently *Staphylococcus aureus*
  - *Streptococcus* spp.
  - *Klebsiella* spp. (more frequent in Asia)
  - *Bacillus cereus* (mostly in case of penetrating trauma)
- **Fungi**:
  - Mostly *Candida albicans*

Treatment

Clinical Considerations

- Endophthalmitis is an ocular emergency because it is a potentially blinding condition
- Systemic antibiotics (in combination with intravitreal antibiotics) should be considered given the severity of this condition, especially when referral to an ophthalmologist is not rapidly available

The cornerstone of treatment is intravitreal injection of antibiotics. Two common approaches to administer intravitreal antibiotics:

1. "Tap and inject": first a sample of vitreous humour is collected for culture (through vitreous aspiration), then antibiotics are injected into the vitreous
2. Vitrectomy is performed (i.e. eye surgery to remove some or all the inflamed vitreous from the eye as a form of source control) and during the procedure, the antibiotic is injected into the vitreous

Antibiotic Treatment Duration

Intravitreal: **Single dose**
- If no clinical improvement after 48 hours, the injection can be repeated

Systemic: Depends on underlying source of bacteremia

Bacterial Endophthalmitis

All dosages are for normal renal function

WATCH Vancomycin 1 mg **INTRAVITREAL INJECTION**

---------- **COMBINED WITH** ----------

WATCH Ceftazidime 2.25 mg **INTRAVITREAL INJECTION**

IF ENDOGENOUS INFECTION, **ADD**

WATCH Ceftriaxone 80 mg/kg/dose q24h **IV**

---------- **COMBINED WITH** ----------

WATCH Vancomycin **IV**
- Neonates: 15 mg/kg/dose q12h
- Children: 15 mg/kg/dose q8h

Keratitis

Bacterial eye infection

Definition

Infection of the cornea (i.e. transparent covering of the eye)

Most Likely Pathogens

High Income Countries:
• Bacteria and viruses are the most common causes

Low and Middle Income Countries:
• Fungi predominate (especially in rural settings where eye trauma from plants is a common risk factor)

Bacteria:
• *Pseudomonas* spp. (mostly in individuals who wear contact lenses)
• *Staphylococcus epidermidis*
• *Staphylococcus aureus*
• *Streptococcus pneumoniae*

Fungi:
• Mostly *Fusarium* spp.
• *Aspergillus* spp.

Viruses:
• Reactivation of herpes simplex virus (especially in patients who are immunocompromised)

Parasites:
• Acanthamoeba (contact lenses)

Diagnosis

Clinical Presentation

Usually painful eye, decreased vision, more tears and corneal oedema with a feeling of "having something in the eye" and difficulty in keeping the eye open +/- eye discharge

Microbiology Tests

• Consider microscopy and culture of a corneal sample (e.g. corneal scrapings or corneal biopsy)
• Consider nucleic acid amplification testing for herpes simplex virus in patients who are immunocompromised

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed; specialist eye examination may be considered

Treatment

Clinical Considerations

• Infectious keratitis is an ocular emergency because it is a potentially blinding condition with poor prospects of visual restoration
• Patients with keratitis should stop wearing contact lenses until the infection is healed
• Consider giving cycloplegic eye drops (cyclopentolate 1% or atropine 1%) to reduce photophobia and to reduce the formation of pupillary adhesions to the lens

Antibiotic Treatment Duration

2 weeks
Duration is often personalized to the individual based on clinical improvement

Bacterial Keratitis

WATCH

Ofloxacin 0.3% **EYE DROPS**
• 1 drop in the affected eye q1h for 48 hours, then q4h until healed

Drops are preferred over ointments because they have a better corneal penetration

Keratitis

Bacterial eye infection

Definition

Infection of the cornea (i.e. transparent covering of the eye)

Most Likely Pathogens

High Income Countries:
• Bacteria and viruses are the most common causes

Low and Middle Income Countries:
• Fungi predominate (especially in rural settings where eye trauma from plants is a common risk factor)

Bacteria:
• *Pseudomonas* spp. (mostly in individuals who wear contact lenses)
• *Staphylococcus epidermidis*
• *Staphylococcus aureus*
• *Streptococcus pneumoniae*

Fungi:
• Mostly *Fusarium* spp.
• *Aspergillus* spp.

Viruses:
• Reactivation of herpes simplex virus (especially in patients who are immunocompromised)

Diagnosis

Clinical Presentation

• Usually painful eye, decreased vision, more tears and corneal oedema with a feeling of "having something in the eye" and difficulty in keeping the eye open +/- eye discharge
• Keratitis is rare in children

Microbiology Tests

• Consider microscopy and culture of a corneal sample (e.g. corneal scrapings or corneal biopsy)
• Consider nucleic acid amplification testing for herpes simplex virus in patients who are immunocompromised

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed; specialist eye examination may be considered

Treatment

Clinical Considerations

• Infectious keratitis is an ocular emergency because it is a potentially blinding condition with poor prospects of visual restoration
• Consider giving cycloplegic eye drops (cyclopentolate 1% or atropine 1%) to reduce photophobia and to reduce the formation of pupillary adhesions to the lens

Antibiotic Treatment Duration

2 weeks
Duration is often personalized to the individual based on clinical improvement

Bacterial Keratitis

WATCH

Ofloxacin 0.3% **EYE DROPS**
• 1 drop in the affected eye q1h for 48 hours, then q4h until healed

Drops are preferred over ointments because they have a better corneal penetration

Periorbital cellulitis

Bacterial eye infection

Definition

Infection of subcutaneous eyelid tissues anterior to the orbital septum (the globe and the tissues within the bony orbit are not involved)

Important: most cases result from adjacent infections (e.g. infection of the eyelid, lacrimal sac, periorbital sinuses, dental infections) or follow bites or trauma of the eyelid

Diagnosis

Clinical Presentation

- Usually unilateral signs of inflammation around the affected eye (e.g. red, swollen, warm and tender eyelid) with no restricted or painful eye movement +/- fever (≥ 38.0 °C)
- Vision is normal

Important:

- This is usually a mild condition that is rare in adults; complications are rare
- It is important to differentiate with orbital cellulitis (where there is usually restricted eye movements, protrusion of the eye and loss of vision)

Microbiology Tests

- Usually not needed
- Cultures are difficult to obtain and blood cultures when performed are usually negative

Other Laboratory Tests

Usually not needed

Imaging

Consider a CT scan of the orbits and sinuses to assess the presence of orbital involvement and possible complications (e.g. abscess)

Most Likely Pathogens

Bacteria:

- *Staphylococcus aureus* (including MRSA strains)
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- Anaerobes should be suspected if there is a history of animal or human bite or if necrosis is present

Viruses:

- Consider a virus (e.g. herpes simplex virus or varicella-zoster virus) if there is a vesicular skin rash

Treatment

Clinical Considerations

Most cases can be managed in the outpatient setting with oral antibiotics especially in adults with no signs of severe infection

Antibiotic Treatment Duration

10-14 days (depending on the severity)

Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL** OR 1 g+200 mg q8h **IV**

OR

ACCESS Cefalexin 500 mg q8h **ORAL**

OR

ACCESS Cloxacillin 500 mg q6h **ORAL** OR 2 g q6h **IV**

Cloxacillin has a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid and cefalexin with limited coverage of Gram-negative bacteria from the upper respiratory tract that may cause periorbital cellulitis. Therefore, when this infection is suspected, amoxicillin+clavulanic acid or cefalexin would be the preferred options

Periorbital cellulitis

Bacterial eye infection • Page 1 of 2

Definition

Infection of subcutaneous eyelid tissues anterior to the orbital septum (the globe and the tissues within the bony orbit are not involved)

Important: most cases result from adjacent infections (e.g. infection of the eyelid, lacrimal sac, periorbital sinuses) or follow bites or trauma of the eyelid

Most Likely Pathogens

Bacteria:
- *Staphylococcus aureus* (including MRSA strains)
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- Anaerobes should be suspected if there is a history of animal or human bite or if necrosis is present

Viruses:
- Consider a virus (e.g. herpes simplex virus or varicella zoster virus) if there is a vesicular skin rash

Diagnosis

Clinical Presentation

- Usually unilateral signs of inflammation around the affected eye (e.g. red, swollen, warm and tender eyelid) with no restricted or painful eye movement +/- fever (≥ 38.0 °C)
- Vision is normal

Important:
- This is usually a mild condition, complications are rare
- It is important to differentiate with **orbital cellulitis** (where there is usually restricted eye movements, protrusion of the eye and loss of vision)

Microbiology Tests

- Usually not needed
- Cultures are difficult to obtain and blood cultures when performed are usually negative

Other Laboratory Tests

Usually not needed

Imaging

Consider a CT scan of the orbits and sinuses to assess the presence of orbital involvement and possible complications (e.g. abscess)

Periorbital cellulitis

Bacterial eye infection • Page 2 of 2

Treatment

Clinical Considerations

Most cases can be managed in the outpatient setting with oral antibiotics especially in children >1 year with no signs of severe infection

Antibiotic Treatment Duration

10-14 days (depending on the severity)

Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS

Amoxicillin+clavulanic acid
IV:
• 1st week of life: 50 mg/kg/dose of amoxicillin component q12h
• > 1st week of life: 50 mg/kg/dose of amoxicillin component q8h
ORAL: 80-90 mg/kg/day of amoxicillin component
• **Oral weight bands**:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin
Oral liquid must be refrigerated after reconstitution

---------- **OR** ----------

ACCESS

Cefalexin 25 mg/kg/dose q12h **ORAL**
• **Oral weight bands**:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

---------- **OR** ----------

ACCESS

Cloxacillin
IV
• Neonates: 25-50 mg/kg/dose q12h
• Children: 25 mg/kg/dose q6h
ORAL: 15 mg/kg/dose q6h
• **Oral weight bands**:

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

Cloxacillin has a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid and cefalexin with limited coverage of Gram-negative bacteria from the upper respiratory tract that may cause periorbital cellulitis. Therefore, when this infection is suspected, amoxicillin+clavulanic acid or cefalexin would be the preferred options

Pathophysiology

Eye infections can result either from external contamination through direct inoculation of the pathogen into the eye/s (exogenous transmission) or from dissemination of the pathogen through the bloodstream from a distant site of infection (endogenous transmission). Exogenous transmission can occur by contact with infected secretions (mostly by rubbing the eye/s with contaminated hands), or as a result of a penetrating eye injury, which includes eye surgery where bacteria from the flora could be introduced. The use of contact lenses and eye contact with water (e.g. during swimming) are also risk factors for exogenous transmission. In addition, certain STIs (e.g. gonococcal and chlamydial infections) can be transmitted from infected mothers to their child during vaginal delivery. Endogenous transmission occurs when pathogens are spread through the bloodstream from other sites of infection (e.g. in the case of endocarditis, UTIs, abdominal abscesses, meningitis and indwelling catheters), mainly in high-risk patients, such as immunocompromised patients and people who inject drugs.

Blepharitis

Definition

Blepharitis is an infection of the eyelid margin. It can be anterior (less common than posterior blepharitis and characterized by inflammation at the base of the eyelashes) or posterior (more common, characterized by inflammation of the inner portion of the eyelid at the level of the meibomian glands).

Hordeolum (stye) is a common acute bacterial infection of one or more eyelid glands.

Epidemiology

Blepharitis is a chronic condition and most cases are not due to infections but to a dysfunction of oil glands in the eyelids. In posterior blepharitis (the most common form), chronic infections may also play a role. The bacteria that comprise the flora in posterior blepharitis are the same as those found on the skin but are present in greater numbers *(82)*.

Most likely pathogens

The most common causative pathogens of blepharitis are shown in Table 10.1.

Table 10.1 – Pathogens most frequently associated with blepharitis (in descending order of frequency)

Type of organism	Pathogen
Bacteria	*Staphylococcus aureus*
	Coagulase-negative *Staphylococcus*
Mites	*Demodex folliculorum*[a]
	Demodex brevis[b]

Note. Blepharitis does not usually have an infectious origin.
[a] *Demodex folliculorum* has been identified in 30% of patients with chronic anterior blepharitis but is also found with about the same prevalence in asymptomatic people. However, this organism is clearly a contributing factor in some patients as evidenced by the improvement seen in response to eradication therapy.
[b] *Demodex brevis* has been associated with posterior blepharitis.

Clinical presentation

Patients with blepharitis typically present with inflamed eyelids that are red, swollen and itchy with crusts at the base of the eyelid and on the eyelashes mostly in the morning. Usually both eyes are affected and most cases are chronic.

Blepharitis is more common in adults than in children, but children can have severe episodes of anterior and/or posterior blepharitis, often characterized by more conjunctival and corneal findings *(83,84)*.

Blepharitis related to *Demodex* infestation characteristically presents with cylindrical dandruff or "sleeves" on the eyelashes *(85)*. Patients with hordeolum usually present with a tender swelling of the eyelid/s with a lash at its apex.

Laboratory tests

Patient microbiology tests

Microbiology tests are not usually needed.

Other tests

Laboratory tests (other than microbiology) are not usually helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

Imaging is usually not needed.

Antibiotic treatment

Antibiotic treatment is not usually needed. Good eyelid hygiene is the most important treatment and cases usually resolve without further measures. Warm compresses 5 to 10 minutes two to four times per day, lid massage and washing, and use of preservative-free artificial tears four to eight times per day can also help.

Patients with severe or refractory symptoms may require additional therapies but this is beyond the scope of this chapter.

Conjunctivitis

Definition

Conjunctivitis is an infection of the conjunctiva, the mucosa that covers the inside part of the eyelids and the outer surface of the eye – the sclera.

Epidemiology

Conjunctivitis is the most frequent eye infection and most cases are of viral origin in both children and adults. Bacterial cases, although less common, can occur, especially in children. Non-infectious causes (mostly allergies but sometimes also toxic irritants) should always be considered in the differential diagnosis *(86)*. Most cases of conjunctivitis are exogenous and infection is mostly acquired by touching the eye with contaminated hands.

Most likely pathogens

Pathogens most frequently associated with conjunctivitis *(86)* are shown in Table10.2.

Table 10.2 – Pathogens most frequently associated with conjunctivitis (in descending order of frequency)

Type of organism	Pathogen
Viruses	**Most infectious cases are of viral origin** Adenovirus (usually) Herpes simplex virus (rarely) Varicella-zoster virus (rarely)
Bacteria *(87)*	**In children** *Staphylococcus aureus* *Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* **In adults** *Staphylococcus aureus* **Consider** *Chlamydia trachomatis* (serovars D–K) and *Neisseria gonorrhoeae* in the context of sexually transmitted infections or in neonates after vaginal delivery from infected mothers. *Chlamydia trachomatis* (serovars A–C) can cause trachoma. Trachoma is covered in a separate chapter.

Clinical presentation

Patients with conjunctivitis (including cases of viral origin) usually present with a red, watery and itchy eye. They often describe a feeling of "sand in the eye" with no pain (if there is pain, this usually indicates corneal involvement) and they have normal vision. In cases of bacterial infection, a thick purulent discharge from the eye is usually present. Patients may refer to all discharge as pus; however, in bacterial conjunctivitis, the complaint of discharge predominates, while in viral and allergic conjunctivitis, patients report a burning and gritty feeling or itching and the eye usually presents with a watery discharge. In most cases, conjunctivitis is a mild self-limiting condition.

A severe form of conjunctivitis is hyperacute bacterial conjunctivitis which is mostly caused by *Neisseria gonorrhoeae*. It is characterized by severe purulent discharge and decreased vision. Usually, eyelid swelling, pain on palpation and preauricular adenopathy are present *(86)*.

In neonates, conjunctivitis can be caused by a range of pathogens. In general, gonococcal or staphylococcal infection is more likely to present early with symptoms in the first 5 days of life, with chlamydial infection generally presenting later (> 5 days after birth).

Laboratory tests

Patient microbiology tests

Usually no test is required unless *Neisseria gonorrhoeae* or *Chlamydia trachomatis* are suspected.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

Imaging is usually not needed.

Antibiotic treatment

Most cases of infectious conjunctivitis are self-limiting, of viral origin and resolve without treatment in 7–10 days. In patients with typical presentation of bacterial conjunctivitis (i.e. red eye with purulent discharge and normal vision), antibiotic treatment could be considered to shorten the duration of symptoms *(88)* based on the patient's preferences. In these cases, antibiotic treatment is usually topical (eye drops or eye ointment) and prescribed empirically (Table 10.3) based on local availability. Systemic antibiotic treatment is only required in cases of systemic infections, for example, conjunctivitis in the context of an STI (Table 10.3). Steroid eye drops (alone or in combination with antibiotic drops) are not usually needed for the treatment of conjunctivitis; in fact, steroids might even make the condition worse if it is caused by herpes virus infection or the cornea is affected.

Urgent referral of the patient to an ophthalmologist, if available, should be considered when hyperacute bacterial conjunctivitis (mostly caused by *Neisseria gonorrhoeae*) is suspected because of the risk of rapid progression to corneal perforation.

Table 10.3 – Empiric antibiotic treatment for bacterial conjunctivitis

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Type of eye infection	Antibiotic treatment	Total treatment duration
Bacterial conjunctivitis (children and adults)	**Gentamicin** (eye drops): 0.3%, 1 drop in the affected eye every 6 hours **OR** **Ofloxacin** (eye drops): 0.3%, 1 drop in the affected eye every 6 hours **OR** **Tetracycline** (eye ointment): 1%, 1 cm in the affected eye every 6 hours	5 days
Gonococcal conjunctivitis (adults, adolescents)	**Ceftriaxone** (IM)[a]: 250 mg **AND** **Azithromycin** (oral): 1 g	Single dose
Gonococcal ophthalmia neonatorum (i.e. gonococcal conjunctivitis of the newborn) Symptoms usually appear within 5 days of birth	**Ceftriaxone** (IM)[b]: 50 mg/kg	Single dose
Chlamydial ophthalmia neonatorum (i.e. chlamydial conjunctivitis of the newborn) Symptoms usually appear > 5 days after birth	**Azithromycin** (oral)[c]: 20 mg/kg given once a day Topical therapy alone is not effective.	3 days
Ocular prophylaxis (topical treatment for the prevention of both gonococcal and chlamydial ophthalmia neonatorum)[d]	**Erythromycin** (eye ointment): 0.5% **OR** **Tetracycline** (eye ointment): 1%	Antibiotic needs to be applied to both eyes soon after birth (single dose)

continues

Table 10.3 *continued*

IM: intramuscular.
Note. All dosages are for normal renal and hepatic function.
[a] Concurrent treatment with azithromycin for chlamydial infection is usually recommended.
[b] Ceftriaxone should not be administered in neonates receiving calcium-containing IV fluids and it should be avoided in infants with hyperbilirubinaemia. Cefotaxime can be used as an alternative. Alternatives to ceftriaxone indicated in the 2016 WHO guidelines but not included the EMLc for this indication are kanamycin (IM) 25 mg/kg or spectinomycin (IM) 25 mg/kg *(89)*.
[c] An alternative indicated in the 2016 WHO guidelines but not included in the EML for this indication is erythromycin (oral) 50 mg/kg per day divided in four doses for 14 days *(89)*.
[d] Alternatives indicated in the 2016 WHO guidelines but not included in the EML for this indication are: povidone–iodine (water-based solution; do not use alcohol-based solutions) 2.5%; silver nitrate (solution) 1%; chloramphenicol (eye ointment) 1% *(89)*.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Endophthalmitis

Definition

Endophthalmitis is an infection of the inner part of the eye globe, in particular, the intraocular fluids: vitreous and aqueous humour, and the retina.

Epidemiology

Endophthalmitis mostly has an exogenous cause and occurs as a result of penetrating eye trauma, after eye surgery or as a complication of keratitis. Endogenous cases of endophthalmitis are rare but can occur because of bacteraemia or fungaemia from distant sites of infection, most often endocarditis and liver abscess depending on the setting *(90,91)*. Injection of drugs is a common risk factor in patients with endogenous infections. Endophthalmitis refers to bacterial or fungal infection within the eye, including involvement of the vitreous and/or aqueous humours. Endophthalmitis is not caused by viruses or parasites; infections due to these organisms are included in the term uveitis *(92)*.

Most likely pathogens

Table 10.4 shows the most common causative pathogens associated with endophthalmitis.

Table 10.4 – Pathogens most frequently associated with endophthalmitis

Type of endophthalmitis	Most common causative pathogens (in descending order of frequency)
Exogenous – most cases	**Bacteria**
	Most cases
	Coagulase-negative staphylococci
	Less frequently
	Staphylococcus aureus (93)
	Streptococcus spp.[a]
	Klebsiella spp. (more frequent in Asia ; often in conjunction with liver abscess)
	Bacillus cereus (mostly in cases of penetrating trauma)
	Fungi[b]
	Fusarium spp.
	Aspergillus spp.
Endogenous – rare	**Bacteria:** same as above
	Fungi[c]
	Mostly *Candida albicans*

[a] *Streptococcus viridans* is more frequently encountered in case of post-intravitreal injection endophthalmitis compared to post-cataract endophthalmitis *(94)*.
[b] In tropical regions, fungal endophthalmitis is often due to molds and is usually exogenous in origin.
[c] In temperate climates, fungal endophthalmitis is usually endogenous and caused by *Candida* spp.

Clinical presentation

Endophthalmitis is usually an acute condition and patients present with a painful red eye, blurred vision and trouble looking at bright light (i.e. photophobia). Most cases are exogenous and typically occur after eye surgery (usually within days or a few weeks) or trauma. In rare cases, endophthalmitis can result from the haematogenous spread of pathogens from distant sites of infection, such as endocarditis and liver abscess. In these cases, signs and symptoms of bacteraemia can be present although in most cases ocular symptoms occur first.

Laboratory tests

Patient microbiology tests

Microbiology tests to consider when endophthalmitis is suspected are shown in Table 10.5.

A positive culture of aqueous or vitreous humour in the presence of compatible signs and symptoms could confirm the diagnosis.

Table 10.5 – Microbiology tests to consider when endophthalmitis is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture of aqueous or vitreous humour aspirate	Microbial morphology and detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Blood cultures and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections in patients with suspected endogenous endophthalmitis	Health care facilities with clinical laboratories

EDL: WHO Model List of Essential In Vitro Diagnostics.

Other tests

Laboratory tests (other than microbiology) are usually not needed.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

Imaging is usually not needed.

Antibiotic treatment

This condition should be treated by an ophthalmologist where available. Urgent referral of the patient to an ophthalmologist, if available, should be considered when endophthalmitis is suspected because this condition could potentially threaten the patient's sight.

With bacterial endophthalmitis, the cornerstone of treatment is intravitreal injection of antibiotics. There are two common approaches:

- "tap and inject": first a sample of vitreous humour is collected for culture (through vitreous aspiration) and then antibiotics are injected into the vitreous
- vitrectomy is performed – that is, eye surgery to remove some or all the inflamed vitreous from the eye as a form of source control – and during the procedure, the antibiotic is injected into the vitreous.

Systemic antibiotics (in combination with intravitreal antibiotics) should also be considered given the severity of this condition, especially when referral to an ophthalmologist is not readily available (Table 10.6). In cases of endogenous infections, systemic antibiotics should always be given. However, evidence of their added benefit (e.g. on visual acuity) compared to intravitreal treatment alone is still controversial. The ability to rapidly reach adequate concentrations of antibiotics in the eye varies by antibiotic *(95)*.

There is limited evidence of the benefit of additive treatment with intravitreal steroid therapy compared to antibiotics alone *(96)*.

Table 10.6 – Empiric antibiotic treatment for bacterial endophthalmitis

Type of bacterial endophthalmitis	Antibiotic treatment	Total treatment duration
Exogenous	**Intravitreal injection** **Vancomycin** 1 mg **AND** **Ceftazidime** 2.25 mg Systemic antibiotics alone are not effective in treating bacterial exogenous endophthalmitis. Whether systemic antibiotics provide any benefit in these cases as adjunctive therapy to intravitreal antibiotics is still debatable.	Intravitreal antibiotics: single dose. If no clinical improvement after 48 hours, the intravitreal injection can be repeated.
Endogenous	**ADD** **Systemic treatment** *Adults* **Ceftriaxone** (IV): 2g given once a day **AND** **Vancomycin** (IV): 15–20 mg/kg given every 12 hours *Neonates and children* **Ceftriaxone** (IV): 80 mg/kg/dose given once a day **AND** **Vancomycin** (IV): • Neonates: 15 mg/kg/ dose given every 12 hours • Children: 15 mg/kg/dose given every 8 hours	Duration of systemic antibiotics should be determined by the need to treat the underlying source of bacteraemia (e.g. 6 weeks in many cases of endocarditis).

IV: intravenous.
Note. All dosages are for normal renal and hepatic function.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Keratitis

Definition

Keratitis is an infection of the cornea, the transparent covering of the eye.

Epidemiology

Keratitis is common and the estimated number of cases is more than 2 million per year *(97)*. The highest (epidemic) burden is in South, South-East and East Asia *(97)*, especially in rural settings among male workers in high-risk professions as eye trauma is the predominant risk factor *(98)*. In high-income countries, the number of cases of keratitis has increased over time, probably because of the increased use of contact lenses; their use is currently the most common risk factor in this setting. The disease is rare in children, but it is also harder to diagnose, mostly because it is more difficult to obtain a clinical history and to collect a sample for microbiology tests.

Most likely pathogens

The most common pathogens causing keratitis *(97,98)* are shown in Table 10.7.

Table 10.7 – Pathogens most frequently associated with keratitis[a] (in descending order of frequency)

Type of organism	Pathogen
Fungi	**Mostly** *Fusarium* spp. *Aspergillus* spp.
Bacteria	*Pseudomonas* spp. (contact lenses) *Staphylococcus epidermidis* *Staphylococcus aureus* *Streptococcus pneumoniae*
Viruses	**Mostly** Herpes simplex virus (usually type 1) Varicella zoster virus
Parasites	*Acanthamoeba* (contact lenses)

[a] Bacteria and viruses are the most common causes of keratitis in high-income countries, while fungi predominate in low- and middle-income countries. Global variations in etiology largely reflect patient-based risk factors such as population demographic, occupation, contact lens use, concomitant ocular and systemic illness, as well as environmental factors such as geographical location, climate and virulence of causative organisms. For example, *Pseudomonas* spp. and *Acanthamoeba* spp. are often associated with the use of contact lenses and fungal keratitis must be considered after any traumatic corneal injury, notably from vegetable matter. In the paediatric population, there appears to be a higher incidence of atypical infections, for example, due to *Acanthamoeba (97)*.

Clinical presentation

Patients with keratitis generally present with a painful eye, decreased vision, more tears and corneal oedema. They often describe a feeling of "having something in the eye" and have difficulty keeping the affected eye open. A discharge from the eye may be seen depending on the causative pathogen. Most infectious cases are of bacterial origin, although in low- and middle-income countries, fungal infections are common, for example, as a result of trauma from plants or sand or mud in rural settings *(97)*. Reactivation of herpes simplex virus could also cause keratitis, especially in patients with HIV infection or in patients with other forms of immunosuppression. Ophthalmologic examination with a slit lamp is usually needed to visualize the cornea and confirm the diagnosis: focal white infiltrates in the corneal stroma with an epithelial defect and underlying tissue loss are the critical sign of keratitis.

Laboratory tests

Patient microbiology tests

A positive culture in the presence of compatible signs and symptoms could confirm the diagnosis (Table 10.8).

Table 10.8 – Microbiology tests to consider when keratitis is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture of corneal scrapings or corneal biopsy material	Microbial morphology and detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: WHO Model List of Essential In Vitro Diagnostics.
Note. Nucleic acid amplification testing (i.e. polymerase chain reaction) for viral etiology (e.g. herpes simplex virus) could be considered based on clinical presentation and individual risk factors.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

Imaging is usually not needed. Specialist eye examination may be considered.

Antibiotic treatment

Patients should stop wearing contact lenses. Topical antibiotic treatment is indicated even though consensus on the most effective treatment is lacking (Table 10.9) *(99)*. Cycloplegic eye drops (cyclopentolate 1% or atropine 1%) can be used for comfort, to reduce photophobia from ciliary spasm and to reduce the formation of pupillary adhesions to the lens.

Oral antibiotics can be considered in selected cases (e.g. scleral extension or impending perforation) or in case of gonococcal infection. With viral keratitis, topical and oral antiviral treatment is usually indicated (but management of viral infections is beyond the scope of this chapter).

Note

Infectious keratitis is an ocular emergency as it is a potentially blinding condition for which the prospect of visual restoration is often poor.

Table 10.9 – Empiric antibiotic treatment for bacterial keratitis

Antibiotic treatment	Total treatment duration
Children and adults **Ofloxacin** [a] (eye drops): 0.3%, 1 drop in the affected eye every hour for 48 hours then every 4 hours until healed	2 weeks but duration is often personalized to the individual based on clinical improvement.

[a] A fluoroquinolone is usually given to patients who wear contact lenses because *Pseudomonas aeruginosa* is often the causative pathogen. For most patients, hourly treatment is indicated for the first 24 to 48 hours. Drops are preferred because ointments have poor corneal penetration. However, ointments may be used at bedtime to allow the patient to sleep through the night, but only after a positive response has been demonstrated to the initial intensive eyedrop treatment.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Orbital cellulitis

Definition

Orbital cellulitis is an infection affecting eye tissues behind the orbital septum within the bony orbit (i.e. fat and ocular muscles within the orbit).

Due to the complexity of this infection, treatment of this condition is not addressed in the AWaRe book, but some general information is presented in the following section.

Epidemiology

Orbital cellulitis is more common in young children and in most cases it is a complication of bacterial sinusitis.

Most likely pathogens

The most common causative pathogens of orbital cellulitis are shown in Table 10.10.

Table 10.10 – Pathogens most frequently associated with orbital cellulitis (in descending order of frequency)

Type of organism	Pathogen
Bacteria	**In adults** *Staphylococcus aureus* *Streptococcus* spp. *Bacteroides* spp. **In children** *Haemophilus influenzae* (rare in vaccinated children *(100)*) **Following eye trauma** *Pseudomonas aeruginosa* *Escherichia coli* **Following a dental abscess** Polymicrobial infection (including anaerobes)
Fungi[a]	**Mostly in immunocompromised patients, such as those with diabetes, receiving chemotherapy and with HIV infection** Zygomycetes (e.g. *Mucor*) *Aspergillus* spp.

[a] Fungal infections are rare but they should be considered in immunocompromised patients including patients with poorly controlled diabetes.

Clinical presentation

Patients with orbital cellulitis typically have unilateral local signs of inflammation around the affected eye. The eyelids are usually swollen, red, warm and tender. Sometimes fever is present (≥ 38.0 °C). These findings are also present in cases of periorbital (or preseptal) cellulitis (see next section); however, in addition to these symptoms, patients with orbital cellulitis present with restricted extraocular motility with pain on attempted eye movement, conjunctival chemosis (i.e. swelling) and hyperaemia (i.e. redness) as critical signs. Usually this condition is accompanied by protrusion of the eye (i.e. proptosis) and loss of vision may be present *(101)*. Signs of optic neuropathy (e.g. afferent pupillary defect and dyschromatopsia) may be present in severe cases. In neglected cases, orbital cellulitis may lead to cavernous sinus thrombosis, brain abscess or even death.

Laboratory tests

Patient microbiology tests

Blood cultures and cultures of samples collected can be considered (Table 10.11).

Table 10.11 – Microbiology tests to consider when orbital cellulitis is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain), culture and antimicrobial susceptibility testing of abscess material	Microbial morphology and detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Blood cultures and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections	Health care facilities with clinical laboratories

EDL: WHO Model List of Essential In Vitro Diagnostics.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

A CT scan of the orbits and sinuses (axial, coronal and parasagittal views, with contrast if possible) should be obtained if available. The reason for doing a CT scan is to assess the presence or absence of orbital involvement when the diagnosis is uncertain and the presence of possible complications, for example, subperiosteal or orbital abscess, cavernous sinus thrombosis and intracranial extension.

Antibiotic treatment

Note

General information is presented but treatment is not addressed in the AWaRe book.

Patients with orbital cellulitis should be admitted to the hospital and an infectious disease physician and otorhinolaryngology/ophthalmology specialists should be consulted. Most patients with uncomplicated orbital cellulitis can be treated with antibiotics alone *(102,103)*.

Surgery for source control (e.g. drainage of purulent collections) may be needed in severe and complicated cases (e.g. in cases of abscess) in combination with systemic antibiotic treatment *(104,105)*. Surgery is almost always indicated in patients with intracranial extension of the infection.

Periorbital (or preseptal) cellulitis

Definition

Periorbital (or preseptal) cellulitis is an infection of subcutaneous eyelid tissues anterior to the orbital septum; in this case, the globe and the tissues within the bony orbit are not involved.

Epidemiology

This is usually a mild condition that most commonly affects children. Most cases are exogenous and result from adjacent infection (hordeolum, dacryocystitis, infection of the periorbital sinuses, severe dental infection) or follow animal and insect bites or trauma of the eyelid. Periorbital (or preseptal) cellulitis is much more common than orbital cellulitis *(106)*.

The most common pathogens associated with periorbital (or preseptal) cellulitis are shown in Table 10.12.

Table 10.12 – Pathogens most frequently associated with periorbital (or preseptal) cellulitis (in descending order of frequency)

Type of organism	Pathogen
Bacteria	*Staphylococcus aureus* (including MRSA)
	Streptococcus pneumoniae
	Haemophilus influenzae (rare in vaccinated children *(100)*)
	Moraxella catarrhalis
	Anaerobes (suspect if there is a history of animal or human bite or if necrosis is present)
Viruses	If the infection is associated with a vesicular skin rash, suspect:
	Herpes simplex virus
	Varicella-zoster virus

MRSA: methicillin-resistant *Staphylococcus aureus*.

Clinical presentation

It is very important to distinguish periorbital (or preseptal) from orbital cellulitis. Patients with periorbital (or preseptal) cellulitis typically present with unilateral local signs of inflammation around the affected eye but do not have restricted or painful eye movements, as occurs in case of orbital cellulitis. The eyelid/s is generally swollen, red, warm and tender and sometimes fever is present (≥ 38.0 °C). In severe cases, conjunctival chemosis (i.e. swelling) may also occur. Vision is normal, while in case of orbital cellulitis loss of vision may be present *(101)*. In periorbital (or preseptal) cellulitis, serious complications are rare *(107)*.

Laboratory tests

Patient microbiology tests

Usually no test is required. Cultures are difficult to obtain and blood cultures when performed are usually negative.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

A CT scan of the orbits and sinuses (axial, coronal, and parasagittal views, with contrast if possible) could be considered. The reason for doing a CT scan is to assess the presence or absence of orbital involvement when the diagnosis is uncertain and the presence of possible complications is suspected, for example, subperiosteal or orbital abscess, cavernous sinus thrombosis, or intracranial extension.

Antibiotic treatment

Systemic antibiotic treatment is indicated and is usually given empirically based on the most likely causative pathogens because cultures are difficult to obtain and blood cultures when performed are usually negative (Table 10.13). Empiric treatment of MRSA may be considered in certain cases based on individual risk factors (e.g. known MRSA colonization) and on the local prevalence of community-acquired MRSA. In these cases, the literature suggests using clindamycin or sulfamethoxazole+trimethoprim; however, no formal recommendation can be made in the AWaRe book as these options are not currently listed in the EML and EMLc for this indication.

Most cases of periorbital (or preseptal) cellulitis can be managed with oral antibiotic treatment; however, in severely ill patients or very young children, intravenous treatment may be considered *(105)*.

Adults and children older than 1 year with mild periorbital (or preseptal) cellulitis and no signs of systemic toxicity can generally be treated as outpatients with oral antibiotics, provided close follow-up can be ensured.

Children younger than 1 year, patients who cannot cooperate fully for an examination, who are severely ill or in case of no noticeable improvement or worsening after 24 to 48 hours of oral antibiotics should generally be admitted to the hospital and managed according to the recommendations for orbital cellulitis.

Table 10.13 – Empiric antibiotic treatment for periorbital (or preseptal) cellulitis[a]

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Note

Cloxacillin has a narrower spectrum of antibacterial activity than amoxicillin+clavulanic acid and cefalexin with limited coverage of Gram-negative bacteria from the upper respiratory tract that may cause periorbital (or preseptal) cellulitis (e.g. *Haemophilus influenzae*, *Moraxella catarrhalis*). Therefore, when this infection is suspected, amoxicillin+clavulanic acid or cefalexin are the preferred options.

Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid IV: 1 g + 200 mg given every 8 hours Oral: 500 mg + 125 mg given every 8 hours **OR** **Cefalexin** (oral): 500 mg given every 8 hours **OR** **Cloxacillin**[b] IV: 2 g given every 6 hours Oral: 500 mg given every 6 hours	**Amoxicillin+clavulanic acid**[c] IV: First week of life: 50 mg/kg of amoxicillin/dose given every 12 hours Beyond first week of life: 50 mg/kg of amoxicillin/dose given every 8 hours Oral: 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours **OR**	10–14 days (depending on the severity)

continues

Table 10.13 *continued*

Adults	Children	Total treatment duration
	Cefalexin (oral): 25 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 125 mg given every 12 hours 6–< 10 kg: 250 mg given every 12 hours 10–< 15 kg: 375 mg given every 12 hours 15–< 20 kg: 500 mg given every 12 hours 20–< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose **OR** **Cloxacillin** [b] IV: • Neonates: 25–50 mg/kg/dose given every 12 hours • Children: 25 mg/kg/dose given every 6 hours Oral: 15 mg/kg/dose given every 6 hours Oral weight bands: 3–< 6 kg: 62.5 mg given every 6 hours 6–< 10 kg: 125 mg given every 6 hours 10–< 15 kg: 250 mg given every 6 hours 15–< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours	

IV: intravenous.
Note. All dosages are for normal renal and hepatic function.
[a] It should be noted that these specific recommendations are not included in the EML and EMLc *(8,9)*. The options presented are based on what is recommended for mild skin and soft tissues infections.
[b] If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used. For oral administration; dicloxacillin and flucloxacillin are preferred options within the class as they have better oral bioavailability.
[c] Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Infectious uveitis

Definition

Uveitis is an infection of the uvea, which is composed of:

- iris – the coloured ring-shaped part of the eye behind the cornea
- ciliary body – the part that extends around the iris, has a muscular component and produces the aqueous humour that keeps the eye in a pressurized state
- choroid – a vascular layer.

Epidemiology

Infectious uveitis can be caused by a large number of pathogens and most cases are associated with systemic infections, but it may also occur as an isolated condition. Therefore, the epidemiology depends on the underlying infection. In general, certain factors can increase the risk of specific infections, for example, cytomegalovirus is mostly associated with uveitis in immunocompromised patients.

Most likely pathogens

Table 10.14 shows the most common causative pathogens of uveitis.

Table 10.14 – Pathogens most frequently associated with uveitis[a] (in alphabetical order)

Type of organism	Pathogen
Bacteria	*Bartonella henselae* (with cat-scratch disease) *Mycobacterium tuberculosis*[b] *Treponema pallidum* (with neurosyphilis)
Parasites	*Toxoplasma gondii*
Viruses	Cytomegalovirus Herpes simplex virus Varicella-zoster virus

[a] Usually in the context of infectious or autoimmune or inflammatory systemic conditions. Therefore consider individual risk factors and presentation to identify the most likely causative pathogen.
[b] Ocular tuberculosis usually results from haematogenous dissemination of the infection from pulmonary or extra-pulmonary sites.

Clinical presentation

The symptoms of uveitis are non-specific and depend on the portion of the uveal tract that is involved. Findings also differ depending upon the location of the involvement, and visual loss may occur with anterior, intermediate or posterior involvement. Anterior uveitis is about four times more common than posterior uveitis *(108)*. Patients with uveitis usually have a painful red eye and decreased vision. Infectious forms of uveitis are mostly of viral origin (e.g. herpes simplex virus, cytomegalovirus) or they may occur as a reactivation of toxoplasmosis.

When uveitis is suspected, patients should be seen by an ophthalmologist, if available, because the list of potential conditions associated with uveitis is large and, in some cases, uveitis is a potentially sight-threatening condition.

Laboratory tests

Patient microbiology tests

The need for microbiology tests should be guided by the type of eye infection suspected (see Table 10.15 for tests to consider).

Table 10.15 – Microbiology tests to consider when uveitis is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture[a]	Microbial morphology and detection and identification of bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.
Note. Nucleic acid amplification testing (i.e. polymerase chain reaction) for viral etiology (e.g. herpes simplex virus) could be considered based on clinical presentation and individual risk factors.
[a] Depending on the type of infection, consider conjunctival swabs, corneal scrapings or corneal biopsy, aqueous or vitreous humour aspirate.

Other tests

Laboratory tests (other than microbiology) are usually not helpful.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

Specialist eye examination may be considered depending on the type of infection.

Antibiotic treatment

Note

General information is presented but treatment is not addressed in the AWaRe book.

Treatment for uveitis depends on the etiology (including non-infectious causes), location and clinical severity. Because of the large variety of conditions associated with uveitis, a review of treatment options is beyond the scope of this chapter.

11. Trachoma

Key messages

- Trachoma is an eye disease caused by specific serovars (A through C) of the bacterium *Chlamydia trachomatis*.
- Repeated infections over the years can lead to permanent corneal damage and blindness.
- Treatment depends on the stage of the disease. It may require eye surgery to prevent blindness if corneal damage has already occurred.
- Mass antibiotic administration programmes in endemic areas aim to reduce the reservoir of *Chlamydia trachomatis*.

Other relevant WHO resources (please check regularly for updates)

- Trachoma – fact sheet *(109)*.
- Resolution WHA51.11. Global elimination of blinding trachoma, 1998 *(110)*.
- The simplified trachoma grading system, amended, 2020 *(111)*.
- Trachoma control: a guide for programme managers, 2006 *(112)*.

Definition

Trachoma is an eye disease caused by specific serovars (A through C) of the bacterium *Chlamydia trachomatis* (other serovars cause urogenital diseases, please see the chapter on sexually transmitted infections – Chlamydia urogenital infections). Trichiasis is the advanced clinical consequence of trachoma characterized by the eyelashes turning inwards which leads over time to permanent corneal damage. Trichiasis is a sight-threatening condition that requires surgical treatment.

Trachoma

Definition

Eye disease caused by specific serovars (A,B and C) of the bacterium *Chlamydia trachomatis* (other serovars cause urogenital diseases, see "Sexually transmitted infections – Chlamydial urogenital infections")

Pathogen

- *Chlamydia trachomatis* is a Gram-negative obligate intracellular bacterium
- Strains associated with trachoma are serovars A, B, Ba, and C

Diagnosis

Clinical Presentation

Acute:

- Usually signs and symptoms of conjunctivitis with redness of the eye, eye discomfort, mucopurulent discharge and light sensitivity
- Rare in adults

Advanced:

- Conjunctival scarring, signs of chronic conjunctival inflammation and eyelashes turned inward
- Mostly seen in adults due to repeated infections over time

WHO has a trachoma grading system used in field assessments to evaluate the extent of disease during examination (Reference: Solomon AW et al. The simplified trachoma grading system, amended. Bull World Health Organ. 2020;98(10):698-705)

Microbiology Tests

- Usually not needed
- Consider testing a conjunctival sample (culture or nucleic acid amplification tests for *Chlamydia trachomatis*) in a selected subgroup of people to decide whether to stop or continue antibiotic treatment at the population level

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Treatment

Clinical Considerations

- Antibiotic treatment is often given as part of mass drug administration programmes in endemic areas to reduce the reservoir of *Chlamydia trachomatis*
- If corneal damage has already occurred due to the inversion of the eyelashes, surgery is needed to correct the eyelid rotation and prevent blindness
- Repeated infections over the years can lead to permanent corneal damage and blindness

Important: Reinforce education on personal and community hygiene measures

- Infection spreads via the hands through direct contact with contaminated people or objects
- Flies can contribute by transporting contaminated eye/nose secretions to non-infected people
- Risk factors include living in overcrowded conditions and poor sanitation; most transmission occurs within families

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Antibiotic Treatment

All dosages are for normal renal function

WATCH

Azithromycin 20 mg/kg (max 1 g) **ORAL**
Treatment duration: Single dose

Administered once a year for 3 years as part of mass drug administration programmes

Topical Treatment

WATCH

Azithromycin 1.5% **EYE DROPS**
- 1 drop in both eyes q12h

Treatment duration: 3 days

OR

ACCESS

Tetracycline 1% **EYE OINTMENT**
- 1 cm in both eyes q12h

Treatment duration: 6 weeks

Topical treatment is used in areas where oral azithromycin is not readily available. Topical azithromycin may be as effective as oral azithromycin

Trachoma

Definition

Eye disease caused by specific serovars A, B and C of the bacterium *Chlamydia trachomatis*

Pathogen

- *Chlamydia trachomatis* is a Gram-negative obligate intracellular bacterium
- Strains associated with trachoma are serovars A, B, Ba, and C

Diagnosis

Clinical Presentation

Acute:

- Usually signs and symptoms of conjunctivitis with redness of the eye, eye discomfort, mucopurulent discharge and light sensitivity
- More common in children living in endemic areas

Advanced:

- Conjunctival scarring, signs of chronic conjunctival inflammation and eyelashes turned inward
- Mostly seen in adults due to repeated infections over time

WHO has a trachoma grading system used in field assessments to evaluate the extent of disease during examination (Reference: Solomon AW et al. The simplified trachoma grading system, amended. Bull World Health Organ. 2020;98(10):698-705)

Microbiology Tests

- Usually not needed
- Consider testing a conjunctival sample (culture or nucleic acid amplification tests for *Chlamydia trachomatis*) in a selected subgroup of people to decide whether to stop or continue antibiotic treatment at the population level

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Treatment

Clinical Considerations

- Antibiotic treatment is often given as part of mass administration programmes in endemic areas to reduce the reservoir of *Chlamydia trachomatis*
- If corneal damage has already occurred due to the inversion of the eyelashes, surgery is needed to correct the eyelid rotation and prevent blindness
- Repeated infections over the years can lead to permanent corneal damage and blindness

Important: Reinforce education on personal and community hygiene measures

- Infection spreads via the hands through direct contact with contaminated people or objects
- Flies can contribute by transporting contaminated eye/nose secretions to non-infected people
- Risk factors include living in overcrowded conditions and poor sanitation; most transmission occurs within families

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Antibiotic Treatment

All dosages are for normal renal function

WATCH

Azithromycin 20 mg/kg (max 500 mg) **ORAL**
Treatment duration: Single dose

Administered once a year for 3 years as part of mass drug administration programmes

Topical Treatment

WATCH

Azithromycin 1.5% **EYE DROPS**
- 1 drop in both eyes q12h

Treatment duration: 3 days

OR

ACCESS

Tetracycline 1% **EYE OINTMENT**
- 1 cm in both eyes q12h

Treatment duration: 6 weeks

Topical treatment is used in areas where oral azithromycin is not readily available. Topical azithromycin may be as effective as oral azithromycin

Pathogen

Trachoma is caused by *Chlamydia trachomatis*, a Gram-negative obligate intracellular bacterium. There are several strains of *Chlamydia trachomatis*, some associated with trachoma and some associated with sexually transmitted urogenital diseases. Strains associated with trachoma are serovars A, B, Ba and C.

Pathophysiology

Chlamydia trachomatis infection spreads via the hands through direct contact with contaminated people or objects. Flies can also spread the infection by transporting contaminated eye and/or nose secretions from infected to non-infected people. Chronic inflammation of the conjunctiva caused by repeated infections over the years can cause inversion of the eyelashes that can lead to permanent corneal damage through formation of scars on the cornea (the transparent front part of the eye). This can eventually lead to vision impairment and blindness *(113)*.

Epidemiology

Trachoma is the leading cause of infectious blindness in the world and is responsible for about 1% of cases of blindness. According to the most recent WHO estimates, more than 137 million people worldwide live with trachoma *(109)*. The infection is a public health problem in over 40 countries, most of which are in Africa *(109)*.

Risk factors of trachoma include living in overcrowded conditions and poor sanitation, and most transmission occurs within families. Active disease (i.e. conjunctivitis) is more common in young children living in endemic areas. Children younger than 10 years and those with intense inflammatory trachoma probably represent the main source of ocular *Chlamydia trachomatis* infection in endemic communities *(114)*. Corneal scars are mostly seen in adults because repeated infections over time need to occur before permanent corneal damage is established. Individuals with corneal scars are at increased risk of blindness.

In 1993, WHO adopted the SAFE strategy for the elimination of trachoma:

- **S**urgery to treat advanced diseases,
- **A**ntibiotics to clear infection,
- **F**acial cleanliness and
- **E**nvironmental improvement to reduce transmission.

In 1996, WHO established the alliance for the global elimination of trachoma, whose goal was to eliminate trachoma as a public health problem by 2020 (Box 11.1). In addition, in

1998, the World Health Assembly adopted a resolution on trachoma to urge WHO Member States to implement measures to target the elimination of trachoma *(110)*. As of July 2020, 13 out of 30 countries that are implementing the SAFE strategy have achieved the WHO elimination targets. As part of the elimination strategy, data reported to WHO for 2019 indicate that about 92 000 people had corrective surgery for trichiasis and 95 million people received antibiotic treatment, that is, 57% of people needing antibiotics for trachoma received them *(109)*.

Box 11.1 – World Health Organization definitions related to trachoma

WHO defines trachoma as a public health problem when:

- the prevalence of follicular trachoma in children aged 1–9 years is ≥ 10% (see the section on clinical presentation for the classification of trachoma), or
- the prevalence of trachomatous trichiasis in people aged ≥ 15 years is at least 1%.

WHO criteria for defining elimination of trachoma as a public health problem are *(115)*:

- the prevalence of follicular trachoma in children aged 1–9 years is < 5% or
- the prevalence of trachomatous trichiasis in people aged ≥ 15 years is < 0.2% and
- there is evidence that the health system can identify and manage cases of trachomatous trichiasis.

Clinical presentation

Trachoma diagnosis is based on clinical signs. Trachoma presents as an active disease (i.e. conjunctivitis) with symptoms such as redness of the eye, eye discomfort, mucopurulent discharge and light sensitivity.

The other presentation is the advanced disease where there is conjunctival scarring, signs of chronic conjunctival inflammation and eyelashes turned inwards.

The WHO trachoma grading system is used in field assessments to evaluate the extent of disease during examination *(111)*.

The grading system includes:

- Trachomatous inflammation, follicular – five or more follicles of > 0.5 mm on a specific area of the upper tarsal conjunctiva
- Trachomatous inflammation, intense – papillary hypertrophy and inflammatory thickening of the upper tarsal conjunctiva obscuring more than half the deep tarsal vessels

- Trachomatous conjunctival scarring – grossly visible scars on the tarsal conjunctiva
- Trachomatous trichiasis – at least one ingrown eyelash touching the globe of the eye or evidence of epilation (eyelash removal)
- Corneal opacity – corneal opacity blurring part of the pupil margin.

Laboratory tests

Patient microbiology tests

The diagnosis of trachoma is mostly clinical and microbiology tests are not routinely done. However, such tests may be considered (Table 11.1) to decide whether to stop or continue antibiotic treatment at the population level, for example, on a selected subgroup of people *(113)*.

Table 11.1 – Microbiology tests to consider if trachoma is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Qualitative test for *Chlamydia trachomatis* (i.e. nucleic acid amplification test)[a]	To diagnose chlamydial infection	Health care facilities with clinical laboratories
Microscopy (Gram stain) and culture[a]	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.
[a] Possible specimens: conjunctival swabs.

Other tests

When trachoma is suspected based on clinical signs and epidemiology of the community, laboratory tests are not usually needed.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

When trachoma is suspected, imaging is not usually needed.

Antibiotic treatment

The appropriate treatment of trachoma depends on the stage of disease.

If trichiasis has already developed, surgery is needed to prevent blindness by stopping the eyelashes continuing to erode the cornea *(112,116)*.

Antibiotic treatment is generally given to treat *Chlamydia trachomatis* infection in association with reinforced education on personal and community hygiene measures. Usually, antibiotic treatment is given once a year for at least 3 years as part of a mass antibiotic administration programme in endemic areas to reduce the reservoir of *Chlamydia trachomatis* (Table 11.2) *(112)*.

Table 11.2 – Empiric antibiotic treatment for trachoma

Adults and children	Total treatment duration
Azithromycin (oral): 20 mg/kg (maximum 1 g (adults); 500 mg (children))	Single dose (azithromycin)
OR	
Azithromycin (eye drops)[a]: 1.5%, 1 drop administered to both eyes every 12 hours	3 days (topical treatment with azithromycin)
OR	
Tetracycline (eye ointment): 1% 1 cm administered to both eyes every 12 hours	6 weeks (topical treatment with tetracycline)
Topical treatment is used in areas where oral azithromycin is not readily available.	

Note. Antibiotic treatment is mostly given once a year for at least 3 years as part of mass administration programmes in endemic areas.
[a] Azithromycin eye drops may be as effective as oral azithromycin *(117)*.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

For prevention of trachoma, please refer to the epidemiology section where the WHO SAFE strategy is described.

12. Community-acquired pneumonia – mild

Key messages

- Rapidly decide if the patient has mild community-acquired pneumonia (CAP), which can be managed in primary care with oral antibiotic treatment, or severe CAP, which has a higher short-term mortality risk and requires hospital admission. Scores can be helpful to make this distinction.
- Clinically relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* (the main bacterial cause of CAP) is rare in most countries and oral Access group penicillins (amoxicillin, phenoxymethylpenicillin) remain first choice for mild and moderate cases of CAP.
- Laboratory tests are usually not needed in mild cases.
- Treatment duration can be limited to 5 days in most cases (3 days in children in areas of low prevalence of human immunodeficiency virus (HIV)).

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.
- Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries *(118)*.
- Coronavirus disease (COVID-19) pandemic *(32)*.
- Living guidance for clinical management of COVID-19: living guidance, 23 November 2021 *(33)*.
- Therapeutics and COVID-19: living guideline, 16 September 2022 *(34)*.
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 *(35)*.
- *Haemophilus influenzae* type b (Hib) vaccination position paper – July 2013: Introduction *(36)*.
- Vaccines against influenza WHO position paper – May 2022 *(37)*.
- WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment *(119)*.

Definition

CAP is an acute illness affecting the lungs caused by pathogens, most often bacteria and viruses. It usually presents with fever, cough, sputum production (in adults), rapid and difficult breathing with new or worsening pulmonary infiltrate(s) on chest imaging.

Community-acquired pneumonia

Definition

An acute illness affecting the lungs usually presenting with cough, sputum production, and rapid and difficult breathing with a new or worsening pulmonary infiltrate on a chest radiograph

Most Likely Pathogens

"Typical" bacteria:

- ***Streptococcus pneumoniae*** (most cases)
- *Haemophilus influenzae* (chronic lung diseases, smoking)
- *Moraxella catarrhalis* (chronic lung diseases, smoking)
- *Staphylococcus aureus* (often associated with influenza)
- *Enterobacterales* (severe comorbidities, e.g. chronic lung diseases, dementia, stroke)

"Atypical" bacteria:

- *Mycoplasma pneumoniae* (more frequent in young adults)
- *Chlamydia pneumoniae* and *psittaci* (more frequent in young adults)
- *Legionella* spp. (chronic lung diseases or other underlying illness, travel, exposure to hot tubs)
- *Coxiella burnetii* (rural areas, exposure to livestock)

Respiratory viruses:

- Influenza viruses (A and B)
- Respiratory syncytial virus (RSV)
- Metapneumovirus
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Adenovirus
- Rhinovirus
- Other respiratory viruses

Pathogens to consider in specific settings:

- *Burkholderia pseudomallei* (SE Asia, Australia)
- *Mycobacterium tuberculosis*
- *Pneumocystis jirovecii* (people with HIV or other immunosuppression)

Investigating for Tuberculosis (TB)

- Consider specific investigations for TB in endemic settings especially in high-risk patients (e.g. HIV)
- A rapid molecular test performed on a single sputum specimen is the preferred first line diagnostic test for pulmonary TB and to detect rifampicin resistance
- Consider a lipoarabinomannan rapid urinary antigen test in severely immunocompromised HIV patients with signs and symptoms of tuberculosis

Diagnosis

Clinical Presentation

- New onset (<2 weeks) or worsening cough with fever (≥ 38.0 °C), sputum production, dyspnea, tachypnea, reduced oxygen saturation, crepitations on lung auscultation, chest pain/discomfort without alternative explanation
- Extrapulmonary features (i.e. confusion, disorientation) may predominate in elderly, and immunocompromised patients and fever may be absent

Microbiology Tests

Mild cases: usually not needed

Severe cases (to guide antimicrobial treatment): blood cultures, urinary antigens for *L. pneumophila* and *S. pneumoniae*

Selected cases (depending on epidemiology and risk factors): sputum rapid molecular test for *M. tuberculosis*, nasopharyngeal swab for influenza viruses and SARS-CoV-2, HIV testing in settings with high HIV prevalence and in case of recurrent and/or severe pneumonia

Other Laboratory Tests

Determine disease severity: blood urea nitrogen (see CURB-65 Scoring System box), blood pH and gases, white blood cell count

Differentiate bacterial and viral (taking into account pre-test probability): C-reactive protein and/or procalcitonin

Note: tests depend on availability and clinical severity (e.g. blood gases will only be done in severe cases)

Imaging

- Chest X-ray not necessary in mild cases
- Infiltrate may not always be evident (e.g. dehydration) and non-infectious etiologies may mimic infiltrates (e.g. lung edema, pulmonary embolism)
- Radiologic appearance cannot be used to accurately predict pathogen

Community-acquired pneumonia

CURB-65 Severity Scoring System

Signs & Symptoms (1 point each)

- Presence of **C**onfusion (new onset)
- **U**rea > 19 mg/dL (or > 7 mmol/L)*
- **R**espiratory rate > 30/min
- Systolic **B**P < 90 mmHg (<12 kPa) or Diastolic BP ≤ 60 mmHg (<8 kPa)
- Age ≥ **65** years

Score 0-1
• Consider outpatient treatment

Score 2
• Consider inpatient treatment
• **Consider adding clarithromycin to beta-lactam for atypical coverage**
• Perform microbiology tests

Score ≥3
• Inpatient treatment (consider ICU)
• **Consider adding clarithromycin**
• Perform microbiology tests

Other considerations such as severe comorbid illnesses or inability to maintain oral therapy should be taken into account. CURB-65 has not been extensively validated in low-income settings.

The **CRB-65 score, which does not require laboratory values for its calculation, can also be used, the score value interpretation is the same as for CURB-65*

Mild to Moderate Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

ACCESS — Amoxicillin 1 g q8h **ORAL**

OR

ACCESS — Phenoxymethylpenicillin (as potassium) 500 mg (800 000 IU) q6h **ORAL**

Second Choice

ACCESS — Amoxicillin+clavulanic acid 875 mg+125 mg q8h **ORAL**

OR

ACCESS — Doxycycline 100 mg q12h **ORAL**

Treatment

Antibiotic Treatment Duration

Treat for **5 days**

If severe disease, consider longer treatment and look for complications such as empyema, if patient not clinically stable at day 5

Severe Cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

WATCH — Cefotaxime 2 g q8h **IV/IM**

OR

WATCH — Ceftriaxone 2 g q24h **IV** (1 g q24h **IM***)

**A larger volume would be painful to give as intramuscular injection*

IF CURB-65 ≥2, CONSIDER ADDING

WATCH — Clarithromycin 500 mg q12h **ORAL** (or **IV**)

Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function

Second Choice

ACCESS — Amoxicillin+clavulanic acid 1 g+200 mg q8h **IV**
• A higher daily dose can be considered: 1 g+200 mg q6h

IF CURB-65 ≥2, CONSIDER ADDING

WATCH — Clarithromycin 500 mg q12h **ORAL** (or **IV**)

Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function

Community-acquired pneumonia

Definition

An acute illness affecting the lungs usually presenting with cough, and rapid and difficult breathing with a new or worsening pulmonary infiltrate on a chest radiograph

Most Likely Pathogens

"Typical" bacteria:

- ***Streptococcus pneumoniae*** (most common cause of CAP beyond the 1st week of life)
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus*
- *Enterobacterales*

"Atypical" pathogens (more frequent in children >5 years compared to younger children):

- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*

Respiratory viruses:

- Respiratory syncytial virus (RSV)
- Influenza viruses (A and B)
- Metapneumovirus
- Parainfluenza virus
- Coronavirus (including SARS-CoV-2)
- Adenovirus
- Rhinovirus
- Other respiratory viruses

Investigating for Tuberculosis (TB)

- Consider specific investigations for TB in endemic settings especially in high-risk patients (e.g. HIV)
- A rapid molecular test performed on a single sputum specimen is the preferred first line diagnostic test for pulmonary TB and to detect rifampicin resistance

Diagnosis

Clinical Presentation

- New onset (<2 weeks) or worsening cough with fever (≥ 38.0 °C), dyspnea, tachypnea, reduced oxygen saturation, crepitations, cyanosis, grunting, nasal flaring, pallor
- Pneumonia is diagnosed on: fast breathing for age and/or chest indrawing
  - Check for hypoxia with oxygen saturometer if available
- Children with runny nose and cough and no signs of severity usually do not have pneumonia and should not receive an antibiotic, only home care advice

Microbiology Tests

Mild cases: usually not needed

Severe cases (to guide antimicrobial treatment): blood cultures

Tests for COVID-19 and influenza can be considered if clinically indicated and available

Other Laboratory Tests

No test clearly differentiates viral or bacterial CAP

Consider: full blood count and C-reactive protein

Note: tests depend on availability and clinical severity (e.g. blood gases will only be done in severe cases)

Imaging

- Chest X-ray not necessary in mild cases
- Look for lobar consolidation or pleural effusion
- Radiologic appearance cannot be used to accurately predict pathogen

Community-acquired pneumonia

Severity Assessment and Considerations

Children with **pneumonia**:

- Should be treated with oral amoxicillin at home with home care advice
- Pneumonia is diagnosed on either:
  1. Fast breathing (respiratory rate > 50 breaths/minute in children aged 2-11 months; resp rate > 40 breaths/min in children aged 1-5 years)
  2. Chest indrawing

Children with **severe pneumonia** (or a child with pneumonia who cannot tolerate oral antibiotics):

- **Should be admitted to hospital and treated with intravenous antibiotics**
- Severe pneumonia is characterized by signs of pneumonia:
  - Fast breathing (+/- chest indrawing)
  PLUS
  - A general danger sign:
    · Inability to breastfeed or drink
    · Convulsions
    · Lethargy or reduced level of consciousness

Antibiotic Treatment Duration

3 days: in areas of low HIV prevalence and no chest indrawing

5 days: in areas of high HIV prevalence and the child has chest indrawing

If severe disease, consider longer treatment and look for complications such as empyema, if patient not clinically stable at day 5

Mild to Moderate Cases

All dosages are for normal renal function

ACCESS

Amoxicillin 80-90 mg/kg/day **ORAL**
• **Oral weight bands**:

3-<6 kg	250 mg q12h
6-<10 kg	375 mg q12h
10-<15 kg	500 mg q12h
15-<20 kg	750 mg q12h
≥20 kg	500 mg q8h or 1 g q12h

Treatment

Severe Cases

Please see Severity Assessment and Considerations for diagnosis of severe cases

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

ACCESS

Amoxicillin 50 mg/kg/dose **IV/IM**
• ≤1wk of life: q12h
• >1wk of life: q8h

OR

ACCESS

Ampicillin 50 mg/kg/dose **IV/IM**
• ≤1wk of life: q12h
• >1wk of life: q8h

OR

ACCESS

Benzylpenicillin 30 mg/kg/dose (50 000 IU/kg/dose) q8h IV

COMBINED WITH

ACCESS

Gentamicin **IV/IM**
• Neonates: 5 mg/kg/dose q24h
• Children: 7.5 mg/kg/dose q24h

IF HIV POSITIVE AND <1 YR OLD
To treat potential Pneumocystis jirovecii pneumonia, **ADD**

ACCESS

Sulfamethoxazole+trimethoprim 40 mg/kg SMX+8 mg/kg TMP q8h **IV/ORAL** for 3 weeks

Second Choice
If NO Clinical Response to First Choice after 48-72 hours

WATCH

Cefotaxime 50 mg/kg/dose q8h **IV/IM**

OR

WATCH

Ceftriaxone 80 mg/kg/dose q24h **IV/IM**

Pathophysiology

CAP occurs when microbial pathogens (usually inhaled in the upper airways) reach the lower respiratory tract and proliferate in the alveoli. Less frequently, these pathogens can also reach the alveoli via the blood or by direct spread, for example, from an infection of the pleural or intra-abdominal space. Once in the alveoli, host immune defences are activated to eliminate the pathogens. Only when these defences fail, pneumonia manifests itself because of the tissue damage and inflammatory response triggered by the proliferation of microorganisms in the affected lung(s).

Epidemiology

CAP is common worldwide and is a leading cause of morbidity and mortality, with an especially high burden in low-income countries *(120)*. According to the Global Burden of Disease study, in 2017 there were an estimated 471 million new cases of lower respiratory tract infections globally among all ages and sexes combined. This number included CAP cases but also a majority of cases of viral bronchitis – therefore caution is needed in interpreting this number *(44)*. The incidence of CAP varies with age and a country's income level. The most common causative pathogens worldwide are *Streptococcus pneumoniae* and viruses (see the following section); viral–bacterial coinfections may occur.

In low-income countries, lower respiratory tract infections (including CAP) were the leading cause of death in 2016, with a crude yearly attributable mortality of about 75 per 100 000 population *(121)*. In general, the incidence of CAP is highest in children younger than 5 years in these countries. In 2015, an estimated 0.9 million children younger than 5 years died of pneumonia and of these, about 0.5 million occurred in sub-Saharan Africa *(122)*. Undernutrition, HIV infection, exposure to smoke and air pollution are common risk factors for severe CAP in children younger than 5 years. As a result of better access to medical care, better nutrition and greater vaccination coverage, global mortality rates in children have declined by more than 30% since 2000. In high-income countries, CAP mainly affects adults 65 years and older and, in general, the incidence of CAP and risk of death increase with age *(123)*.

Most likely pathogens

In **neonates and young infants aged up to 2 months**, pneumonia is mainly caused by *Streptococcus pneumoniae*, group B *Streptococcus*, Enterobacterales or *Staphylococcus aureus*.

In **children aged 2 months to 5 years**, pneumonia is more likely to be of viral origin, for example, respiratory syncytial virus, influenza and parainfluenza virus. The most important bacterial pathogen in children younger than 5 years is *Streptococcus pneumoniae*.

In **older children** *Streptococcus pneumoniae* is still common but atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may be the cause. So-called atypical bacteria have intrinsic resistance to beta-lactam antibiotics and cannot by visualized by Gram staining. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* also cause CAP in some children (Table 12.1).

In **adults**, viruses are common causes of CAP, either by directly causing pneumonia or by favouring superinfection with bacteria. Among bacteria, the most common causative agents are *Streptococcus pneumoniae*, followed by atypical bacteria (see definition in the paragraph above) such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* are also quite common (Table 12.1).

However, determining the cause of bacterial pneumonia is difficult in all age groups and no causative pathogen is identified in most cases, even if extensive microbiological tests are performed, which is usually not the case for mild cases. Furthermore, there may be important geographic differences in the cause of pneumonia; for example, *Burkholderia pseudomallei* is a cause of CAP in South-East Asia, while *Coxiella burnetii* is more common in regions where exposure to livestock is common.

Table 12.1 – Pathogens most frequently associated with community-acquired pneumonia (in descending order of frequency)

Typical bacteria	Atypical bacteria[b]	Respiratory viruses	Other pathogens to consider in specific settings
Streptococcus pneumoniae[a] *Haemophilus influenzae* *Moraxella catarrhalis* *Staphylococcus aureus* Enterobacterales (e.g. *Escherichia coli*, *Klebsiella pneumoniae*)	*Mycoplasma pneumoniae*[b] *Chlamydia pneumoniae*[b] and *Chlamydia psittaci*[b] *Legionella* spp. *Coxiella burnetii*	Influenza virus (A and B) Respiratory syncytial virus[c] Metapneumovirus Parainfluenza virus Coronavirus (including SARS-CoV-2) Adenovirus Rhinovirus Other respiratory viruses	*Burkholderia pseudomallei* (South-East Asia, Australia) *Mycobacterium tuberculosis* *Pneumocystis jirovecii* (in people with HIV or other types of cellular immunosuppression)

HIV: human immunodeficiency virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2.

[a] The most common bacterial cause of community acquired pneumonia in all age groups (beyond the first week of life) is *Streptococcus pneumoniae*.

[b] Atypical bacteria remain colourless with Gram staining. They also have intrinsic resistance to beta-lactams. *Mycoplasma pneumoniae* and *Chlamydia* spp. are more frequent in children > 5 years (compared with younger children) and in young adults. Risk factors for *Chlamydia psittaci* include exposure to birds.

[c] Up to 50% of cases of pneumonia in children < 5 years are caused by a virus, most commonly respiratory syncytial virus.

Community-acquired pneumonia caused by antibiotic-resistant pathogens

AMR is a potential problem with all pathogens associated with CAP. However, clinically relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* is still rare globally. Resistance to macrolides in *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* is highly prevalent in some settings *(124,125)*.

Note

CAP caused by low-level and intermediate-level pneumococcal penicillin resistance can be successfully treated with higher oral doses of the Access antibiotics amoxicillin or penicillin in children and adults.

There is no evidence of improved clinical outcomes in patients with pneumococcal pneumonia in the primary health care setting treated with oral cephalosporins, amoxicillin+clavulanic acid or macrolides compared to amoxicillin and penicillin, and these antibiotics are associated with higher rates of toxicity.

Clinical presentation

Nearly all respiratory diseases can mimic the symptoms of CAP. Based on clinical features alone it is often impossible to distinguish bacterial from viral pneumonia or from other non-infectious causes. Local epidemiology and laboratory tests may help.

Well established clinical features of CAP include a combination of new onset (less than 2 weeks) of symptoms, worsening cough with or without sputum production, dyspnoea (difficulty in breathing), tachypnoea (abnormal respiratory rates to diagnose rapid breathing vary with age), reduced oxygen saturation, crepitations on lung auscultation, or chest pain or discomfort without an alternative explanation. Fever ≥ 38.0 °C for 3–4 days is usually present but may be absent, especially in elderly people. Extrapulmonary features such as confusion or disorientation may be the main symptoms in elderly people, immunocompromised patients and malnourished children. The severity of signs and symptoms may range from a mild disease that can be safely managed in an outpatient setting with oral antibiotic treatment to severe pneumonia with respiratory distress, sepsis requiring intensive care and intravenous antibiotic treatment, and a high associated mortality.

In children, WHO defines fast breathing pneumonia as a child with a high respiratory rate for their age (> 50 breaths/minute in children 2–11 months of age; > 40 breaths/minute in children aged 1–5 years). They may or may not have chest indrawing.

Laboratory tests

Patient microbiology tests

In mild cases that can be managed in the outpatient setting, microbiology tests are usually not needed. Tests for COVID-19 and influenza can be considered if clinically indicated and available. The TB lipoarabinomannan rapid antigen urinary test should be considered in patients living with HIV who are severely immunocompromised and who present with signs and symptoms of TB.

For more information on this topic, the interested reader can refer to the 2019 WHO policy update: *Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV: policy update 2019 (126)*.

Other tests

In mild cases, laboratory tests are usually not needed. If available, point-of-care testing for C-reactive protein could be considered in adult patients if there is diagnostic uncertainty.

In general, C-reactive protein has good negative predictive value, and a negative test can be used to help rule out bacterial pneumonia, unless the pre-test probability is high or the clinical presentation is severe.

Using microbiology surveillance data

The great majority of episodes of CAP in the primary care setting are caused by pneumococcal isolates that clinically respond to oral penicillins. Therefore, routine clinical microbiology surveillance of CAP does not help to inform local empiric guidance.

Imaging

When mild CAP is suspected clinically, a chest X-ray is usually not necessary.

Scores to determine disease severity and guide treatment decisions

WHO recommends that children who meet the criteria of severe pneumonia should be admitted to hospital (see the hospital facility section for the management of severe cases).

As a general rule for children, hospitalization is indicated in cases of severe illness (e.g. cough and severe respiratory distress, marked tachypnoea and tachycardia) and/or if the child is unable to take oral therapy.

In children, severe pneumonia is characterized by signs of pneumonia (fast breathing with or without chest indrawing) plus a general danger sign, such as inability to breastfeed or drink, convulsions, lethargy or a reduced level of consciousness *(118)*.

In adults, several scores exist that measure severity and help predict 30-day mortality. These scores, in addition to clinical judgement, can be used to determine the need for hospitalization in immunocompetent adults diagnosed with CAP. In view of its simplicity, one of the more frequently used scores is the CURB-65 *(127)*, or its modification, CRB-65, which does not require laboratory values for its calculation (Table 12.2). However, it should be noted that these scores have not been extensively validated in low-income settings and for this reason there is no clear consensus about their use in these settings *(128)*. As well as severity scores, other factors, such as severe comorbid illnesses (e.g. HIV infection) or inability to maintain oral therapy, should always be taken into account in determining the need for hospital admission.

Table 12.2 – CURB-65 criteria and scoring, and treatment decisions for community-acquired pneumonia

Criterion	**Points**
Presence of confusion (new onset)	1
Urea > 19 mg/dL (or > 7 mmol/L)[a]	1
Respiratory rate > 30 breaths/min	1
Systolic blood pressure < 90 mmHg (< 12 kPa) or diastolic blood pressure ≤ 60 mmHg (≤ 8 kPa)	1
Age ≥ 65 years	1
CURB-65 score/CRB-65 score	**Where to treat**
0–1	**Candidate for outpatient treatment** Low 30-day mortality risk (< 1.5%)
2	**Consider inpatient treatment** 30-day mortality risk ≈ 10% Consider adding clarithromycin (see Community-acquired pneumonia – severe) If tests are available, consider testing for atypical pathogens (e.g. *Legionella* spp., *Mycoplasma* spp.)

continues

Table 12.2 *continued*

CURB-65 score/CRB-65 score	Where to treat
≥ 3	**Inpatient treatment (consider admission to intensive care)** High 30-day mortality risk (≈ 20%) Consider adding clarithromycin (see Community-acquired pneumonia – severe) Consider testing for atypical pathogens (e.g. *Legionella* spp., *Mycoplasma* spp.)

Note. The CURB-65 score is not validated in low-and middle-income countries.
[a] Urea is not required for the calculation of the CRB-65 score, a modification of the CURB-65 score that does not require laboratory tests.

Ruling out tuberculosis

TB is a cause of subacute lower respiratory tract infection and should be considered in settings endemic for TB, especially in high-risk patients (e.g. children or adults with HIV), with a slow onset of symptoms and persistent cough, or those who do not respond to the initial antibiotic treatment. In such cases, specific investigations for TB should be done. A rapid molecular test (GeneXpert® MTB/RIF assay) performed on a single sputum specimen is currently the preferred first-line diagnostic test for pulmonary TB and to detect rifampicin resistance in both children and adults. When this rapid test is not available, microscopy examination of sputum smears could be considered for the detection of acid-fast bacilli *(129)*. For TB management and treatment, refer to the *WHO consolidated guidelines on tuberculosis (119)*.

Symptomatic care

Patients and/or their caregivers in the primary health care setting should be informed about the natural course of CAP, including the possibility of a viral etiology that would not benefit from antibiotic treatment and that cough and other symptoms often take 2–3 weeks to fully recover from. Patients should also receive clear advice on seeking medical care with any worsening of symptoms and recommended symptomatic treatment (e.g. antipyretics) (Table 12.3).

Table 12.3 – Medicines to consider for symptomatic treatment of community-acquired pneumonia

Important

Medicines are listed in alphabetical order and they should all be considered equal treatment options.

Medicine	Formulation	Dose and frequency
Ibuprofen[a]	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	**Adults**: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) **Children**: • Pain control/antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours 6–< 10 kg: 50 mg given every 8 hours 10–< 15 kg: 100 mg given every 8 hours 15–< 20 kg: 150 mg given every 8 hours 20–< 30 kg: 200 mg given every 8 hours ≥ 30 kg: use adult dose
Paracetamol (acetaminophen)[b]	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	**Adults**: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)[c] **Children**: • Pain control/antipyretic treatment: 10–15 mg/kg given every 6 hours 3–< 6 kg: 60 mg given every 6 hours 6–< 10 kg: 100 mg given every 6 hours 10–< 15 kg: 150 mg given every 6 hours 15–< 20 kg: 200 mg given every 6 hours 20–< 30 kg: 300 mg given every 6 hours ≥ 30 kg: use adult dose

[a] Not for children < 3 months.
[b] Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.
[c] In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

The primary goal of empiric antibiotic treatment in CAP is to provide effective and timely treatment for *Streptococcus pneumoniae* infection because this is the predominant bacterial

pathogen and untreated pneumococcal pneumonia is associated with high mortality (see Table 12.4 for adults and Table 12.5 for children for treatment recommendations). Amoxicillin or phenoxymethylpenicillin (sometimes also called penicillin V) are the recommended first choice options for mild-to-moderate CAP.

Empiric treatment should be guided by the age of the patient, severity of symptoms, presence of comorbidities and previous antibiotic treatment. Clinical improvement should be evident within 48–72 hours of starting antibiotic therapy. If there is no response to treatment, a complication (such as empyema) should be considered. Duration of treatment should be guided by measures of clinical improvement (e.g. resolution of fever); usually 5 days of treatment are adequate for adults and 3–5 days for children.

Table 12.4 – Empiric antibiotic treatment for mild cases of community-acquired pneumonia in adults

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

	Adults	Total treatment duration *(130,131)*
First choice	**Amoxicillin** (oral): 1 g given every 8 hours **OR** **Phenoxymethylpenicillin** (oral): 500 mg (800 000 IU[a]) given every 6 hours	5 days
Second choice	**Amoxicillin+clavulanic acid** (oral): 875 mg + 125 mg given every 8 hours **OR** **Doxycycline** (oral): 100 mg given every 12 hours	5 days

IU: international units.
Note. All dosages are for normal renal and hepatic function.
[a] Units of the potassium salt.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Table 12.5 – Empiric antibiotic treatment for mild cases of community-acquired pneumonia in children

	Children	Total treatment duration
Pneumonia (fast breathing and/or chest indrawing) – treat at home with oral antibiotic	**Amoxicillin** (oral): 80–90 mg/kg/day Oral weight bands: 3–< 6 kg: 250 mg given every 12 hours 6–< 10 kg: 375 mg given every 12 hours 10–< 15 kg: 500 mg given every 12 hours 15–< 20 kg: 750 mg given every 12 hours ≥ 20 kg: 500 mg given every 8 hours or 1 g given every 12 hours Children with fast-breathing pneumonia who fail to respond to first-line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second-line treatment.	3 days for children in areas of low HIV prevalence and no chest indrawing 5 days if the child has chest indrawing or lives in region of higher HIV prevalence

HIV: human immunodeficiency virus.
Note: All dosages are for normal renal and hepatic function.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Vaccination can prevent many cases of CAP. Available vaccines are active against pneumococcal infection, *Haemophilus influenzae* type b disease and influenza, and several vaccines against SARS-CoV-2 are available. Vaccines are never 100% effective and because they are serogroup-specific, they do not protect against all strains of bacteria or viruses. Duration of protection is also variable. As a result, even vaccinated people can develop CAP. *Haemophilus influenzae* type b conjugate vaccines and pneumococcal conjugate vaccines should be included in all routine infant immunization programmes as they have been very successful in reducing invasive disease and in many countries, in reducing rates of pneumococcal resistance. Countries should consider the inclusion of yearly seasonal influenza vaccination for high-risk populations (pregnant women, elderly people, patients with chronic medical conditions and health care workers) in their vaccination plan.

13. Exacerbation of chronic obstructive pulmonary disease

Key messages

- **Antibiotics are not needed** for most mild cases.
- Avoid routine sputum culture in mild cases as patients may be colonized by multiple bacteria, making results difficult to interpret.
- Supplementary oxygen and short-acting inhaled beta-2-agonists are the mainstay of treatment. Steroids are also recommended in many guidelines as they can improve lung function and shorten time to recovery.
- Consider antibiotics only in severe cases requiring hospital admission. Most exacerbations are not due to acute bacterial infection.

Other relevant WHO resources (please check regularly for updates)

- Chronic obstructive pulmonary disease (COPD) – fact sheet *(132)*.
- Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach *(133)*.
- Coronavirus disease (COVID-19) pandemic *(32)*.
- Living guidance for clinical management of COVID-19: living guidance, 23 November 2021 *(33)*.
- Therapeutics and COVID-19: living guideline, 16 September 2022 *(34)*.
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019 *(35)*.
- Vaccines against influenza WHO position paper – May 2022 *(37)*.

Definition

An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication in patients with underlying COPD *(134)*.

Exacerbation of chronic obstructive pulmonary disease

Definition

Acute worsening of patient's respiratory symptoms beyond normal day-to-day variations that results in additional therapy in patients with underlying chronic obstructive pulmonary disease (COPD). COPD refers to a group of diseases that block airflow and impair breathing and includes emphysema and chronic bronchitis

Most Likely Pathogens

Respiratory viruses (most cases):
- Influenza virus (A and B)
- Respiratory syncytial virus (RSV)
- Parainfluenza virus
- Rhinovirus
- Coronavirus (including SARS-CoV-2)
- Other respiratory viruses

Bacteria (more rarely):
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Streptococcus pneumoniae*
- Gram-negative bacteria including *Pseudomonas aeruginosa* (including multidrug-resistant strains)

Prevention

Recommend smoking cessation, reduced indoor air pollution, use of long-acting inhaled β_2-agonists (± anticholinergics) and vaccination (e.g. against influenza, *S. pneumoniae* and SARS-CoV-2)

Diagnosis

Clinical Presentation

Recent and sustained worsening of dyspnea and cough with increased sputum production compared to the baseline in a patient with COPD

Important: symptoms can overlap with pneumonia (pneumonia more likely if tachycardia, tachypnea at rest and crepitations that persist after coughing are present)

Microbiology Tests

Usually not needed but can be considered in severe cases; the respiratory tract of people with COPD may be colonized with bacteria (e.g. *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *P. aeruginosa*, *S. maltophilia*) and a positive culture may indicate colonization rather than acute infection

Other Laboratory Tests

Consider C-reactive protein and/or procalcitonin, complete blood count, and blood pH and gases

Imaging

Consider a chest radiograph in patients requiring hospitalization to exclude other diagnoses and in outpatients if pneumonia suspected

Exacerbation of chronic obstructive pulmonary disease

Treatment

No Antibiotic Care

- Details of COPD exacerbations management are not discussed here, refer to specific guidelines
- Supplementary oxygen and short-acting inhaled β_2-agonists (± anticholinergics)
- Systemic steroids are usually recommended (improve lung function and favour faster recovery)

Clinical Considerations

Antibiotics are not needed for most cases

- Their use could be considered in patients with dyspnea and an increased volume of purulent sputum
- In case of frequent exacerbations consider risk of infections caused by multidrug-resistant pathogens and previous colonization of the respiratory tract

Antibiotic Treatment Duration

5 days

Mild to Moderate Cases

Antibiotic treatment is not required in the great majority of cases (see "Clinical Considerations" when antibiotics may be indicated)

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

First Choice

ACCESS Amoxicillin 500 mg q8h **ORAL**

Second Choice

ACCESS Cefalexin 500 mg q8h **ORAL**

---------- **OR** ----------

ACCESS Doxycycline 100 mg q12h **ORAL**

Severe Cases

All dosages are for normal renal function

ACCESS Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**

Pathophysiology

Exacerbations of COPD are a worsening of the existing underlying chronic inflammation of the respiratory tract and are caused in most cases by irritants (e.g. pollution, smoking, dusts and chemicals) or respiratory tract infections. Exacerbations can accelerate a decline in lung function (i.e. disease progression). The frequency of exacerbations of COPD is variable among individuals with COPD but they occur more often in cases of severe COPD *(135)*.

Epidemiology

According to the Global Burden of Diseases study, in 2017, there were 299 million prevalent cases of COPD and 3.19 million deaths caused by COPD *(44,136)*. In 2014, more than 90% of deaths occurred in low- and middle-income countries *(137)*.

COPD includes emphysema and chronic bronchitis. The most prevalent risk factor is exposure to tobacco smoke and indoor household air pollution *(138)*. The incidence of exacerbations increases with age, especially in smokers, and mortality is higher in severe episodes.

Most likely pathogens

Exacerbations of COPD are triggered by viral infections in most cases when a pathogen is identified (Table 13.1). However, in most cases of exacerbation of COPD, no pathogen is identified *(139,140)*.

Table 13.1 – Pathogens most frequently associated with exacerbations of chronic obstructive pulmonary disease (in descending order of frequency)

Respiratory viruses (most cases)	Bacteria (less frequently)
Influenza virus (A and B)	*Haemophilus influenzae*
Respiratory syncytial virus	*Moraxella catarrhalis*
Parainfluenza virus	*Streptococcus pneumoniae*
Rhinovirus	Gram-negative bacteria, including *Pseudomonas aeruginosa* (including multidrug-resistant strains such as those producing ESBL and carbapenemases)
Coronavirus (including SARS-CoV-2)	
Other respiratory viruses	

ESBL: extended-spectrum beta-lactamases; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Clinical presentation

An exacerbation of COPD should be suspected in cases of recent and sustained worsening of dyspnoea and cough with increased sputum production compared with the baseline of patients with COPD, that is, chronic bronchitis and emphysema. Symptoms can overlap with those of pneumonia; however, tachycardia, tachypnoea at rest and crepitations that persist (i.e. that do not clear) after coughing suggest pneumonia.

The decision to hospitalize a person with an exacerbation of COPD should be guided by the severity of symptoms, assessment of comorbidities and availability of home support.

Laboratory tests

Patient microbiology tests

When an exacerbation of COPD is suspected clinically, sputum Gram stain and culture are not recommended routinely. In people with COPD, the respiratory tract may for example be colonized with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*, and a positive culture may indicate colonization rather than acute infection.

Other tests

When exacerbations of COPD are suspected clinically, certain laboratory tests could be considered, in particular tests that can help identify patients with bacterial infections and that can help assess the severity of the exacerbation. The rationale is that these patients would benefit the most from antibiotic treatment. For example, C-reactive protein *(141,142)*, procalcitonin, and complete blood count and blood gas analysis may be useful. However, there is no clear consensus across guidelines about which tests should be performed routinely in the hospital setting and such tests may not be available in many settings.

Using microbiology surveillance data

Routine surveillance of clinical isolates from patients presenting with exacerbations of COPD is not helpful to inform local or national prescribing guidance.

Imaging

A chest X-ray could be considered in patients requiring hospitalization in order to exclude other diagnoses (e.g. pneumonia, pulmonary oedema) or in outpatients if pneumonia is suspected and chest radiography is available.

No antibiotic care

The core treatment of an exacerbation episode consists of supplementary oxygen and short-acting inhaled beta-2-agonists (with or without anticholinergics). Most guidelines currently recommend using systemic steroids because they help improve lung function and shorten time to recovery.

A detailed discussion of non-antibiotic management of COPD is beyond the scope of this chapter. Additional information can be found on the WHO website *(132)*.

Antibiotic treatment

Most exacerbations of COPD are not triggered by bacterial infections, therefore only certain cases will benefit from antibiotic treatment.

Note

Antibiotic treatment is not required in the great majority of cases of acute exacerbations of chronic obstructive pulmonary disease.

Antibiotics are not needed for most cases. Their use could be considered in severe exacerbations of COPD. Most guidelines suggest antibiotic treatment for patients hospitalized because of an acute exacerbation of COPD, especially if an increased volume and purulence of sputum is present, because these cases are more likely to be caused by a bacterial infection. Severe exacerbations benefit more from antibiotic treatment (see Table 13.2 for antibiotic options). Current evidence suggests that the benefit in terms of reduced short-term mortality and reduced treatment failure is limited to hospitalized patients in intensive care units *(143)*. Previous colonization of the respiratory tract (e.g. with *Pseudomonas aeruginosa*) needs to be taken into account when choosing empiric treatment. Patients with frequent episodes of COPD exacerbations may have received multiple courses of antibiotic treatment during the year and have a higher risk of infections caused by multidrug-resistant pathogens.

Table 13.2 – Empiric antibiotic treatment for exacerbation of chronic obstructive pulmonary disease

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Severity	First choice	Second choice	Total treatment duration
Mild to moderate cases	Amoxicillin (oral): 500 mg given every 8 hours	Cefalexin (oral): 500 mg given every 8 hours **OR** Doxycycline (oral): 100 mg given every 12 hours	5 days
Severe cases	Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours	–	5 days

Note. All dosages are for normal renal and hepatic function.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Appropriate measures to prevent further exacerbations include smoking cessation, reduced indoor air pollution, use of long-acting inhaled beta-2-agonists (with or without anticholinergics) and vaccination against influenza, *Streptococcus pneumoniae* infection and COVID-19 *(35,37)*. Currently, there is no clear consensus on the prophylactic use of antibiotics (e.g. macrolides) in patients with severe COPD and frequent episodes of exacerbation *(144)*. For specific preventive measures for chronic respiratory diseases, refer to the WHO publication on global surveillance, prevention and control of chronic respiratory diseases *(133)*.

14. Acute infectious diarrhoea/ gastroenteritis

Note

This chapter does not include enteric fever and *Clostridioides difficile* infection; please refer to the respective chapters when these infections are suspected.

Key messages

- **Antibiotics are not needed** in the great majority of cases of watery diarrhoea with or without a fever.
- Most cases of infectious diarrhoea are self-limiting and are caused by viruses.
- Antibiotics should only be used in patients with severe bloody diarrhoea (dysentery) or in immunocompromised patients.
- When an antibiotic is needed, ciprofloxacin is the first choice, but azithromycin is preferred in areas with a high prevalence of ciprofloxacin resistance among specific bacteria causing infectious diarrhoea (e.g. intestinal/non-invasive/diarrhoeal *Salmonella*, *Shigella* spp.).
- Cholera should be treated with antibiotics only in the context of outbreaks to prevent transmission but the most important intervention is rehydration.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.
- The treatment of diarrhoea: a manual for physicians and other senior health workers, fourth revision. *(145)*.
- Diarrhoeal disease – fact sheet *(146)*.
- Cholera vaccines: WHO position paper – August 2017 *(147)*.
- Global Taskforce on Cholera Control. Use of antibiotics for the treatment and control of cholera *(148)*.
- Rotavirus vaccines: WHO position paper – July 2021 *(149)*.
- Schistosomiasis – health topic *(150)*.

Definition

Acute diarrhoeal disease (also known as gastroenteritis) is a disease characterized by acute onset (usually defined as a duration of < 14 days) of diarrhoea. Diarrhoea is defined as the passage of unusually loose or watery stools occurring at least three times a day (or more frequently than is normal for the individual). Consistency (how liquid/runny) rather than frequency (how often) is the most important factor to consider and frequent passing of formed stool is not diarrhoea. In breastfed babies, frequent loose pale-coloured stools are not considered diarrhoea *(145)*. Most cases of acute diarrhoea have an infectious origin, but non-infectious causes are also possible, for example: adverse effects of medicines, including antibiotics and cytotoxic chemotherapy; endocrine diseases; inflammatory bowel diseases; and irritable bowel syndrome. Acute diarrhoea can be further subclassified as **watery** diarrhoea or **bloody** diarrhoea (i.e. presence of visible blood in the stool).

Acute infectious diarrhoea/gastroenteritis

This guidance excludes Clostridioides difficile infection or enteric fever (see separate chapters)

Definition

New (<14 days) onset of diarrhoea (≥3 unformed/liquid stools in 24 hrs or more than normal for individual).
Diarrhoea can be watery or bloody (dysentery)

Important: Non-infectious causes are also possible and must be considered (e.g. adverse effects of medicines including antibiotics, bowel and endocrine diseases)

Most Likely Pathogens

Most cases have a viral origin
Always consider these risk factors as they may influence the most likely etiologic agents:
- History of recent travel
- Recent consumption of potentially unsafe food
- Recent antibiotic exposure (risk of *C. difficile*)
- Immunosuppression
- Severe malnutrition

Watery diarrhoea:
- Most likely cause is viral (mostly norovirus and rotavirus)
- Consider cholera in endemic settings or in the context of outbreaks

Bloody diarrhoea (dysentery):
- Most likely cause are bacteria, mostly:
  - *Shigella* spp.
  - *Campylobacter* spp.
  - Diarrhoeal non-typhoidal *Salmonella*
  - Enterotoxigenic *Escherichia coli*

Consider parasites if symptoms do not resolve:
- Usually parasites are responsible for persistent (14-29 days duration) or chronic (>30 days duration) rather than acute diarrhoea
  - *Entamoeba histolytica*
  - *Giardia intestinalis*
  - Other protozoal parasites and very rarely *Schistosoma* (intestinal species)

Prevention

- Access to safe drinking-water, use of improved sanitation, hand washing with soap, good food hygiene, health education about how these infections spread
- Vaccination against cholera in endemic areas and during outbreaks

Diagnosis

Clinical Presentation

- Diarrhoea, nausea, vomiting, bloating, abdominal pain and cramping; fever may be absent
- Most cases are self-limiting in a few days
- Patients may present with varying degrees of dehydration and can present with severe malnutrition (both a risk factor and a consequence of diarrhoea)

Important:
- Rapidly evaluate the degree of dehydration (especially in the elderly)
- Signs of severe dehydration (two or more must be present):
  - Lethargy and/or unconsciousness
  - Sunken eyes
  - Inability to drink
  - Skin pinch goes back very slowly (≥2 seconds)

Microbiology Tests

Usually not needed

Consider testing if:
- Bloody diarrhoea
- Immunocompromised patients (to exclude parasitic infections)
- Recent antibiotic use (to exclude *C. difficile*)
- Suspected cholera outbreak

Tests to consider:
- Stool culture
- Stool microscopy (for parasites)
- Vibrio cholerae antigen (e.g. in outbreaks)
- Test for *C. difficile* (if recent antibiotic exposure)

Other Laboratory Tests

Usually not needed but consider in severe cases (e.g. check electrolytes)

Imaging

Usually not needed

Acute infectious diarrhoea/gastroenteritis

Treatment

No Antibiotic Care

Important: Rehydration and electrolyte replacement is the main treatment for acute infectious diarrhoea

Fluid losses can be compensated by drinking adequate fluids

Antidiarrhoeal and antiemetic drugs are not routinely needed (they do not prevent dehydration or improve nutritional status)

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Cholera Antibiotic Treatment

Treat with antibiotics only in:
- *Patients hospitalized with severe dehydration OR*
- *Regardless of degree of dehydration:*
  - *High purging or failure of first 4 hour course of rehydration therapy OR*
  - *Coexisting conditions (e.g. pregnancy) OR*
  - *Co-morbidities (e.g. severe acute malnutrition, HIV)*

All dosages are for normal renal function

First Choice

WATCH Azithromycin 1 g **ORAL**
Treatment duration: single dose

Azithromycin preferred because of the decreasing susceptibility of cholera to tetracyclines and fluoroquinolones

OR

ACCESS Doxycycline 300 mg single dose **ORAL**
Treatment duration: 3 days
- If single dose is not tolerated: 100 mg q12h

Second Choice

WATCH Ciprofloxacin 1 g **ORAL**
Treatment duration: single dose

Clinical Considerations

- **Antibiotics usually not needed**, including in cases with severe dehydration
- Consider antibiotic treatment ONLY if:
  - Significant acute bloody diarrhoea
  - Severely immunocompromised patients

Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

If symptoms do not resolve within 24-48 hours of treatment, consider giving metronidazole for treatment of Entamoeba histolytica and Giardia intestinalis

First Choice

WATCH Ciprofloxacin 500 mg q12h **ORAL**
Treatment duration: 3 days

Second Choice

WATCH Azithromycin **ORAL**
- Day 1: 500 mg q24h
- Day 2-4: 250 mg q24h

Treatment duration: 4 days

Azithromycin is preferred in case of high prevalence of ciprofloxacin resistance among bacteria frequently associated with acute infectious diarrhoea (e.g. Salmonella spp., Shigella spp.)

OR

WATCH Cefixime 400 mg q24h **ORAL**
Treatment duration: 3 days

OR

ACCESS Sulfamethoxazole+trimethoprim 800 mg + 160 mg q12h **ORAL**
Treatment duration: 5 days

Use only if local data suggest susceptibility
In patients taking sulfamethoxazole-trimethoprim for prophylaxis, treat with a different antibiotic unless susceptibility is confirmed

OR

WATCH Ceftriaxone 1 g q24h **IV/IM**
Treatment duration: 3 days

Acute infectious diarrhoea/gastroenteritis

Definition

New (<14 days) onset of diarrhoea (≥3 unformed/liquid stools in 24 hrs or more than normal for individual).
Diarrhoea can be watery or bloody (dysentery)

Important: Non-infectious causes are also possible and must be considered (e.g. adverse effects of medicines including antibiotics, bowel and endocrine diseases)

Most Likely Pathogens

Most cases have a viral origin
Always consider these risk factors as they may influence the most likely etiologic agents:
- History of recent travel
- Recent consumption of potentially unsafe food
- Immunosuppression
- Severe malnutrition

Watery diarrhoea:
- Most likely cause is viral, mostly:
  - Rotavirus
  - Norovirus
  - Adenovirus
- Consider cholera in endemic settings or in the context of outbreaks

Bloody diarrhoea (dysentery):
- Most likely cause are bacteria, mostly:
  - *Shigella* spp.
  - *Campylobacter* spp.
  - Diarrhoeal non-typhoidal *Salmonella*
  - Enterotoxigenic *Escherichia coli*

Consider parasites if symptoms do not resolve:
- Usually parasites are responsible for persistent (14-29 days duration) or chronic (>30 days duration) rather than acute diarrhoea
  - *Entamoeba histolytica*
  - *Giardia intestinalis*
  - Other protozoal parasites and very rarely *Schistosoma* (intestinal species)

Prevention

- Access to safe drinking-water, use of improved sanitation, hand washing with soap, good food hygiene, health education about how these infections spread
- Exclusive breastfeeding for the first 6 months of life
- Vaccination against rotavirus and against cholera (in endemic areas and during outbreaks)

This guidance excludes enteric fever (see separate chapter)

Diagnosis

Clinical Presentation

- Diarrhoea, nausea, vomiting, bloating, abdominal pain and cramping; fever may be absent
- Most cases are self-limiting in a few days
- Patients may present with varying degrees of dehydration and can present with severe malnutrition (both a risk factor and a consequence of diarrhoea)

Important:
- Rapidly evaluate the degree of dehydration
- Signs of severe dehydration (two or more must be present):
  - Lethargy and/or unconsciousness
  - Sunken eyes
  - Inability to drink
  - Skin pinch goes back very slowly (≥2 seconds)

Microbiology Tests

Usually not needed

Consider testing if:
- Bloody diarrhoea
- Immunocompromised patients (to exclude parasitic infections)
- Suspected cholera outbreak

Tests to consider:
- Stool culture
- Stool microscopy (for parasites)

Other Laboratory Tests

Usually not needed but consider in severe cases (e.g. check electrolytes)

Imaging

Usually not needed

Acute infectious diarrhoea/gastroenteritis

Treatment

No Antibiotic Care

Important: Rehydration and electrolyte replacement is the main treatment for acute infectious diarrhoea

- Low-osmolarity oral rehydration solution (ORS) is recommended
- In addition to ORS, zinc tablets (10-20 mg/day) for 10-14 days can shorten duration and severity of symptoms

Antidiarrhoeal and antiemetic drugs are not routinely needed (they do not prevent dehydration or improve nutritional status)

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Cholera Antibiotic Treatment

Treat with antibiotics only in:
- *Patients hospitalized with severe dehydration OR*
- *Regardless of degree of dehydration:*
  - *High purging or failure of first 4 hour course of rehydration therapy OR*
  - *Co-morbidities (e.g. severe acute malnutrition, HIV)*

All dosages are for normal renal function

First Choice

WATCH — Azithromycin 20 mg/kg **ORAL**
Treatment duration: single dose

Azithromycin preferred because of the decreasing susceptibility of cholera to tetracyclines and fluoroquinolones

Second Choice

WATCH — Ciprofloxacin 15 mg/kg **ORAL**
Treatment duration: single dose

OR

ACCESS — Doxycycline **ORAL**
- <45 kg (<12 yrs): 2-4 mg/kg
- >45 kg (>12 yrs): 300 mg

Treatment duration: single dose

Clinical Considerations

- **Antibiotics usually not needed**, including in cases with fever and/or severe dehydration
- Consider antibiotic treatment ONLY if:
  - Significant bloody diarrhoea
  - Severely immunocompromised patients

Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

If symptoms do not resolve within 24-48 hours of treatment, consider giving metronidazole for treatment of Entamoeba histolytica and Giardia intestinalis

First Choice

WATCH — Ciprofloxacin 15 mg/kg/dose q12h **ORAL**
- **Oral weight bands**:

3-<6 kg	50 mg q12h
6-<10 kg	100 mg q12h
10-<15 kg	150 mg q12h
15-<20 kg	200 mg q12h
20-<30 kg	300 mg q12h
≥30 kg	500 mg q12h

Treatment duration: 3 days

Second Choice

WATCH — Azithromycin 10 mg/kg/dose q24h **ORAL**
Treatment duration: 4 days

For children with bloody diarrhoea/dysentery ONLY azithromycin is preferred if suspected ciprofloxacin resistance

OR

WATCH — Cefixime 10 mg/kg/dose q24h **ORAL**
Treatment duration: 5 days

OR

ACCESS — Sulfamethoxazole+trimethoprim 20 mg/kg + 4 mg/kg q12h **ORAL**
- **Oral weight bands**:

3-<6 kg	100 mg+20 mg q12h
6-<10 kg	200 mg+40 mg q12h
10-<30 kg	400 mg+80 mg q12h
≥30 kg	800 mg+160 mg q12h

Treatment duration: 5 days

Use only if local data suggest susceptibility

In patients taking sulfamethoxazole-trimethoprim for prophylaxis, treat with a different antibiotic unless susceptibility is confirmed

OR

WATCH — Ceftriaxone 80 mg/kg/dose q24h **IV/IM**
Treatment duration: 3 days

Pathophysiology

Acute diarrhoeal diseases can be acquired through ingestion of food or water contaminated with viral or bacterial pathogens (rarely protozoal or fungal pathogens) or through direct contact with someone carrying the pathogen. Establishment of an enteric infection depends on the capacity of the pathogen to invade the mucosa and overcome the host defences. It is dependent on several factors, including the inoculum, the virulence of the organism and the status of host defences. Production of enterotoxins (i.e. bacterial proteins that act on the host's intestinal cells) is a frequently encountered mechanism of disease.

Epidemiology

In 2017, 6.2 billion episodes of diarrhoeal disease were estimated to have occurred worldwide, including 500 000 incident cases of intestinal/non-invasive/diarrhoeal non-typhoidal *Salmonella* disease *(44)*.

Children younger than 5 years are often affected. About 1.7 billion cases of acute diarrhoeal disease occur each year in this age group where it is an important cause of death (about 450 000 deaths in 2016). Acute malnutrition, living in or travelling to areas with limited access to safe drinking-water and adequate sanitation are the leading risk factors for acute diarrhoeal diseases *(146,151)*.

Most likely pathogens

Most cases of community-acquired acute watery diarrhoeal disease have a viral origin. However, bacteria and parasites can also be causes *(152)*. For returning travellers, it is important to consider travel-associated diarrhoea. Table 14.1 and Table 14.2 give the pathogens most frequently associated with acute diarrhoeal disease (in children and adults respectively), and Table 14.3 the pathogens associated with chronic or persistent diarrhoea.

Table 14.1 – Pathogens most frequently associated with acute infectious diarrhoea in children (in descending order of frequency)

Setting	Viruses (most cases)	Bacteria	Parasites
Low income	Rotavirus Measles virus[a]	*Escherichia coli* *Shigella* spp.	*Cryptosporidium* spp.
High income	Norovirus Rotavirus Adenovirus Measles virus[a]	Intestinal/non-invasive/ diarrhoeal non-typhoidal *Salmonella* *Campylobacter* spp.	–

[a] Diarrhoea is the most common complication in measles.

Table 14.2 – Pathogens most frequently associated with acute infectious diarrhoea in adults (in descending order of frequency)

Setting	Viruses (most cases)	Bacteria
Low income	Norovirus	*Campylobacter* spp. Intestinal/non-invasive/diarrhoeal non-typhoidal *Salmonella* *Shigella* spp. *Escherichia coli*
High income	Norovirus	Intestinal/non-invasive/diarrhoeal non-typhoidal *Salmonella* *Campylobacter* spp. *Escherichia coli* *Shigella* spp. *Listeria monocytogenes*

Table 14.3 – Pathogens most frequently associated with persistent (14–29 days) or chronic (> 30 days) infectious diarrhoea in people living with HIV[a] (in descending order of frequency)

Parasites	Viruses	Fungi (rarely)[b]
Cryptosporidium spp.	*Cytomegalovirus*	*Histoplasma capsulatum*
Microsporidium spp.		*Coccidioides* spp.
Cystoisospora belli		*Penicillium* spp.

HIV: human immunodeficiency virus.
[a] It should be noted that in these cases, patients often receive unnecessary antibiotic treatment.
[b] Rarely in the context of disseminated infections in patients with low CD4 count.

Clinical presentation

In acute diarrhoea, the main symptom is new onset (< 14 days) of three or more unformed stools a day, with or without fever. Nausea, vomiting, bloating, abdominal pain and cramping may also be present. In most cases, the disease is self-limiting. Since some causative pathogens can be endemic in certain settings and absent in others, it is always important to consider where the patient became infected (including history of recent travel) and recent consumption of potentially unsafe food (e.g. raw meat or unpasteurized milk products). Recent antibiotic use (past 3 months), cytotoxic chemotherapy or the presence of immunosuppression (e.g. HIV infection) also need to be investigated.

Five common clinical presentations can help identify cases that require specific treatment and management *(145)*.

1. Patients with **watery diarrhoea**. In these patients, the most likely cause is viral, mostly rotavirus and norovirus. A mild fever and vomiting may also occur. The main risk is severe dehydration and management is symptomatic (e.g. fluid replacement).

2. Patients with **bloody diarrhoea** (dysentery or invasive diarrhoea with damage to the intestinal mucosa). In these patients, the most likely cause are bacteria, mostly *Shigella* spp., *Campylobacter* spp., intestinal/non-invasive/diarrheal non-typhoidal *Salmonella* or enterotoxigenic *Escherichia coli*. These cases may benefit from antibiotic treatment. In addition to dehydration, these infections can be complicated by sepsis and malnutrition. *Entamoeba histolytica* can rarely also cause bloody diarrhoea weeks or months after the infection; often these infections are responsible for chronic rather than acute bloody diarrhoea. Other protozoal parasites and very rarely *Schistosoma* can also cause bloody diarrhoea; only *Schistosoma mansoni* and *Schistosoma japonicum*, the intestinal species.

3. Patients with **persistent diarrhoea** (symptoms lasting > 14 days). In these patients, a parasite is often implicated (e.g. *Giardia intestinalis*, *Entamoeba histolytica*) and the main risks are malnutrition and dehydration.
4. **Diarrhoea with severe malnutrition**. In these patients, malnutrition is both a cause and consequence of diarrhoea.
5. **Diarrhoea with recent antibiotic exposure** (*Clostridioides difficile*). This condition is mostly hospital-acquired; please refer to the chapter on *Clostridioides difficile* infection if this is suspected.

Patients may present with varying degrees of dehydration and this should be promptly assessed, especially in children and elderly people. In children, the degree of dehydration can be rated on a scale of three as indicated in Table 14.4 *(146)*.

Table 14.4 – Classification of dehydration

Severity of dehydration	Signs
Severe dehydration: at least two signs from the list on the right must be present	• Lethargy and/or unconsciousness • Sunken eyes • Inability to drink • Skin pinch goes back very slowly (≥ 2 seconds)
Some dehydration: at least two signs from the list on the right must be present	• Restlessness, irritability • Sunken eyes • Drinks eagerly, is thirsty
No dehydration	Too few signs to classify as some or severe dehydration

Source: WHO Pocket book of hospital care for children *(31)*.

Laboratory tests

Patient microbiology tests

Routine stool testing is not needed since most cases are self-limiting and knowing the causative agent would not alter management. Testing may be done for infection control purposes, if there is a high risk of spreading the disease in specific settings.

However, in certain cases and based on local availability, a stool test (e.g. stool microscopy, stool culture, antigen testing and nucleic acid amplification tests) could be considered (Table 14.5), but only when identifying the causative pathogen may benefit the

patient, for example, because specific treatment can be provided or a multidrug-resistant pathogen may be detected.

Selected cases that could benefit from stool testing include:

- patients with bloody diarrhoea
- patients with suspected cholera in the context of outbreaks
- immunocompromised patients with acute diarrhoea
- history of diarrhoea following antibiotic use (suspicion of *Clostridioides difficile* infection). Please refer to the chapter on *Clostridioides difficile* infection if this infection is suspected.

Table 14.5 – Microbiology tests to consider in certain cases of diarrhoeal disease as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Stool culture and antimicrobial susceptibility testing	To detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Stool microscopy	To detect and identify parasites and their ova (eggs) or cysts	Health care facilities with clinical laboratories
Vibrio cholerae antigen[a] (RDT)	To detect or exclude a cholera outbreak (not for use in case management)	Community settings and health facilities without laboratories

EDL: Model List of Essential In Vitro Diagnostics; RDT: rapid diagnostic test.
[a] Possible specimens include stool and rectal swab.

Other tests

Routine laboratory tests are usually not needed. However, for severe cases, electrolytes should be checked if available.

Using microbiology surveillance data

Targeted clinical microbiological surveys of cases of acute bloody diarrhoea in the primary care setting in children and adults, specifically focusing on quinolone and macrolide resistance rates in *Shigella* and intestinal/non-invasive/diarrhoeal non-typhoidal *Salmonella*, may be helpful to inform local empiric antibiotic guidance.

Imaging

Routine imaging is not needed for acute diarrhoeal disease.

No antibiotic care

Rehydration is the main treatment for acute diarrhoeal disease (oral or intravenous). In children, treating any diarrhoea with oral rehydration therapy using a low-osmolarity oral rehydration solution to prevent dehydration is recommended *(145)*. In addition, zinc tablets (10–20 mg/day) for 10–14 days are usually recommended to shorten the duration and severity of symptoms *(31,145)*.

In adults, an oral rehydration solution is not usually needed, and fluid losses can be compensated by drinking adequate fluids. However, in severely dehydrated adult patients, an oral rehydration solution can be given. Antidiarrhoeal and antiemetic medicines are not routinely needed because they do not prevent dehydration and do not improve nutritional status *(145)*.

Antibiotic treatment

Antibiotics are not needed in most cases of acute diarrhoeal disease because they are of viral origin and the illness is usually self-limiting regardless of the causative pathogen. Rehydration is the main treatment for acute diarrhoeal disease *(145)*. Even in cases with severe dehydration, antibiotic treatment is not routinely needed.

However, in patients with significant acute bloody diarrhoea and in severely immunocompromised patients, antibiotics may be given (see Table 14.6 for empiric options based on the risk of fluoroquinolone resistance). Bloody diarrhoea could be caused by certain strains of *Escherichia coli* (Shiga toxin-producing *Escherichia coli* also known as enterohaemorrhagic *Escherichia coli*). In these cases (mostly in children), the use of antibiotics is controversial because there is a theoretical concern that it could worsen symptoms of haemolytic uraemic syndrome, characterized by haemolytic anaemia, renal injury and low platelets. However as there is clear evidence of benefit in shigellosis, empiric treatment with antibiotics should not be withheld because of a concern of causing haemolytic uraemic syndrome.

If symptoms do not resolve after 24–48 hours of antibiotic treatment, adding a treatment course of metronidazole for possible *Entamoeba histolytica* infection could be considered.

In addition, antibiotic treatment should be considered in the context of cholera in the following cases (see Table 14.7 for antibiotic options):

- suspected cholera in patients hospitalized with severe dehydration
- regardless of degree of dehydration:
  - high purging or failure of first 4-hour course of rehydration therapy or
  - coexisting conditions (e.g. pregnancy) or
  - comorbidities (e.g. severe acute malnutrition, HIV infection) that pose elevated risk in cholera illness.

Note

Only certain cases of diarrhoeal disease benefit from antibiotic treatment, namely patients with significant acute bloody diarrhoea and/or who are severely immunocompromised.

Table 14.6 – Empiric antibiotic treatment for selected cases of infectious acute diarrhoea

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

	Adults	Children	Total treatment duration
First choice	**Ciprofloxacin** [a,b] (oral): 500 mg given every 12 hours	**Ciprofloxacin** [a] (oral): 15 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 50 mg given every 12 hours 6–< 10 kg: 100 mg given every 12 hours 10–< 15 kg: 150 mg given every 12 hours 15–< 20 kg: 200 mg given every 12 hours 20–< 30 kg: 300 mg given every 12 hours ≥ 30 kg: use adult dose	3 days

continues

Table 14.6 *continued*

	Adults	Children	Total treatment duration
Second choice	**Oral options** **Azithromycin** [c] (oral): 500 mg given once a day (on day 1) followed by 250 mg given once a day for 3 days **OR** **Cefixime** [d] (oral): 400 mg given once a day **OR** **Sulfamethoxazole+ trimethoprim** [d,e] (oral): 800 mg + 160 mg given every 12 hours **Parenteral option** **Ceftriaxone** [d] (IV/IM): 1 g given once a day	**Oral options** **Azithromycin** [c] (oral): 10 mg/kg/dose given once a day **OR** **Cefixime** [d] (oral): 10 mg/kg/dose given once a day **OR** **Sulfamethoxazole+ trimethoprim** [d,e] (oral): 20 mg/kg + 4 mg/kg given every 12 hours Oral weight bands (mg of the sulfamethoxazole/ trimethoprim component): 3–< 6 kg: 100 mg/20 mg given every 12 hours 6–< 10 kg: 200 mg/40 mg given every 12 hours 10–< 15 kg: 400 mg/80 mg given every 12 hours 15–< 20 kg: 400 mg/80 mg given every 12 hours 20–< 30 kg: 400 mg/80 mg given every 12 hours ≥ 30 kg: use adult dose **Parenteral option** **Ceftriaxone** [d] (IV/IM): 80 mg/kg/dose given once a day	**Azithromycin**: 4 days **Cefixime**: 3 days (adults) 5 days (children) **Sulfamethoxazole+ trimethoprim**: 5 days **Ceftriaxone**: 3 days

IM: intramuscular; IV: intravenous.
Note. All dosages are for normal renal and hepatic function.
[a] If symptoms do not resolve within 24–48 hours of treatment, consider *Entamoeba histolytica* or *Giardia intestinalis* as possible causes and provide appropriate treatment.
[b] The use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemic coma; (iii) increased risk of tendinitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).

continues

Table 14.6 *continued*

[c] Azithromycin is preferred in cases of high prevalence of ciprofloxacin resistance among bacteria frequently associated with acute infectious diarrhoea (e.g. Intestinal/non-invasive/diarrhoeal non-typhoidal *Salmonella*, *Shigella* spp.). Of note azithromycin can cause abnormal changes in the electrical activity of the heart leading to a potentially fatal irregular heart rhythm, especially in patients with known risk factors such as long QT interval or arrhythmias.
[d] Cefixime, ceftriaxone and sulfamethoxazole+trimethoprim are not active against *Campylobacter* spp.
[e] Ideally, sulfamethoxazole+trimethoprim should only be used if local data suggest susceptibility or if the isolated strain is susceptible. As per WHO 2005 guidelines, this antibiotic should not be used empirically when shigellosis is suspected *(145)*. In patients taking sulfamethoxazole+trimethoprim for prophylaxis, a different antibiotic should be used for treatment unless susceptibility is confirmed.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Table 14.7 – Empiric antibiotic treatment for cholera

Note

For indications for antibiotic use, please refer to the technical note on the use of antibiotics for the treatment and control of cholera from the Global Task Force on Cholera Control *(148)*.

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Adults	Children
First choice **Azithromycin** [a] (oral): 1 g, single dose **OR** **Doxycycline** (oral): 300 mg, single dose (or 100 mg given every 12 hours for 3 days if single dose is not tolerated)	**First choice** **Azithromycin** [a] (oral): 20 mg/kg, single dose
Second choice **Ciprofloxacin** (oral): 1 g, single dose	**Second choice** **Ciprofloxacin** (oral): 15 mg/kg, single dose **OR** **Doxycycline** (oral) • < 45 kg (< 12 years): 2 to 4 mg/kg, single dose • > 45 kg (> 12 years): 300 mg, single dose

Note. All dosages are for normal renal and hepatic function.
[a] Azithromycin is preferred because of the decreasing susceptibility of cholera to tetracyclines and fluoroquinolones. Because of the long half-life of azithromycin, it should only be recommended for outbreak situations, where single-dose treatment is especially useful.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Key measures to prevent acute diarrhoeal diseases include access to safe drinking-water, use of improved sanitation, handwashing with soap, exclusive breastfeeding for the first 6 months of life, good personal and food hygiene, health education about how infections spread and vaccination against rotavirus, particularly in countries with a high rate of death associated with rotavirus *(146)*. Vaccination against cholera should also be considered, especially in endemic areas, in humanitarian crises (high risk of cholera) and during outbreaks. Vaccination against cholera should always be accompanied with other prevention and control strategies. Vaccination against measles could also substantially reduce the incidence and severity of diarrhoeal diseases and therefore every infant should be immunized against measles at the recommended age. For updated information on vaccination against rotavirus, cholera and measles, refer to the most recent WHO position papers *(147,149,153)*.

15. Enteric fever

Key messages

- Most cases of enteric fever are caused by *Salmonella* Typhi (70–80% of cases).
- Access to safe water and appropriate hygiene among food handlers is key to prevent the infection. Vaccination should also be offered in endemic areas and during outbreaks.
- Symptoms are often difficult to distinguish from other febrile illnesses.
- Blood cultures should be taken in all cases requiring hospitalization.
- Choice of empiric antibiotic treatment depends on the risk of fluoroquinolone resistance of *Salmonella* Typhi.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.
- Typhoid vaccines: WHO position paper – March 2018 *(154)*.

Definition

Enteric fever is a severe systemic illness characterized by fever and abdominal pain caused by the bacterium *Salmonella enterica*, serotypes Typhi or Paratyphi.

Enteric fever

Definition

- A severe systemic illness characterized by fever and abdominal pain caused by infection with *Salmonella enterica*
- Acquired through ingestion of contaminated food/water

Severity:
- *Mild*: Not critically ill with no signs of intestinal perforation, peritonitis, sepsis or septic shock
- *Severe*: Critically ill with confirmed/suspected intestinal perforation, peritonitis, sepsis or septic shock

Pathogen

Enteric fever is caused by *Salmonella enterica* serotypes Typhi or Paratyphi A, B or C

Diagnosis

Clinical Presentation

- **It can be difficult to distinguish enteric fever from other febrile illnesses**
- Symptoms include protracted fever (≥ 38.0 °C for >3 days) +/- headache, loss of appetite and nausea; gastrointestinal symptoms may also be present (diarrhoea more frequent in people living with HIV)
- Consider peritonitis if there is severe pain, diffuse rebound tenderness upon sudden release of pressure on the abdomen and abdominal muscular tensing; peritonitis occurs as a result of intestinal bleeding and perforation
- Encephalopathy can also occur in severe cases

Microbiology Tests

- *Mild Cases*: Usually not needed
- *Severe Cases*: Blood cultures (ideally before starting antibiotics)
- Bone marrow culture is the reference standard test but is often not feasible
- *Note: the Widal serology is not a reliable method to diagnose acute illness (a positive result may be due to previous infection)*

Other Laboratory Tests

- *Mild Cases*: Usually not needed
- *Severe Cases*: Complete blood count, creatinine, electrolytes, glucose, C-reactive protein and / or procalcitonin

Imaging

Usually not needed

Prevention

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination

Treatment

Clinical Considerations

- Antibiotic treatment should be started as soon as the diagnosis is suspected; delays are associated with higher risk of complications and severe disease
- **Empiric treatment should be chosen based on**:
  - Severity of presentation
  - Local prevalence of fluoroquinolone resistance among *Salmonella enterica* serotypes Typhi or Paratyphi
- Fever usually decreases slowly after 3-5 days of treatment
- If initially treated IV, step down from IV to oral antibiotics is suggested when the patient has clinically improved, is afebrile and is able to tolerate oral treatment

Antibiotic Treatment Duration

Mild Cases: **7 days***
Severe Cases: **10 days***
**if clinical improvement and the patient is afebrile for 48 hours*

Low Risk of Fluoroquinolone Resistance

All dosages are for normal renal function

Mild and Severe Cases

WATCH Ciprofloxacin 500 mg q12h **ORAL**

High Risk of Fluoroquinolone Resistance

All dosages are for normal renal function

Mild Cases

WATCH Azithromycin 1 g once on day 1, then 500 mg q24h **ORAL**

Severe Cases

WATCH Ceftriaxone 2 g q24h **IV**

Enteric fever

Definition

- A severe systemic illness characterized by fever and abdominal pain caused by infection with *Salmonella enterica*
- Acquired through ingestion of contaminated food/water

Severity:
- *Mild*: Not critically ill with no signs of intestinal perforation, peritonitis, sepsis or septic shock
- *Severe*: Critically ill with confirmed/suspected intestinal perforation, peritonitis, sepsis or septic shock

Pathogen

Enteric fever is caused by *Salmonella enterica* serotypes Typhi or Paratyphi A, B or C

Diagnosis

Clinical Presentation

- **It can be difficult to distinguish enteric fever from other febrile illnesses**
- Symptoms include protracted fever (≥ 38.0 °C for >3 days) +/- headache, loss of appetite and nausea; gastrointestinal symptoms may also be present
- Diarrhoea is common
- Consider peritonitis if there is severe pain, diffuse rebound tenderness upon sudden release of pressure on the abdomen and abdominal guarding; peritonitis occurs as a result of intestinal bleeding and perforation
- Encephalopathy can also occur in severe cases

Microbiology Tests

- *Mild Cases*: Usually not needed
- *Severe Cases*: Blood cultures (ideally before starting antibiotics)
- Note: the Widal serology is not a reliable method to diagnose acute illness (a positive result may be due to previous infection)

Other Laboratory Tests

- *Mild Cases*: Usually not needed
- *Severe Cases*: Complete blood count, creatinine, electrolytes, glucose, C-reactive protein

Imaging

Routine imaging is not needed

Prevention

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers, and typhoid vaccination

Treatment

Clinical Considerations

- Antibiotic treatment should be started as soon as the diagnosis is suspected; delays are associated with higher risk of complications and severe disease
- **Empiric treatment should be chosen based on**:
  - Severity of presentation
  - Local prevalence of fluoroquinolone resistance among *Salmonella enterica* serotypes Typhi or Paratyphi
- Fever usually decreases slowly after 3-5 days of treatment
- If initially treated IV, step down from IV to oral antibiotics is suggested when the patient has clinically improved, is afebrile and is able to tolerate oral treatment

Antibiotic Treatment Duration

Mild Cases: **7 days***
Severe Cases: **10 days***
**if clinical improvement and the patient is afebrile for 48 hours*

Low Risk of Fluoroquinolone Resistance

All dosages are for normal renal function

Mild and Severe Cases

WATCH

Ciprofloxacin 15 mg/kg/dose q12h **ORAL**
- **Oral weight bands**:

3-<6 kg	50 mg q12h
6-<10 kg	100 mg q12h
10-<15 kg	150 mg q12h
15-<20 kg	200 mg q12h
20-<30 kg	300 mg q12h
≥30 kg	500 mg q12h

High Risk of Fluoroquinolone Resistance

All dosages are for normal renal function

Mild Cases

WATCH

Azithromycin 20 mg/kg/dose q24h **ORAL**

Severe Cases

WATCH

Ceftriaxone 80 mg/kg/dose q24h IV

Pathogen

Enteric fever is caused by *Salmonella enterica* serotypes Typhi or Paratyphi A, B or C, a Gram-negative bacterium. Non-typhoidal *Salmonella* is not a cause of enteric fever but may cause infectious gastroenteritis, bloodstream infections, meningitis or bone and joint infections. Please refer to the relevant chapters if these infections are suspected.

Pathophysiology

Enteric fever is acquired through ingestion of food or water contaminated with *Salmonella* Typhi or Paratyphi or through direct contact with someone carrying the pathogen. Humans are the only source of these bacteria. Once the pathogen is ingested, it invades the intestinal mucosa primarily through the distal ileum. Once there, host immune defences are activated to eliminate the pathogen. However, these white cells can also act as carriers of the infection through the lymphatic system to the liver, spleen, bone marrow and lymph nodes, and ultimately to the bloodstream. Natural infection does not provide complete protection so recurrent illness is possible *(155)*.

Epidemiology

Most cases of enteric fever are caused by *Salmonella* Typhi (70–80% of cases). Even though the absolute number of new cases of enteric fever has declined by 45% and the number of deaths by 41% since the 1990s, the disease is still endemic, mostly in sub-Saharan Africa and in South Asia. Based on available data, India, Pakistan and Bangladesh are the countries with the highest incidence of enteric fever with > 500 cases per 100 000 population in 2017. In 2017, about 14.3 million cases of enteric fever occurred worldwide. In endemic countries, children are affected the most with almost 60% of cases occurring in children younger than 15 years. Based on the data available, when appropriately treated with antibiotics, the case fatality rate for enteric fever is about 1% *(156)*. Complications (e.g. intestinal perforation) in hospitalized cases are estimated to occur in 20–30% of cases, with a higher risk in people presenting for care after having had symptoms for more than 10 days *(157)*.

Clinical presentation

Symptoms of enteric fever are often non-specific, making it difficult to distinguish enteric fever from other febrile illnesses. As a result, misdiagnosis of cases can occur. In patients with enteric fever, protracted fever (≥ 38.0 °C for more than 3 days) is the main symptom. Headache is often present as well as loss of appetite and nausea. Gastrointestinal symptoms may not be present, and diarrhoea is seen more frequently in children and in people with HIV. The clinical presentation can vary from mild illness with a low-grade fever and malaise to severe disease presenting with septic shock and peritonitis because of intestinal bleeding

and perforation. Encephalopathy can also occur in severe cases. Of note, clinical features are also not useful to distinguish infections caused by *Salmonella enterica* serotype Typhi from those caused by *Salmonella enterica* serotype Paratyphi.

Laboratory tests

Patient microbiology tests

In patients with suspected enteric fever, the diagnosis is largely dependent on the clinical presentation and detection of the pathogen in blood cultures, even though the sensitivity is low, especially when antibiotic treatment has already been started. **A blood culture should be taken in all possible cases with fever requiring hospitalization, ideally before starting antibiotic treatment**. Bone marrow cultures is the most sensitive diagnostic method, but these cultures are very rarely done because they are more difficult to perform and invasive. Stool cultures are usually negative in the early phases of the infection and therefore they are of limited diagnostic use (Table 15.1). Widal serology is still widely used in low- and middle-income countries; however, it is not a reliable method to diagnose acute illness because a positive result may represent a previous infection, and in returning travellers, vaccination prior to travel affects the results. Ideally the Widal serology requires two samples taken 10 days apart to demonstrate a four-fold rise of anti-*Salmonella* Typhi antibodies and this is not practical in many low-resource settings.

Table 15.1 – Microbiology tests to consider when enteric fever is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Blood cultures[a] and antimicrobial susceptibility testing	To detect bacterial and fungal bloodstream infections (sepsis)	Health care facilities with clinical laboratories
Bone marrow culture[b] and antimicrobial susceptibility testing	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Stool culture[c] and antimicrobial susceptibility testing	Initial step in detection and identification of bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.
[a] Often the mainstay of diagnosis. Without antibiotic treatment, blood cultures are often positive (5–7 out of 10 patients) however sensitivity is low, if antibiotics have already been started.
[b] The gold standard for diagnosis but it is often not feasible to do.
[c] Low sensitivity and not useful in the early phase (first week) of disease when the test is often negative.

Other tests

Routine laboratory testing is not always needed but could be considered in severe cases (i.e. routine haematology and biochemistry).

Using microbiology surveillance data

Targeted clinical microbiological surveys of enteric fever-related bloodstream infection focusing on *Salmonella enterica* serotype Typhi and Paratyphi resistance rates may help inform local and national empiric antibiotic guidance.

Imaging

Routine imaging is not needed.

Antibiotic treatment

Antibiotic treatment options are shown in Table 15.2. In cases of enteric fever, antibiotic treatment should be started promptly because delays are associated with higher risk of complications and severe disease. In general, antibiotic treatment is given to shorten the duration of symptoms and to reduce the risk of complications, such as intestinal perforation and chronic carriage. Chronic carriers are asymptomatic people who continue to harbour the pathogen for months or even years after their initial infection and can transmit the infection. Fever usually decreases slowly, after around 3–5 days of effective treatment. Mild cases can be treated as outpatients with oral treatment, while severe cases should be treated as inpatients with systemic intravenous treatment.

The choice of oral antibiotic, if possible, should be based on the sensitivity of the isolated pathogen. When choosing empiric treatment, the local prevalence of fluoroquinolone resistance should be considered because of the increasing number of resistant isolates, mostly in Asia *(158)*. In these settings, a third-generation cephalosporin or azithromycin are appropriate options because resistance to these antibiotics is still low in most settings; < 5% for ceftriaxone and only sporadic cases with resistance to azithromycin. Of note, antibiotics that were widely used in the 1980s and 1990s but fell into disuse because of resistance or toxicity concerns (e.g. ampicillin, chloramphenicol and sulfamethoxazole+trimethoprim) are again effective in some settings, mostly in Asia. However, the empiric use of these older options for treatment is discouraged because it could prompt a rebound of multidrug-resistant organisms.

In recent years, outbreaks of enteric fever caused by extensively antibiotic-resistant *Salmonella* Typhi have been reported, for example, in Pakistan since 2016 *(159)*. These extensively antibiotic-resistant isolates are resistant to ampicillin, sulfamethoxazole+trimethoprim, chloramphenicol, fluoroquinolones and third-generation cephalosporins and represent a public health threat including the risk of travel/migration-related spread to other countries and regions.

Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics which allows discharge of the patient home when clinically appropriate.

Table 15.2 – Empiric antibiotic treatment for enteric fever

Risk of fluoroquinolone resistance[a]	Adults	Children	Total treatment duration
Low	**Ciprofloxacin** [b] (oral): 500 mg given every 12 hours	**Ciprofloxacin** (oral): 15 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 50 mg given every 12 hours 6–< 10 kg: 100 mg given every 12 hours 10–< 15 kg: 150 mg given every 12 hours 15–< 20 kg: 200 mg given every 12 hours 20–< 30 kg: 300 mg given every 12 hours ≥ 30 kg: use adult dose	Mild cases: 7 days Severe cases: 10 days if the patient is clinically improving and without a fever for 48 hours
High	**Mild cases** **Azithromycin** [c] (oral): 1 g given once a day (on day one) followed by 500 mg given once a day **Severe cases** **Ceftriaxone** [d] (IV): 2 g given once a day	**Mild cases** **Azithromycin** (oral): 20 mg/kg/dose given once a day **Severe cases** **Ceftriaxone** [d] (IV): 80 mg/kg/dose given once a day	

IV: intravenous.
Note. All dosages are for normal renal and hepatic function.
[a] It should be noted that there is no clearly defined prevalence of resistance in a certain setting that defines low versus high risk of fluoroquinolone resistance.
[b] The use of fluoroquinolones (such as ciprofloxacin) can be associated with important side-effects including: (i) mental health disturbances such as disorientation, agitation, nervousness, memory impairment and delirium; (ii) serious blood sugar disturbances such as hypoglycaemic coma; (iii) increased risk of tendinitis and tendon rupture; (iv) worsening symptoms in those with myasthenia gravis; and (v) potential irreversible neuropathy (serious nerve damage).
[c] Azithromycin can cause abnormal changes in the electrical activity of the heart leading to a potentially fatal irregular heart rhythm especially in patients with known risk factors such as long QT interval or arrhythmias.

continues

Table 15.2 *continued*

[d] In settings where ceftriaxone-resistance is increasing, azithromycin should be prioritized. Outbreaks of enteric fever caused by extensively antibiotic-resistant *Salmonella* Typhi have been reported, for example, in Pakistan since 2016 *(159)* and in travel-related cases across the world *(162–164)*. In general, when ceftriaxone is used, changing to oral treatment could be considered when there is symptomatic improvement. If available, the choice of oral options to use could be guided by results of susceptibility testing, including the possibility of using certain first-choice options that were used in the past.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Combination treatment

Currently, a single antibiotic regimen is recommended. However, the combination of a third-generation cephalosporin (ceftriaxone) and azithromycin has been reported to reduce the duration of symptoms. This approach is suggested in some guidelines for severe cases *(160,161)*.

Prevention

Access to safe water and adequate sanitation, health education, appropriate hygiene among food handlers and typhoid vaccination are all effective strategies for prevention and control of enteric fever. For updated information on vaccines to prevent enteric fever, please refer to the 2018 WHO position paper on typhoid vaccines *(154)*. Vaccination should be prioritized in countries with the highest burden of enteric fever (especially where antibiotic resistance is high) and in response to confirmed outbreaks. Single-dose typhoid conjugated vaccines are also available that can be used in younger children (from the age of 6 months onwards) and confer prolonged duration of protection. Recommendations on these newer vaccines can also be found in the 2018 WHO position paper *(154)*.

16. Skin and soft tissue infections – mild bacterial impetigo, erysipelas and cellulitis

This chapter does not cover severe skin infections or skin infections caused by viral, fungal or parasitic pathogens, or management of diabetic foot infections. Please refer to the specific chapters about other skin and soft tissue infections – traumatic wounds (including bite wounds), burn wounds, necrotizing fasciitis, pyomyositis, if these infections are suspected.

Key messages

- Topical treatment can be used for mild impetigo.
- Diagnostic tests are usually not needed in mild cases (avoid swabs of intact skin).
- The most likely causative pathogens are *Staphylococcus aureus* and *Streptococcus* spp.
- Oral antibiotics of the Access group are adequate for most cases.
- There is no need to empirically treat for MRSA in most cases.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.

Definition

The terminology used to define skin and soft tissue infections has changed over the years. In general, the terms bacterial skin and soft tissue infections and bacterial skin and skin structures infections are often used interchangeably.

While there is no universally accepted classification of skin infections, there are numerous ways to classify skin and soft tissue infections based on certain characteristics of the infection such as anatomic location (folliculitis, fasciitis, myositis), body location (e.g. extremities, face), timing (acute, chronic, recurrent), presence of tissue necrosis (necrotizing or not necrotizing), macroscopic presence of pus (purulent or non-purulent) or involvement

of deep subcutaneous tissue and/or severity of disease (complicated or uncomplicated). Further classifications are based on the origin of the infection (bites, burns; see corresponding chapters) or host characteristics (e.g. immunosuppression, diabetes).

A more recent definition by the United States Food and Drug Administration uses the term acute bacterial skin and skin structure infections (ABSSSI) to include a subset of conditions such as cellulitis and erysipelas, wound infections and major cutaneous abscesses, provided the area of the skin surface affected is at least 75 cm^2. This definition was introduced "to assist sponsors developing drugs for the treatment of skin infections" and has limited clinical applicability outside trials *(165)*.

This chapter focuses on the mild superficial forms of skin infections that do not affect deeper tissue layers: impetigo, erysipelas and cellulitis. For the more severe forms of skin and soft tissue infections, please refer to the corresponding chapters: necrotizing fasciitis, pyomyositis, burn wounds and severe infections with sepsis. The following syndromes are not covered in the current edition of the AWaRe book: acne, diabetic foot infections and surgical site infections.

Impetigo / Erysipelas / Cellulitis

Skin and soft tissue infection

Definition

Superficial bacterial skin infections, not affecting the deeper tissue layers

Diagnosis

Clinical Presentation

Impetigo: Acute onset of superficial skin lesions usually without systemic symptoms
- Most cases: papules progressing to vesicles and pustules that break to form crusts (**non-bullous form**)
- Minority of cases: vesicles evolve to form larger bullae (**bullous form**)

Erysipelas: Acute onset of a painful red skin lesion with well-defined indurated margins usually on face or legs
- Bullae may be present or develop in first days
- Fever (≥ 38.0 °C) and other signs of systemic infection may be present

Cellulitis: Acute onset of a skin lesion presenting with redness, swelling and induration, warmth and pain or tenderness of the affected area
- Most commonly affected areas: legs and face
- Fever (≥ 38.0 °C) and other signs of systemic infection may be present
- Redness alone may not indicate an infection
- **A clear clinical distinction between cellulitis and erysipelas is often difficult to make**

Microbiology Tests

Not needed in most mild cases
- Tissue swab cultures are to be avoided, especially in case of intact skin

Other Laboratory Tests

Not needed in most mild cases

Imaging

Routine imaging of mild cases not necessary
- Ultrasound may be considered if abscess or subdermal involvement suspected

Most Likely Pathogens

Bacteria (most cases):
- *Streptococcus pyogenes* (group A *Streptococcus*) - especially in case of erysipelas
- *Staphylococcus aureus* (including MRSA)

Additional bacteria (more rarely e.g immunocompromised and/or diabetic patients, traumatic skin lesions):
- *Enterobacterales*
- *Pseudomonas* spp.
- Anaerobes

This guidance excludes skin infections caused by viral, fungal or parasitic pathogens; diabetic foot infections; necrotizing fasciitis; pyomyositis; severe infections with sepsis; and surgical site infections

Treatment

Clinical Considerations

- **Empiric antibiotic options** need to have good activity against both *Streptococcus pyogenes* (group A *Streptococcus*) and MSSA
- **Empiric treatment against community-acquired MRSA**: Consider in selected cases based on individual risk factors, known colonization and local prevalence
- **Mild infections**: Oral treatment is adequate
- **Intravenous antibiotics**: May be required if infection rapidly spreading and not responding to oral antibiotics

Antibiotic Treatment Duration

Treat for **5 days**
Longer durations may be required in case of no clinical improvement or if an underlying medical condition is present

Topical Treatment

Localized non-bullous impetigo: Topical treatment is preferred over an oral antibiotic, whenever possible.
For example, a 5 day course with mupirocin 2% ointment

Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**

OR

ACCESS Cefalexin 500 mg q8h **ORAL**

OR

ACCESS Cloxacillin 500 mg q6h **ORAL**

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible (except for bite wounds)

If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Impetigo / Erysipelas / Cellulitis

Skin and soft tissue infection • Page 1 of 2

This guidance excludes skin infections caused by viral, fungal or parasitic pathogens; necrotizing fasciitis; pyomyositis; severe infections with sepsis; and surgical site infections

Definition

Superficial bacterial skin infections, not affecting the deeper tissue layers

Most Likely Pathogens

Bacteria (most cases):
• *Streptococcus pyogenes* (group A *Streptococcus*) - especially in case of erysipelas
• *Staphylococcus aureus* (including MRSA)

Diagnosis

Clinical Presentation

Impetigo: Acute onset of superficial skin lesions usually without systemic symptoms
• Most cases: papules progressing to vesicles and pustules that break to form crusts (**non-bullous form**)
• Minority of cases: vesicles evolve to form larger bullae (**bullous form**)

Erysipelas: Acute onset of a painful red skin lesion with well-defined indurated margins usually on face or legs
• Bullae may be present or develop in first days
• Fever (≥ 38.0 °C) and other signs of systemic infection may be present

Cellulitis: Acute onset of a skin lesion presenting with redness, swelling and induration, warmth and pain or tenderness of the affected area
• Most commonly affected areas: legs and face
• Fever (≥ 38.0 °C) and other signs of systemic infection may be present
• Redness alone may not indicate an infection
• **A clear clinical distinction between cellulitis and erysipelas is often difficult to make**

Microbiology Tests

Not needed in most mild cases
• Tissue swab cultures are to be avoided, especially in case of intact skin

Other Laboratory Tests

Not needed in most mild cases

Imaging

Routine imaging of mild cases not necessary
• Ultrasound may be considered if abscess or subdermal involvement suspected

Impetigo / Erysipelas / Cellulitis

Skin and soft tissue infection • Page 2 of 2

Treatment

Clinical Considerations

- **Empiric antibiotic options** need to have good activity against both Group A *Streptococcus* and MSSA
- **Empiric treatment against community-acquired MRSA**: Consider in selected cases based on individual risk factors, known colonization and local prevalence
- **Mild infections**: Oral treatment is adequate
- **Intravenous antibiotics**: May be required if infection rapidly spreading and not responding to oral antibiotics

Antibiotic Treatment Duration

Treat for **5 days**

Longer durations may be required in case of no clinical improvement or if an underlying medical condition is present

Topical Treatment

Localized non-bullous impetigo: Topical treatment is preferred over an oral antibiotic, whenever possible.
For example, a 5 day course with mupirocin 2% ointment

Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS

Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**
• **Oral weight bands**:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin
Oral liquid must be refrigerated after reconstitution

OR

ACCESS

Cefalexin 25 mg/kg/dose q12h **ORAL**
• **Oral weight bands**:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR

ACCESS

Cloxacillin 15 mg/kg/dose q6h **ORAL**
• **Oral weight bands**:

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

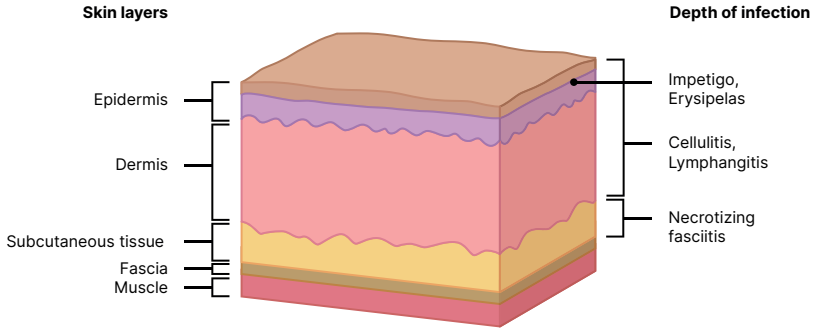
Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible (except for bite wounds)

If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Pathophysiology

Damage of the skin can lead to infections of the deeper layers beneath the epidermis. When such damage occurs, both endogenous pathogens (i.e. that naturally reside in the body) and exogenous pathogens (i.e. that enter the body from the environment) can penetrate the epidermis and spread to deeper structures through the lymphatic system. Depending on the depth of the infection, different clinical diseases can occur: impetigo and erysipelas (infections of the upper layer of the skin) and cellulitis (infection of the deep dermis and subcutaneous tissue) (Figure 16.1). Cellulitis of the face can also occur as a consequence of local spreading of a dental infection, for example, dental abscess spreading to the surrounding soft tissue can result in cellulitis.

Figure 16.1 – Anatomy of the skin and locations of common infections



Epidemiology

Bacterial skin infections occur worldwide and can affect all age groups; erysipelas is more frequent in children and elderly patients. In 2013, skin diseases (not limited to bacterial infections) were the fourth leading cause of non-fatal diseases *(166)*. Cellulitis, the most common skin infection, accounted for 0.04% (4 in 10 000) of the overall burden of all diseases combined in 2013. It was the only skin condition that showed a significant decrease (–13.2%) between 2005 and 2013 in disability-adjusted life years (DALYs), a proxy for morbidity and mortality. This decrease was attributed to reduced mortality *(166)*. In 2017, the Global Burden of Disease study reported 43 million new cases of cellulitis worldwide *(44)*. Diabetes, peripheral arterial disease, HIV infection and other causes of immunosuppression are risk factors for severe skin infections.

Most likely pathogens

The most common pathogens causing skin infections are listed in Table 16.1.

Table 16.1 – Pathogens most frequently associated with skin infections (in descending order of frequency)

Most cases	More rarely (e.g. in immunocompromised and/or diabetic patients, traumatic skin lesions)	Cases with specific environmental exposures
Streptococcus pyogenes (group A *Streptococcus*), especially in the case of erysipelas *Staphylococcus aureus* (including MRSA)	Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases) *Pseudomonas aeruginosa* (including multidrug-resistant strains such as those producing ESBL and carbapenemases) Anaerobes	*Aeromonas hydrophila* (exposure to fresh water) *Erysipelothrix rhusiopathiae* (contact with animals colonized with the organism, mostly pigs and fish) *Vibrio vulnificus* (exposure to seawater)

ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*.

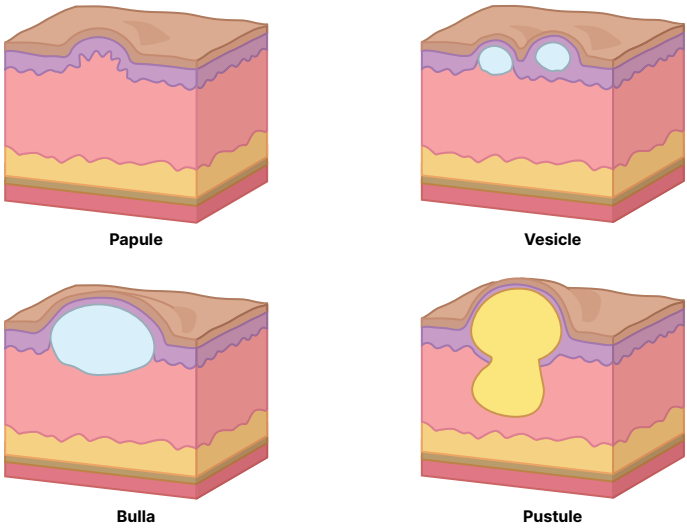
Clinical presentation (only mild cases are covered)

The morphology of different skin lesions is described in Table 16.2 and illustrated in Figure 16.2.

Table 16.2 – Morphology of skin lesions

Type of skin lesion	Morphology
Bulla	Larger (> 10 mm) fluid-filled blister
Papule	Small (< 10 mm), elevated lesion that can be palpated
Pustule	Small (< 10 mm) vesicle containing pus
Vesicle	Small (< 10 mm) fluid-filled blister

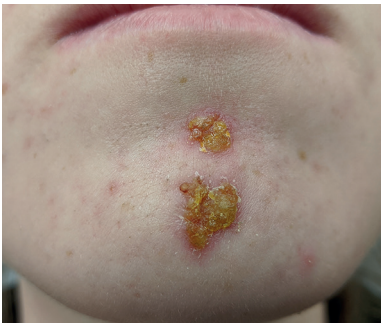
Figure 16.2 – Types and morphology of skin lesions



Impetigo

Impetigo is characterized by acute onset of superficial skin lesions usually without associated systemic symptoms. In most cases, impetigo presents with papules that progress to vesicles and pustules which break to finally form crusts (non-bullous form) (Figure 16.3). In a minority of cases (mostly in young children), vesicles develop to form larger bullae (bullous form).

Figure 16.3 – Case of impetigo on the chin

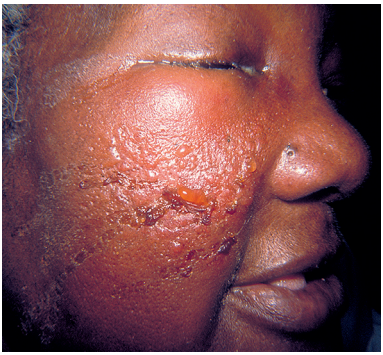


Source:© James Heilman, MD, CC BY-SA 4.0, via Wikimedia Commons

Erysipelas

Erysipelas is characterized by acute onset of a red skin lesion with well defined indurated margins, usually on the face or legs (Figure 16.4). Bullae may be present or develop in the first few days. The lesion is usually painful. Fever (≥ 38.0 °C) and other signs of systemic infection (e.g. tachycardia, leukocytosis) may be present.

Figure 16.4 – Case of erysipelas on the cheek



Source: CDC Public Health Image Library/Dr Thomas F. Sellers, Emory University

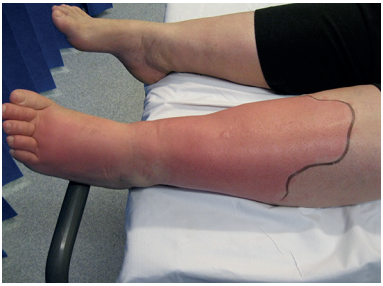
Cellulitis

While erysipelas affects only the superficial skin layers and has clearly demarcated borders, cellulitis also affects subcutaneous tissues. Cellulitis is characterized by an acute onset of a skin lesion presenting with a combination of redness, swelling and induration, warmth and pain (or tenderness) of the affected area (see Figure 16.5). The condition can occur anywhere on the body, but predominantly affects the skin of the lower part of the legs and feet or the face.

In patients with cellulitis, fever (≥ 38.0 °C) and other signs of systemic infection (e.g. tachycardia, leukocytosis) may be present. Skin redness alone may not indicate an infection, for example, redness is often present in patients with chronic venous stasis – bilateral versus unilateral involvement may indicate a non-infectious etiology, although bilateral cellulitis can occasionally occur. The severity of the infection should always be carefully assessed, especially to exclude the possibility of involvement of the muscular fascia (fasciitis). Facial and neck cellulitis, commonly arising from dental infection, can lead to potentially fatal deep space infections such as Ludwig angina. Cellulitis of the face can spread to the brain

and lead to serious complications such as cavernous sinus thrombosis. These are medical emergencies but are overall rare.

Figure 16.5 – Case of cellulitis in the lower leg



Source: John Campbell, CC0 1.0 Universal (CC0 1.0), via Flickr

Laboratory tests

Patient microbiology tests

Most mild cases of impetigo, erysipelas and cellulitis do not require routine microbiology tests. Surface swabs of intact, unbroken skin should not be taken in cases of erysipelas or cellulitis to avoid detecting pathogens that colonize the skin leading to unnecessary antibiotic treatment.

Tissue swab cultures can be considered in certain cases (Table 16.3). For example, cultures could be done for lesions that are clearly purulent (therefore most likely due to *Staphylococcus aureus*) to diagnose or exclude the presence of methicillin-resistant *Staphylococcus aureus* (MRSA). However, in many settings doing tissue swab cultures is not standard practice outside of the operating theatre. When swabs are taken, the lesion should always be cleaned and debrided before sample collection to identify the pathogens causing the infection and not colonizing organisms. For a correct interpretation of cultures, it is very important that the origin of the culture (exact location, superficial swab or intraoperatively obtained culture) is adequately documented.

Cultures can be considered for chronic lesions such as diabetic foot infections (not covered in this chapter) to exclude the presence of multidrug-resistant organisms, for example, those producing extended-spectrum beta-lactamases (ESBLs).

Table 16.3 – Microbiology tests to consider for the diagnosis of skin infections in certain cases as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Tissue swab culture and antimicrobial susceptibility testing	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

Other tests

Routine laboratory tests are not required in mild cases *(167)*.

Using microbiology surveillance data

Routine surveillance is not helpful in informing empiric guidance.

Imaging

Routine imaging of mild cases of impetigo, erysipelas and cellulitis is not necessary. However, initial imaging (e.g. ultrasound, X-ray) may be considered if an abscess or subdermal involvement are suspected. In these cases, management often requires a surgical approach, for example, incision and drainage in case of abscess and management of the primary dental cause.

Topical treatment (only for localized non-bullous impetigo)

For localized non-bullous impetigo, topical treatment could be considered as an alternative to oral antibiotics. This treatment can be as effective as oral antibiotic treatment and has the advantage that the risk of adverse events is minimal because of less systemic absorption *(168)*.

Of the different topical treatments available, mupirocin ointment (2%) could be considered for a short course of treatment (5 days). However, widespread use of mupirocin can rapidly increase resistance to mupirocin in *Staphylococcus aureus* and limit its usefulness for targeted preventive purposes in carriers of *Staphylococcus aureus*; mupirocin is active against both methicillin-susceptible *Staphylococcus aureus* and MRSA. Alternative treatments are available but they are not included in the EML and EMLc *(8,9)*. These alternatives are fusidic acid and hydrogen peroxide cream (1%). Topical corticosteroids should not be used routinely in these cases.

Antibiotic treatment (for widespread impetigo, erysipelas and cellulitis)

In most cases of mild infections, oral antibiotic treatment is adequate (Table 16.4). Empiric antibiotic options need to have good activity against the most likely pathogens (*Streptococcus* spp. and *Staphylococcus aureus*). Empiric treatment against community-acquired MRSA may be considered in certain cases (e.g. clearly purulent lesions) based on individual risk factors (e.g. known MRSA colonization) and on the local prevalence of community-acquired MRSA. In these cases, the literature suggests using clindamycin or sulfamethoxazole+trimethoprim; these options are however not currently listed in the EML and EMLc for this indication.

Table 16.4 – Empiric antibiotic treatment for mild skin infections

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Note

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these two antibiotics are the preferred options whenever possible.

Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours **OR** **Cefalexin** (oral): 500 mg given every 8 hours **OR** **Cloxacillin** [a] (oral): 500 mg given every 6 hours	**Amoxicillin+clavulanic acid** [b] (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours **OR**	5 days[d]

continues

Table 16.4 *continued*

Adults	Children	Total treatment duration
	Cefalexin (oral): 25 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 125 mg given every 12 hours 6–< 10 kg: 250 mg given every 12 hours 10–< 15 kg: 375 mg given every 12 hours 15–< 20 kg: 500 mg given every 12 hours 20–< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose **OR** **Cloxacillin** [a,c] (oral): 15 mg/kg/dose given every 6 hours Oral weight bands: 3–< 6 kg: 62.5 mg given every 6 hours 6–< 10 kg: 125 mg given every 6 hours 10–< 15 kg: 250 mg given every 6 hours 15–< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours	

Note. All dosages are for normal renal and hepatic function.
[a] If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used.
[b] Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.
[c] The WHO *Pocket book of hospital care for children (31)* suggests amoxicillin plus cloxacillin. However, cloxacillin can be safely used as a single antibiotic option because it has good activity against both methicillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes* (often referred to as group A *Streptococcus*). Amoxicillin alone is not suitable because it has variable activity against methicillin-susceptible *Staphylococcus aureus*.
[d] The optimal duration of antibiotic treatment is not known *(169)*; duration is often individualized based on clinical response.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

17. Burn wound-related infections

Key messages

- Burn wounds predispose to infections (damage of the skin's protective barrier, immunosuppression in severe cases) and should be monitored for signs of cellulitis (redness, pain and swelling around the wound).
- Avoid the routine use of antibiotics to prevent infections if there are no signs of systemic infection and in otherwise healthy patients.
- Mild infections should be treated with antibiotics with good activity against the most likely pathogens (Gram-positive bacteria from the skin microbiota)
- Multidrug-resistant organisms are a major concern in patients with severe burn wounds often because of prolonged hospitalization and frequent antibiotic exposure.
- Sepsis and septic shock are a frequent complication of severe burns.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.
- Burns – fact sheet *(170)*.

Definition

A burn wound is an injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction or contact with chemicals. Burns can be classified based on the cause and depth of the burn.

Burn wound-related infections

Definition

An injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction or contact with chemicals. Burns can be classified based on cause and depth of the burn

Diagnosis

Clinical Presentation

Diagnosis of a wound infection relies on the clinical examination
- Burn wounds should be monitored for signs of infection such as increased pain, redness or swelling of the area surrounding the wound
- Redness alone may not indicate infection
- Signs of invasive infection (e.g. change in wound colour, signs of sepsis) should be carefully monitored

Microbiology Tests

- Routine testing (including wound cultures) is not needed in mild cases with no signs of systemic infection
- Identifying the pathogen in mild cases will not benefit the patient as it will rarely change management
- In severe cases, refer to the Sepsis infographic if this is suspected

Other Laboratory Tests

- Routine testing is not needed in mild cases with no signs of systemic infection
- Because of the inflammatory response associated with the burn, biomarkers of infection are of limited use to diagnose bacterial infections

Imaging

Routine imaging not necessary

Most Likely Pathogens

Mostly polymicrobial. Hospital-acquired multidrug-resistant organisms are a major concern in burn patients often because of prolonged hospitalization and frequent antibiotic exposure

Early after the injury:
- *Streptococcus* spp.
- *Staphylococcus aureus* (including MRSA)
- *Staphylococcus* spp. other than *S. aureus*
- *Enterobacterales**

During hospitalization:
- *Pseudomonas aeruginosa**
- *Acinetobacter baumannii**
- Fungi (e.g. *Candida* spp.)

**Including multidrug-resistant strains*

This guidance excludes severe infections

Treatment

Clinical Considerations

- Meticulous observation of infection control procedures to prevent transmission of multidrug-resistant organisms
- Irrigation and debridement of necrotic tissue to prevent infection of the wound
- Appropriate daily cleaning and dressing of the wound
- Only infected wounds should be treated
- Coverage against MRSA may be considered based on local prevalence and on individual risk factors

Antibiotic Treatment Duration

Treat for **5 days (mild cases)**
(Potentially longer if severe systemic infections)

Prophylactic Antibiotics

Avoid the routine use of antibiotics to prevent infections (no clear evidence of a benefit and increased risk of colonization with resistant bacteria)

Topical Treatment

Local antiseptics could be considered based on local protocols

Antibiotic Treatment

Only infected wounds should be treated

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**

OR

ACCESS Cefalexin 500 mg q8h **ORAL**

OR

ACCESS Cloxacillin 500 mg q6h **ORAL**

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible

If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Burn wound-related infections

This guidance excludes severe infections

Definition

- An injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction or contact with chemicals
- Burns can be classified based on cause and depth of the burn

Most Likely Pathogens

Mostly polymicrobial. Hospital-acquired multidrug-resistant organisms are a major concern in burn patients often because of prolonged hospitalization and frequent antibiotic exposure

Early after the injury:
- *Streptococcus* spp.
- *Staphylococcus aureus* (including MRSA)
- *Staphylococcus* spp. other than *S. aureus*
- *Enterobacterales**

During hospitalization:
- *Pseudomonas aeruginosa**
- *Acinetobacter baumannii**
- Fungi (e.g. *Candida* spp.)

**Including multidrug-resistant strains*

Diagnosis

Clinical Presentation

Diagnosis of a wound infection relies on the clinical examination
- Burn wounds should be monitored for signs of infection such as increased pain, redness or swelling of the area surrounding the wound
- Redness alone may not indicate infection
- Signs of invasive infection (e.g. change in wound colour, signs of sepsis) should be carefully monitored

Microbiology Tests

- Routine testing (including wound cultures) is not needed in mild cases with no signs of systemic infection
- Identifying the pathogen in mild cases will not benefit the patient as it will rarely change management
- In severe cases, refer to the Sepsis infographic if this is suspected

Other Laboratory Tests

- Routine testing is not needed in mild cases with no signs of systemic infection
- Because of the inflammatory response associated with the burn, biomarkers of infection are of limited use to diagnose bacterial infections

Imaging

Routine imaging not necessary

Burn wound-related infections

Treatment

Clinical Considerations

- Meticulous observation of infection control procedures to prevent transmission of multidrug-resistant organisms
- Irrigation and debridement of necrotic tissue to prevent infection of the wound
- Appropriate daily cleaning and dressing of the wound
- Only infected wounds should be treated
- Coverage against MRSA may be considered based on local prevalence and on individual risk factors

Antibiotic Treatment Duration

Treat for **5 days (mild cases)**
(Potentially longer if severe systemic infections)

Prophylactic Antibiotics

Avoid the routine use of antibiotics to prevent infections (no clear evidence of a benefit and increased risk of colonization with resistant bacteria)

Topical Treatment

Local antiseptics could be considered based on local protocols

Antibiotic Treatment

Only infected wounds should be treated

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS

Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**
• **Oral weight bands**:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin
Oral liquid must be refrigerated after reconstitution

OR

ACCESS

Cefalexin 25 mg/kg/dose q12h **ORAL**
• **Oral weight bands**:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR

ACCESS

Cloxacillin15 mg/kg/dose q6h **ORAL**
• **Oral weight bands**:

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. From an antibiotic stewardship perspective, these would be the preferred options whenever possible

If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Pathophysiology

Burns predispose to infection because they allow entry of pathogens from the patient's own skin microbiota and the environment into the wound. Burns can also cause immunosuppression that allows rapid bacterial colonization and proliferation. Sepsis and septic shock are a frequent complication of severe burns.

Epidemiology

Burn wounds are an important public health problem in low- and middle-income countries where they are among the leading causes of DALYs lost. An estimated 180 000 deaths every year are caused by burns and most occur in low- and middle-income countries *(170)*. Infections (including but not limited to the skin) are the most frequent complications encountered in patients with burn injuries and are the leading cause of death in patients with severe wounds. Skin infections (e.g. cellulitis) are in general the first infections to occur, usually in the first week of the injury.

Most likely pathogens

Table 17.1 gives the pathogens that often infect burn wounds. In most cases, infection is caused by several pathogens. Multidrug-resistant organisms are a major concern in burn patients often because of prolonged hospitalization and frequent antibiotic exposure *(171)*.

Table 17.1 – Pathogens most frequently associated with infected burn wounds (in descending order of frequency)

Time infection acquired	Bacteria	Fungi
Soon after the injury	*Streptococcus* spp. *Staphylococcus aureus* (including MRSA) *Staphylococcus* spp. other than *Staphylococcus aureus* Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	Infrequent

continues

Table 17.1 *continued*

Time infection acquired	Bacteria	Fungi
Additionally, during hospitalization	*Pseudomonas aeruginosa* *Acinetobacter baumannii* (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	*Candida* spp.

ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*.

Clinical presentation

Diagnosis of a burn wound infection requires clinical examination. For this reason, burn wounds should be monitored for signs of infection, such as increased pain and redness or swelling of the area surrounding the wound. Redness alone may represent inflammation and does not necessarily indicate infection. Signs of invasive infection (e.g. change in the colour of the wound, signs of sepsis) should also be carefully monitored. Please also refer to the chapter on sepsis if suspected. Patients with burn injuries may also develop other complications dependent on their supportive care such as pneumonia, UTIs or catheter-related infections.

Laboratory tests

Patient microbiology tests

In mild cases of infection of a burn wound where there are no signs of systemic infection, routine testing (including wound cultures) is not required. These tests are not needed because identifying the causative pathogen in mild cases will not benefit the patient as it will not change management. In severe cases, blood cultures can be considered. Please also refer to the chapter on sepsis if suspected.

Other tests

Routine testing in mild cases with no signs of systemic infection is not required. In addition, because of the inflammatory response associated with the burn itself, results of laboratory tests (e.g. biomarkers of infection) may be of limited help.

In severe cases, certain laboratory tests can be considered to make an initial assessment of the patient and to help guide the duration of antibiotic treatment. Please also refer to the chapter on sepsis if suspected.

Using microbiology surveillance data

Targeted clinical surveys of bloodstream infection isolates at a local unit level may be helpful to inform empiric guidance. Empiric guidance should not usually be informed by routine surface skin swabs.

Imaging

Routine imaging is not required unless a complication is suspected.

Management

Irrigation and debridement of necrotic tissue to prevent infection of the burn wound is suggested. Appropriate daily cleaning and dressing of the wound are the cornerstone of treatment.

Infection control procedures should be meticulously observed to prevent transmission of multidrug-resistant organisms.

Topical treatment

Local antiseptics could be considered based on local protocols.

Preventive antibiotic use

Routine use of antibiotics to prevent infection in burn wounds should be avoided if there are no signs of systemic infection or in otherwise healthy patients. Use of antibiotics as a preventive treatment is controversial because there is no clear evidence that it can prevent infection *(172,173)*. In addition, such use can lead to colonization with resistant microorganisms, so caution is needed.

Antibiotic treatment

Empiric treatment of mild infections should include antibiotics with good activity against the most likely pathogens, *Staphylococcus aureus* and *Streptococcus* spp. Antibiotic options are shown in Table 17.2. Empiric treatment against community-acquired MRSA may be considered and should be based on local prevalence of invasive isolates and individual patient risk factors (e.g. known MRSA colonization).

It is important to note that because hospital-acquired multidrug-resistant organisms are frequently found in burn units, the results of microbiology cultures should where possible guide antibiotic treatment. Empiric use of RESERVE group antibiotics should, however, generally be avoided unless there is a high suspicion of the infection being caused by multidrug-resistant organisms. Please also refer to the chapter on sepsis if suspected.

Note

Only infected wounds should be treated with antibiotics

Table 17.2 – Empiric antibiotic treatment for mild burn wound infections

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Note

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these two antibiotics are the preferred options whenever possible.

Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours **OR** **Cefalexin** (oral): 500 mg given every 8 hours **OR** **Cloxacillin** [a] (oral): 500 mg given every 6 hours	**Amoxicillin+clavulanic acid** [b] (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours **OR**	5 days

continues

Table 17.2 *continued*

Adults	Children	Total treatment duration
	Cefalexin (oral): 25 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 125 mg given every 12 hours 6–< 10 kg: 250 mg given every 12 hours 10–< 15 kg: 375 mg given every 12 hours 15–< 20 kg: 500 mg given every 12 hours 20–< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose **OR** **Cloxacillin** [a,c] (oral): 15 mg/kg/dose given every 6 hours Oral weight bands: 3–< 6 kg: 62.5 mg given every 6 hours 6–< 10 kg: 125 mg given every 6 hours 10–< 15 kg: 250 mg given every 6 hours 15–< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours	

Note. All dosages are for normal renal and hepatic function.

[a] If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used.

[b] Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

[c] The WHO *Pocket book of hospital care for children* suggests amoxicillin plus cloxacillin; however, cloxacillin can be safely used as a single antibiotic option since it has good activity against both methicillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes*. Amoxicillin alone is not suitable because it has variable activity against methicillin-susceptible *Staphylococcus aureus*.

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

18. Wound and bite-related infections

Note

This chapter does not include severe infections, surgical wounds and management of bites from poisonous animals or arthropods (insects, ticks, mites).

Please refer to the specific chapters about other skin and soft tissue infections – burn wounds, impetigo/erysipelas/cellulitis, necrotizing fasciitis, pyomyositis, if these infections are suspected.

Key messages

- In general, uninfected wounds **do not require antibiotic treatment** except in very select cases.
- Skin wounds predispose to infection (e.g. cellulitis) but not every wound becomes infected. In fact, only a minority of wounds become infected in immunocompetent people.
- Adequate cleaning and debridement of the skin wound are the cornerstone of initial treatment.
- Need for post-exposure prophylaxis for certain infectious diseases (e.g. tetanus, rabies) should always be evaluated on a case-by-case basis.
- The presence of signs of invasive infection should always be carefully evaluated.

Other relevant WHO resources (please check regularly for updates)

- Prevention and management of wound infections, 2013 *(174)*.
- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.
- Snakebite envenoming – health topic *(175)*.
- Snakebite envenoming: a strategy for prevention and control, 2019 *(176)*.
- Global status report on road safety, 2018 *(177)*.
- Tetanus vaccines: WHO position paper – February 2017 *(178)*.
- Rabies vaccines: WHO position paper – April 2018 *(179)*.
- Hepatitis B vaccines: WHO position paper – July 2017 *(180)*.
- Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update *(181)*.

Definition

Skin wounds include any traumatic injury characterized by damage to and exposure of deeper skin tissue. Examples of skin wounds include those caused by human or animal bites or burns, road traffic injuries, and gunshot and stab wounds. The severity of the clinical findings can vary from mild wounds with no systemic involvement to severe infections including tetanus (infection by *Clostridium tetani*) and gas gangrene (infection by gas-producing bacteria such as *Clostridium perfringens*).

Wound and bite-related infections

This guidance excludes severe infections, surgical wounds and management of bites from arthropods and poisonous animals

Definition

Any traumatic skin injury characterized by damage and exposure of deeper skin tissue

Diagnosis

Clinical Presentation

Infection may or may not be present at time of clinical evaluation

- *Superficial infections*: Symptoms of cellulitis (redness, swelling, warmth, lymphangitis, pain around wound)
- *Invasive wound infection*: Change in wound colour, signs of sepsis (should be carefully monitored)

Laboratory Tests

Routine testing not needed in mild cases with no signs of systemic infection

Imaging

Routine imaging not necessary

- May be considered in selected cases based on extent and depth of lesion

Most Likely Pathogens

Infection commonly polymicrobial (mix of human skin and animal oral microbiota, and environmental organisms)

Wounds

Most cases:
- *Streptococcus* spp.
- *Staphylococcus aureus* (including MRSA)

More rarely:
- Anaerobes
- Enterobacterales
- *Enterococcus* spp.
- *Clostridium tetani* (soil contaminant)

Bites

Human:
- Anaerobes
- *Streptococcus* spp.
- *Staphylococcus aureus*

Dog:
- Anaerobes
- *Capnocytophaga canimorsus*
- *Pasteurella multocida*
- *Staphylococcus aureus*

Reptile:
- Anaerobes
- Enterobacterales
- *Pseudomonas aeruginosa*

Cat:
- Anaerobes
- *Pasteurella multocida*
- *Staphylococcus aureus*

Monkey:
- Anaerobes
- *Streptococcus* spp.
- *Staphylococcus aureus*

Rodent:
- *Pasteurella multocida*

Wound and bite-related infections

Treatment

Clinical Considerations

- **Rapidly after injury**: Thorough washing and flushing of the wound (~15 minutes), with soap or detergent and copious amounts of water followed by debridement and immobilization
- **Risk of tetanus and rabies**: Quickly evaluate need to provide adequate post-exposure prophylaxis
- **Signs/symptoms of infection**: Empiric treatment should include antibiotics with good activity against most likely pathogens *(Staphylococcus* spp. and *Streptococcus* spp. and anaerobes)
- **Animal/human bites**: Empiric treatment against both aerobic and anaerobic bacteria required; empiric treatment against community-acquired MRSA usually not required

WHO Guidance

- Rabies: https://apps.who.int/iris/handle/10665/272372
- Tetanus: https://apps.who.int/iris/handle/10665/254583

Antibiotic Treatment Duration

Treat for **5 days**

Prophylactic Antibiotics

- In the absence of systemic signs of infection avoid antibiotics to prevent infections in otherwise healthy patients
- No clear evidence that antibiotics can prevent the infection
- Consider in selected cases (e.g. severely immunocompromised patients) and/or high-risk clinical areas (face, hands, near joints)
- Duration: 3 days

Bite-related wounds

Only infected wounds should be treated

All dosages are for normal renal function

ACCESS Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**

Amoxicillin+clavulanic acid is the preferred treatment option for bite wound infections because of its activity against anaerobic bacteria.

Not bite-related wounds

Only infected wounds should be treated

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**

OR

ACCESS Cefalexin 500 mg q8h **ORAL**

OR

ACCESS Cloxacillin 500 mg q6h **ORAL**

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in other cases of mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these would be the preferred options whenever possible (except for bite wounds)

If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Wound and bite-related infections

This guidance excludes severe infections, surgical wounds and management of bites from arthropods and poisonous animals

Definition

Any traumatic skin injury characterized by damage and exposure of deeper skin tissue

Diagnosis

Clinical Presentation

Infection may or may not be present at time of clinical evaluation

- *Superficial infections*: Symptoms of cellulitis (redness, swelling, warmth, lymphangitis, pain around wound)
- *Invasive wound infection*: Change in wound colour, signs of sepsis (should be carefully monitored)

Laboratory Tests

Routine testing not needed in mild cases with no signs of systemic infection

Imaging

Routine imaging not necessary

- May be considered in selected cases based on extent and depth of lesion

Most Likely Pathogens

Infection commonly polymicrobial (mix of human skin and animal oral microbiota, and environmental organisms)

Wounds

Most cases:
- *Streptococcus* spp.
- *Staphylococcus aureus* (including MRSA strains)

More rarely:
- Anaerobes
- Enterobacterales
- *Enterococcus* spp.
- *Clostridium tetani* (soil contaminant)

Bites

Human:
- Anaerobes
- *Streptococcus* spp.
- *Staphylococcus aureus*

Dog:
- Anaerobes
- *Capnocytophaga canimorsus*
- *Pasteurella multocida*
- *Staphylococcus aureus*

Reptile:
- Anaerobes
- Enterobacterales
- *Pseudomonas aeruginosa*

Cat:
- Anaerobes
- *Pasteurella multocida*
- *Staphylococcus aureus*

Monkey:
- Anaerobes
- *Streptococcus* spp.
- *Staphylococcus aureus*

Rodent:
- *Pasteurella multocida*

Wound and bite-related infections

Treatment

Clinical Considerations

- **Rapidly after injury**: Thorough washing and flushing of the wound (~15 minutes), with soap or detergent and copious amounts of water followed by debridement and immobilization
- **Risk of tetanus and rabies**: Quickly evaluate need to provide adequate post-exposure prophylaxis
- **Signs/symptoms of infection**: Empiric treatment should include antibiotics with good activity against most likely pathogens (*Staphylococcus* spp. and *Streptococcus* spp. and anaerobes)
- **Animal/human bites**: Empiric treatment against both aerobic and anaerobic bacteria required; empiric treatment against community-acquired MRSA usually not required

WHO Guidance

- Rabies: https://apps.who.int/iris/handle/10665/272372
- Tetanus: https://apps.who.int/iris/handle/10665/254583

Prophylactic Antibiotics

- In the absence of systemic signs of infection avoid antibiotics to prevent infections in otherwise healthy patients
- No clear evidence that antibiotics can prevent the infection
- Consider in selected cases (e.g. severely immunocompromised patients) and/or high-risk clinical areas (face, hands, near joints)
- Duration: 3 days

Bite-related wounds

Only infected wounds should be treated

All dosages are for normal renal function

ACCESS

Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**
- **Oral weight bands**:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin
Oral liquid must be refrigerated after reconstitution
Amoxicillin+clavulanic acid is the preferred treatment option for bite wound infections because of its activity against anaerobic bacteria.

Antibiotic Treatment Duration

Treat for **5 days**

Not bite-related wounds

Only infected wounds should be treated

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS

Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**
- **Oral weight bands**:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Amox = amoxicillin
Oral liquid must be refrigerated after reconstitution

OR

ACCESS

Cefalexin 25 mg/kg/dose q12h **ORAL**
- **Oral weight bands**:

3-<6 kg	125 mg q12h
6-<10 kg	250 mg q12h
10-<15 kg	375 mg q12h
15-<20 kg	500 mg q12h
20-<30 kg	625 mg q12h
≥30 kg	500 mg q8h

OR

ACCESS

Cloxacillin15 mg/kg/dose q6h **ORAL**
- **Oral weight bands**:

3-<6 kg	62.5 mg q6h
6-<10 kg	125 mg q6h
10-<15 kg	250 mg q6h
15-<20 kg	375 mg q6h
≥20 kg	500 mg q6h

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in other cases of mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these would be the preferred options whenever possible (except for bite wounds)
If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used

Pathophysiology

Skin wounds predispose to infection because they facilitate entry of pathogens from the patient's own skin microbiota and the environment into the wound. With bites, pathogens from the oral cavity of the biting animal can also penetrate the skin.

Epidemiology

Traumatic wounds

Road traffic injuries occur worldwide but the majority of deaths (> 90%) occur in low- and middle-income countries. Overall each year about 1.3 million people die as a result of road traffic incidents with many more suffering from non-fatal injuries (between 20 and 50 million people) *(177,182)*. In people younger than 30 years, this is the leading cause of death.

In 2016, the Global Burden of Disease study reported about 251 000 deaths from firearm injuries globally (outside of war settings), the majority caused by homicides (64%), followed by suicides (27%) and unintentional firearm deaths (9%). Overall, the global age-standardized rate of firearm deaths decreased by about 0.9% a year between 1990 and 2016 with differences between countries. Most firearm injury deaths occur among people aged 20 to 24 years *(183)*.

Bite wounds

Human and animal bites occur worldwide; most cases are caused by animals (dogs in > 90% of cases) *(184)*. Less frequently, bites are caused by other mammals such as cats, rodents (e.g. rats, mice) and bats. In certain countries (e.g. in Africa and in South-East Asia), snake and monkey bites are also frequently reported. Children are more likely to have animal bites *(185)*. The risk of developing a bacterial infection from a dog bite is unclear and depends on many different factors related to the patient (i.e. the person bitten), the characteristics of the bite (depth, location) and the initial management of the bite. However, available data suggest that in 10–20% of cases of dog bites, the wound will become infected *(185,186)*. In comparison, wounds caused by cat bites have a higher risk of becoming infected (up to 50%) because of the deeper penetration of their teeth *(185,186)*.

Animal bites are a significant risk factor for transmission of rabies, especially in settings where prophylaxis with rabies vaccine in domestic and wild animals is not routinely given. The Global Burden of Disease study estimated 13 400 new cases of rabies worldwide in 2017 *(44)*. Deaths from rabies and dog bites are a problem mostly in low- and middle-income countries where post-exposure treatment and appropriate access to health care may be lacking *(184)*.

Small rodents are vectors of numerous pathogens and are a reservoir for many zoonotic diseases. Rodents (mostly rats) are also responsible for an appreciable proportion of bites to humans *(187)*. Rat bites primarily affect people (mostly children < 5 years) living in poorer conditions in rat-infested environments, including in high-income countries. Most bites occur on the face and hands and usually occur at night while sleeping. Although rare, rat bites can cause severe infections, such as rat-bite fever, caused by *Streptobacillus moniliformis* or *Spirillum minus*. Tetanus infection can also be caused by bites and it should be considered in patients who have not been immunized against the infection. In 2019, almost 15 000 cases of tetanus were reported globally *(188)*.

Most likely pathogens

Traumatic wounds

In most cases, infections from traumatic wounds are polymicrobial with a mix of human skin microbiota and environmental organisms (Table 18.1).

Table 18.1 – Pathogens most frequently associated with traumatic skin wounds (in descending order of frequency), except bites, see Table 18.2

Most cases[a]	More rarely
Streptococcus spp.	Anaerobes
Staphylococcus aureus (including MRSA)	Enterobacterales
	Enterococcus spp.
	Clostridium tetani (soil contaminant)

MRSA: methicillin-resistant *Staphylococcus aureus*.
[a] Mostly Gram-positive pathogens from the skin microbiota.

Bite wounds

In infections from bites, causative pathogens may also be from the animal/human oral microbiota with differences among species (Table 18.2) *(187)*.

Table 18.2 – Pathogens most frequently associated with bites

Species causing the bite	Pathogens
Human	**Common bacterial pathogens** Anaerobes from the oral microbiota such as *Prevotella* and *Fusobacterium* spp. *Streptococcus* spp. *Staphylococcus aureus* **Non-bacterial pathogens** Hepatitis B virus Hepatitis C virus HIV
Cat	**Common bacterial pathogens** Anaerobes such as *Bacteroides* spp., *Cutibacterium* spp., *Fusobacterium* spp., *Peptostreptococcus* spp. and *Prevotella* spp. *Pasteurella multocida* *Staphylococcus aureus* **Other bacterial pathogens** *Bartonella henselae* (agent of cat-scratch disease) *Francisella tularensis* (agent of tularaemia) **Non-bacterial pathogens** Rabies virus **Soil contaminants** *Clostridium tetani* (agent of tetanus)
Dog	**Common bacterial pathogens** Anaerobes such as *Bacteroides* spp., *Cutibacterium* spp., *Fusobacterium* spp., *Peptostreptococcus* spp. and *Prevotella* spp. *Capnocytophaga canimorsus* *Pasteurella multocida* *Staphylococcus aureus* **Other bacterial pathogens** *Francisella tularensis* (agent of tularaemia) *Leptospira* spp. (agent of leptospirosis) **Non-bacterial pathogens** Rabies virus **Soil contaminants** *Clostridium tetani* (agent of tetanus)

continues

Table 18.2 *continued*

Species causing the bite	Pathogens
Monkey	**Bacterial pathogens** Anaerobes such as *Bacteroides* spp., *Cutibacterium* spp., *Fusobacterium* spp., *Peptostreptococcus* spp. and *Prevotella* spp. *Streptococcus* spp. *Staphylococcus aureus* **Non-bacterial pathogens** Hepatitis B virus (macaques) Herpes B virus Monkeypox virus Rabies virus **Soil contaminants** *Clostridium tetani* (agent of tetanus)
Rodent (e.g. mice, rats)	**Bacterial pathogens** *Francisella tularensis* (agent of tularaemia) *Leptospira* spp. (agent of leptospirosis) *Pasteurella multocida* *Spirillum minor* (agent of rat-bite fever in Asia) *Streptobacillus moniliformis* (agent of rat-bite fever in North America) **Non-bacterial pathogens** Rabies virus Monkeypox virus **Soil contaminants** *Clostridium tetani* (agent of tetanus)
Reptile (e.g. crocodiles, lizards, snakes, turtles)	**Bacterial pathogens** Anaerobes such as *Prevotella* and *Fusobacterium* spp. Enterobacterales *Pseudomonas aeruginosa* Non-typhoidal *Salmonella* spp. **Soil contaminants** *Clostridium tetani* (agent of tetanus)

Clinical presentation (only mild cases are covered)

Wounds range in severity from minor superficial abrasions to deep wounds with involvement and destruction of the deep tissues. An infection may or may not be present at the time of clinical evaluation. Usually, signs and symptoms of infection appear > 12 hours after the injury. Superficial infections may manifest with signs and symptoms of cellulitis characterized by redness, swelling, warmth, lymphangitis and pain of the area surrounding the wound. Fever (≥ 38.0 °C) may be present. Patients should also be carefully monitored for signs of invasive infection, for example, change in colour of the wound due to necrosis and signs of sepsis.

Laboratory tests

Patient microbiology tests

In mild cases with no signs of systemic infection, routine testing, including wound cultures, is not required. These tests are not needed because identifying the causative pathogen in mild cases is rare even when microbiology tests are performed, most infections are polymicrobial and microbiology results will not affect management of the condition in most cases.

Other tests

Routine testing in mild cases with no signs of systemic infection is not required.

Using microbiology surveillance data

Routine surveillance is not helpful in informing empiric guidance.

Imaging

Routine imaging is not required. Imaging may be considered in certain cases based on the size and depth of the wound, particularly if a complication, such as development of an abscess or necrotizing infection, is suspected.

No antibiotic care

Initial management of wounds

It is important to provide rapid and appropriate treatment of a wound after an injury has occurred to minimize the risk of infection. For prevention and management of wound infections, please refer to the 2013 WHO guidance publication *(174)*.

Adequate cleaning and debridement are the cornerstone of initial treatment. It is important to thoroughly wash and flush the wound for about 15 minutes with soap or detergent and a lot of clean water, followed by debridement and immobilization of the wound.

Post-exposure prophylaxis

Traumatic wounds

After any wound, the risk of tetanus needs to be promptly evaluated to provide adequate post-exposure prophylaxis by vaccination with or without passive immunization using tetanus immunoglobulin when needed according to local/international recommendations.

For tetanus post-exposure prophylaxis, please refer to the WHO tetanus vaccines position paper *(178)*.

Bite wounds

With animal bites, in addition to the risk of tetanus, the risk of rabies needs also to be rapidly evaluated based on the exposure category to provide adequate post-exposure prophylaxis when needed (Table 18.3).

For rabies post-exposure prophylaxis, please refer to the WHO rabies vaccines position paper *(179)*.

With human bites, the risk of hepatitis B and C virus and HIV transmission also needs to be evaluated and post-exposure prophylaxis offered when applicable *(180,181)*.

Table 18.3 – Risk of rabies exposure according to the type of contact with the animal suspected of having rabies *(179)*

Category[a]	Type of contact	Risk of exposure
I	Touching or feeding animals, animal licks on intact skin	No exposure
II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Exposure
III	Single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats	Severe exposure

[a] The category of exposure determines the indicated post-exposure prophylaxis procedure.

Preventive antibiotic use

Routine use of antibiotics to prevent infection of the wound is not required in most cases (unless there are systemic signs of infection in which case antibiotics would be used as treatment and not as prophylaxis) and should be discouraged.

Preventive antibiotic use may be considered in very few specific cases where the potential risk of infection is judged to outweigh the risk of overusing antibiotics.

These cases include:

- Wounds in high-risk clinical areas (e.g. face, hands, areas near a joint)
- Severely immunocompromised patients.

However, there is no clear evidence that use of antibiotics can prevent infection after a wound has occurred, including bite wounds. In addition, such use exposes the patient to the negative effects of antibiotics, for example, alteration of the intestinal microbiota, and selection of resistant microorganisms.

Antibiotic treatment

If signs and symptoms of infection are present, empiric treatment should include antibiotics with good activity against the most likely pathogens, *Staphylococcus aureus* and *Streptococcus* spp. and anaerobic organisms. With animal bites, the type of animal should also be considered (see Table 18.2), but in general, empiric treatment against both aerobic and anaerobic bacteria is required, since most infections are caused by multiple pathogens (polymicrobial infections). Empiric treatment against community-acquired MRSA is usually not required. If cellulitis around the wound develops, refer to the chapter on bacterial impetigo, erysipelas and cellulitis. Antibiotic options for empiric treatment are given in Table 18.4.

Note

Only infected wounds should be treated with antibiotics.

Table 18.4 – Empiric antibiotic treatment for mild infections from traumatic wounds and bites

Important

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Note

Amoxicillin+clavulanic acid is the preferred treatment option for **bite wound infections** because of its activity against anaerobic bacteria.

Cloxacillin and cefalexin have a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid with good efficacy in **other** cases of mild skin and soft tissue infections. Therefore, from an antibiotic stewardship perspective, these would be the preferred options whenever possible, except for bite wounds.

Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours **OR** Cefalexin (oral): 500 mg given every 8 hours **OR** Cloxacillin [a] (oral): 500 mg given every 6 hours	Amoxicillin+clavulanic acid [b] (oral): 80–90 mg/kg/day of amoxicillin component Oral weight bands: 3–< 6 kg: 250 mg of amoxicillin/dose given every 12 hours 6–< 10 kg: 375 mg of amoxicillin/dose given every 12 hours 10–< 15 kg: 500 mg of amoxicillin/dose given every 12 hours 15–< 20 kg: 750 mg of amoxicillin/dose given every 12 hours ≥ 20 kg: 500 mg of amoxicillin/dose given every 8 hours or 1 g of amoxicillin/dose given every 12 hours **OR**	3 days (preventive treatment of wounds at high risk of infection) 5 days (treatment of infected wounds)

continues

Table 18.4 *continued*

Adults	Children	Total treatment duration
	Cefalexin (oral): 25 mg/kg/dose given every 12 hours Oral weight bands: 3–< 6 kg: 125 mg given every 12 hours 6–< 10 kg: 250 mg given every 12 hours 10–< 15 kg: 375 mg given every 12 hours 15–< 20 kg: 500 mg given every 12 hours 20–< 30 kg: 625 mg given every 12 hours ≥ 30 kg: use adult dose **OR** **Cloxacillin** [a] (oral): 15 mg/kg/dose given every 6 hours Oral weight bands: 3–< 6 kg: 62.5 mg given every 6 hours 6–< 10 kg: 125 mg given every 6 hours 10–< 15 kg: 250 mg given every 6 hours 15–< 20 kg: 375 mg given every 6 hours ≥ 20 kg: 500 mg given every 6 hours	

Note. All dosages are for normal renal and hepatic function.
[a] If cloxacillin is unavailable, dicloxacillin or flucloxacillin could be used.
[b] Oral liquid formulations must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

19. Sexually transmitted infections – chlamydial urogenital infection

Note

In general this chapter applies to adults and young people older than 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.

Key messages

- *Chlamydia trachomatis* urogenital infection is a common sexually transmitted infection (STI) globally, especially among young sexually active people.
- Symptoms overlap with gonococcal infection and co-infection is frequent. Therefore, patients should be tested for both pathogens simultaneously, when available and evaluated for other STIs (e.g. human immunodeficiency virus (HIV) infection, syphilis, trichomoniasis).
- Asymptomatic people should also be treated because they can transmit the infection to others.
- Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis to people at high risk of HIV infection) and sexual partners should be informed and treated.
- Reporting of this infection to health authorities is encouraged according to local regulations.

Other relevant WHO resources (please check regularly for updates)

- Sexually transmitted infections (STIs) – fact sheets *(189)*.
- WHO guidelines for the treatment of *Chlamydia trachomatis (190)*.
- WHO guidelines for the management of symptomatic sexually transmitted infections *(191)*.
- Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus *(192)*.
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 *(193)*.

Definition

Chlamydial urogenital infection is an STI caused by certain biovars of the bacterium *Chlamydia trachomatis*.

Chlamydial urogenital infection

Sexually transmitted infection • Page 1 of 2

In general this guidance applies to adults and young people aged over 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse

For Chlamydial ocular infections (Trachoma) see separate infographic

Definition

A sexually transmitted infection (STI) caused by certain strains of the bacterium *Chlamydia trachomatis*

Pathogen

Chlamydia trachomatis is an intracellular Gram-negative bacterium; strains associated with urogenital infection are mostly genital tract biovars (serovars D to K) and rarely lymphogranuloma venereum biovar (serovars L1, L2, L3)

Prevention

Important elements of prevention include:

- Sexuality education
- Promoting consistent use of condoms
- Pre- and post-test counselling
- Safe sex and risk reduction counselling
- Interventions targeting high-risk groups

Important:

- Sexual partners should be informed of the disease and treated
- Reporting of this infection to health authorities is encouraged according to local regulations

Diagnosis

Clinical Presentation

- Most persons remain asymptomatic though they can still transmit the infection
- If symptoms occur they overlap with those of gonococcal infection (co-infection possible and common)

Most common symptoms:

- *In men*: acute urethritis with "clear" urethral discharge and dysuria
- *In women*: vaginal discharge, dyspareunia (painful intercourse), and dysuria
- *Additionally in both sexes*:
  - Symptoms of acute proctitis with pain, pruritus, anal discharge and bleeding
- Symptoms of lymphogranuloma venereum (men>women):
  - Ulcerative lesion or a papule usually on the genitalia or rectum and inguinal or femoral lymphadenopathy (usually unilateral)
  - Often the lesion remains unnoticed in women or when located in the rectum

Imaging

Usually not needed

Other Laboratory Tests

Usually not needed

Microbiology Tests

- See WHO guidance "Laboratory diagnosis of sexually transmitted infections" https://apps.who.int/iris/handle/10665/85343
- **Important**: all patients with suspected chlamydial urogenital infection should also be tested for gonococcal infection (as symptoms overlap) and other STIs (e.g. HIV, syphilis)

Reference standard:

- Nucleic acid amplification test (a test for both *Chlamydia* and *Neisseria gonorrhoeae* is available)
  - Samples that can be used: urine (lower sensitivity and specificity in women), urethral, vulvovaginal, endocervical or anorectal samples collected with a swab
  - Perform *Chlamydia* genovar testing for lymphogranuloma venereum in anorectal samples of men who have sex with men

Other tests to consider:

- Microscopy (Gram stain)
  - In a symptomatic patient, it can be used to exclude *Neisseria gonorrhoeae* (therefore suggesting non-gonococcal urethritis)
  - Leukocytes are usually present but not a specific finding for chlamydial infection
- Culture: if symptoms persist despite adequate treatment (but it is rarely performed)
- *Note: urines are not good specimens for microscopy and culture*

Chlamydial urogenital infection

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Treatment

Clinical Considerations

Treatment is aligned with the WHO 2016 guidelines for chlamydial urogenital infections (https://apps.who.int/iris/handle/10665/246165) and the WHO 2021 guidelines for the management of symptomatic sexually transmitted infections (https://apps.who.int/iris/handle/10665/342523) but only options listed in the 2021 EML are reported

Treatment is always indicated when infection is diagnosed, including in asymptomatic persons because they can transmit the infection to others

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used, please refer to the corresponding antibiotic section for treatment duration

Lymphogranuloma Venereum

All dosages are for normal renal function

ACCESS Doxycycline 100 mg q12h **ORAL**
Treatment duration: 21 days

Uncomplicated Urogenital Infection

All dosages are for normal renal function

ACCESS Doxycycline 100 mg q12h **ORAL**
Treatment duration: 7 days

OR

WATCH Azithromycin 1 g **ORAL**
Treatment duration: single dose

Recent data suggest that doxycycline is more effective than azithromycin, therefore it could be given priority if adherence is not a concern (except in pregnant women where it is contraindicated)

Anorectal Infection

All dosages are for normal renal function

ACCESS Doxycycline 100 mg q12h **ORAL**
Treatment duration: 7 days

Infection in Pregnant Women

All dosages are for normal renal function

WATCH Azithromycin 1 g **ORAL**
Treatment duration: single dose

Pathogen

Chlamydial urogenital infection is caused by *Chlamydia trachomatis*, an intracellular Gram-negative bacterium. There are several strains of *Chlamydia trachomatis* and not all are associated with STI (see the chapter on trachoma). Chlamydial urogenital infections associated with STI are caused mostly by genital tract biovars (serovars D to K) and, more rarely, lymphogranuloma venereum biovar (serovars L1, L2, L3). Lymphogranuloma venereum is an ulcerative disease extending to regional lymph nodes (often the inguinal and anorectal area) and is more common in men (see the paragraph on lymphogranuloma venereum later in this chapter). This disease is endemic in many tropical and sub-tropical regions; in other settings, the infection is most commonly seen among men who have sex with men.

Pathophysiology

Chlamydia trachomatis infects the mucosa of the urogenital tract during sexual contact and produces a local inflammatory response that causes vaginal, urethral or anal discharge. Invasive infections caused by more invasive serovars of *Chlamydia trachomatis* can also spread to regional lymph nodes.

Epidemiology

Chlamydial urogenital infection is one of the most common STIs worldwide, including in low-income settings where it is probably under-reported *(194,195)*. Young sexually active adults are at particularly high risk. Undiagnosed and untreated, chlamydial urogenital infections can lead to complications such as pelvic inflammatory disease (infection of the upper female reproductive tract), ectopic pregnancy and infertility in women *(196,197)*. Maternal infection can cause serious health problems to the child, such as preterm birth, low birth weight or conjunctivitis. The 2021 WHO global progress report on HIV, viral hepatitis and STIs reported an estimated 128 million new chlamydial infections in 2020 among adults aged 15 to 49 years *(193)*.

Clinical presentation

Signs and symptoms of chlamydial infection mostly overlap with those of gonococcal infection.

In most cases, the infection is asymptomatic, and it is therefore impossible to determine how long a person has been infected. Even in the absence of symptoms, infected individuals can transmit the infection.

When symptoms occur (usually 1–2 weeks after being infected), particularly in men, the most common clinical presentation is acute urethritis characterized by profuse usually clear urethral discharge and dysuria. Most women with chlamydial cervical infection are

asymptomatic. The ones who may be symptomatic have vaginal discharge, dyspareunia (painful intercourse) and dysuria. Some women may have lower abdominal pain or pelvic tenderness because of ascending infection, causing pelvic inflammatory disease.

In both sexes (but in males more than females), symptoms of acute proctitis with pain, pruritus, discharge and bleeding of the rectum may occur. Pharyngitis (mostly manifesting as a mild sore throat) and conjunctivitis are other conditions that usually coexist with genital infection.

Lymphogranuloma venereum is characterized by inguinal or femoral lymphadenopathy (usually unilateral) with or without an associated primary lesion. The classic lesion is a transient, ulcerative lesion or a papule usually located on the genitalia or rectum. In many cases, the lesion may remain unnoticed; for example, the infection may be completely asymptomatic in women when located on the cervix or can sometimes present with symptoms of acute urethritis in men. Rectal exposure can cause proctitis with pain, pruritus, discharge and bleeding of the rectum.

Laboratory tests

Patient microbiology tests

Molecular testing has greatly improved the detection of *Chlamydia trachomatis* (and *Neisseria gonorrhoeae*) among both symptomatic and asymptomatic men and women. Molecular testing has become the recommended reference standard technology to diagnose and screen populations for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Table 19.1 indicates the types of specimens that can be used for this purpose.

For more comprehensive information on the diagnosis of chlamydial infection, please refer to the most recent (2013) WHO guideline for the laboratory diagnosis of STIs *(192)*. Please check the WHO website regularly for possible updates.

Patients with chlamydial urogenital infection should be offered testing for HIV and other STIs, such as hepatitis B, hepatitis C, gonococcal infection and syphilis. Test of cure (i.e. testing after the end of treatment) could be considered in pregnant women 3–4 weeks after the end of treatment.

Tests to consider when chlamydial infection is suspected are listed in Table 19.1. Additional tests for other STIs that could be considered when chlamydial urogenital infection is confirmed or suspected are shown in Table 19.2. Surveillance, including etiologic studies of STI syndromes, will be important to inform local and national guidance.

If symptoms persist at review, partner notification and treatment history should be checked. People with recurrent or persistent infection should be referred to a centre with laboratory capacity to diagnose *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Trichomonas vaginalis* and to test for antibiotic-resistant *Neisseria gonorrhoeae* and *Mycoplasma genitalium*.

Table 19.1 – Microbiology tests to consider when chlamydial infection is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Qualitative test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections (i.e. nucleic acid amplification test)[a,b] **This is the recommended reference standard**	To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection	Health care facilities with clinical laboratories
Microscopy (Gram stain)[c] Gram stain of vaginal and urethral discharge will usually show the presence of leukocytes (> 10 leukocytes/high power field for urethral discharge and > 20 leukocytes/high power field for vaginal discharge) but this finding is not specific for chlamydial infections. If carried out by an experienced person, a Gram stain negative for intracellular diplococci (*Neisseria gonorrhoeae* is an intracellular diplococcus) with the presence of > 5 leukocytes/high power field in the context of urethral discharge in a man can be presumed to suggest non-gonococcal urethritis.	To assess microbial morphology, and presence or absence of white blood cells	Health care facilities with clinical laboratories
Culture[c,d] and antimicrobial susceptibility testing (rarely performed)	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

[a] Usually chlamydial and gonococcal infections are tested at the same time since their clinical presentations are very similar.

[b] Possible specimens among women, are a vulvovaginal specimen, which may be self-collected. An endocervical swab can also be an alternative but requires a speculum. First-catch urine is another option, but the sensitivity and specificity tend to be lower in women. Among men, possible specimens are first-catch urine or urethral swabs. Anorectal and pharyngeal samples are also adequate. For anorectal samples among men who have sex with men, *Chlamydia* genovar testing for lymphogranuloma venereum should be done to guide the appropriate treatment regimen for this condition.

[c] Possible specimens are urethral swabs, endocervical swabs, vaginal swabs, rectal swabs, oropharyngeal swabs and conjunctival swabs. Note. Urine samples are not good specimens for microscopy and culture.

[d] Consider culture if symptoms persist despite adequate treatment: note, urine samples are not good specimens for culture. Processing *Chlamydia trachomatis* for culture requires highly experienced laboratories and technicians and is too complex, laborious and time-consuming to be of economic value. It is rarely performed in middle- or high-income countries nowadays except for special purposes.

Table 19.2 – Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected chlamydial urogenital infection as indicated in the WHO EDL *(6)*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Gonorrhoea	*Neisseria gonorrhoeae* NAAT	To diagnose gonorrhoeal urogenital disease and extragenital infection	Health care facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories[a]
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people aged > 12 months	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)

continues

Table 19.2 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Health care facilities with clinical laboratories (immunoassay)
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people aged > 18 months	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
Syphilis	Antibodies to *Treponema pallidum*[b] (RDT)	To diagnose or help to diagnose *Treponema pallidum*	Community settings and health facilities without laboratories[a]
Syphilis and HIV (combined test)	Combined antibodies to *Treponema pallidum* and to HIV-1 and HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or *Treponema pallidum*	Community settings and health facilities without laboratories[a]
Trichomoniasis	Microscopy	To assess microbial morphology, and presence or absence of white blood cells	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; NAAT: nucleic acid amplification test; RDT: rapid diagnostic test.

[a] Community and health settings without laboratories are facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are assumed to be available at health care facilities with laboratories.

[b] Usually, a non-treponemal test (e.g. rapid plasma reagin, Venereal Disease Research Laboratory test) is used for screening. Please refer to the chapter on syphilis for more details on testing.

Other tests

When chlamydial urogenital infection is suspected, laboratory tests other than microbiology are not usually needed.

Using microbiology surveillance data

Targeted surveillance may be helpful to inform treatment policies.

Imaging

When chlamydial urogenital infection is suspected, imaging is not usually needed.

Antibiotic treatment

Antibiotic treatment is always indicated when the infection is diagnosed. Table 19.3 gives recommendations taken from the 2016 WHO guidelines on the treatment of chlamydial infections *(190)* and the 2021 WHO guidelines on the management of symptomatic STIs *(191)*. Please check the WHO website regularly for possible updates. Recommendations in the EML overlap with the WHO guidelines (azithromycin or doxycycline are the recommended treatment options) but fewer treatment alternatives are included in the EML *(8)*.

If symptoms persist at review:

- check partner notification and treatment history; and
- for people with recurrent or persistent urethral discharge, refer to a centre with laboratory capacity to diagnose *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Trichomonas vaginalis* and test for antibiotic-resistant *Neisseria gonorrhoeae* and *Mycoplasma genitalium*.

Prevention

Important elements of prevention include counselling and behavioural approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling and promoting consistent use of condoms. Interventions targeting high-risk groups (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs) may be considered. Also consider offering pre-exposure prophylaxis for HIV to people at high risk of HIV infection. Sexual partners should always be informed of the infection and treated *(189)*. Reporting of this infection to health authorities according to local regulations should also be done.

Table 19.3 – Antibiotic treatment for chlamydial urogenital infections as indicated in the most recent WHO guidelines *(190,191)*

Please check the WHO website regularly for possible updates

Type of chlamydial infection	Treatment	Total treatment duration
Uncomplicated urogenital infection[a]	**Doxycycline**[b] (oral): 100 mg given every 12 hours **OR** **Azithromycin** (oral): 1g	7 days (doxycycline) Single dose (azithromycin)
Anorectal infection[c]	**Doxycycline** (oral): 100 mg given every 12 hours	7 days
Infection in pregnant women[d]	**Azithromycin** (oral): 1g	Single dose
Lymphogranuloma venereum[e]	**Doxycycline** (oral): 100 mg given every 12 hours	21 days
Ophthalmia neonatorum[f] (i.e. chlamydial conjunctivitis)	**Azithromycin** (oral): 20 mg/kg given once a day	3 days
Ocular prophylaxis[g] (topical treatment for the prevention of both gonococcal and chlamydial ophthalmia neonatorum)	**Erythromycin** (eye ointment): 0.5%	Antibiotic needs to be applied to both eyes soon after birth (single dose)

EML: Model List of Essential Medicines; EMLc: Model List of Essential Medicines for children.
Note. All dosages are for normal renal and hepatic function.
[a] Alternatives indicated in the 2021 WHO guidelines but not included the WHO EML for this indication are: erythromycin (oral): 500 mg every 6 hours; ofloxacin (oral): 200–400 mg every 12 hours. The recommended duration of treatment is 7 days for both options.
[b] According to recent data, doxycycline is more effective than azithromycin and could be given priority if adherence to treatment is not a concern *(198–200)*. The 2021 WHO guidelines for the management of symptomatic sexually transmitted infections recommend doxycycline as the first-line option and azithromycin as an effective substitute *(191)*. Therefore, exceptionally in this case, alternative antibiotic options are not presented in alphabetical order and doxycycline is mentioned first in the Table.
[c] Alternatives indicated in the 2021 WHO guidelines but not included in the EML for this indication are: erythromycin (oral): 500 mg every 6 hours. The recommended duration of treatment is 14 days.
[d] Alternatives indicated in the 2021 WHO guidelines but not included in the EML for this indication are: erythromycin (oral): 500 mg every 6 hours. The recommended duration of treatment is 7 days.

continues

Table 19.3 *continued*

[e] Alternatives indicated in the 2021 WHO guidelines but not included in the EML for this indication are: erythromycin (oral): 500 mg every 6 hours. The recommended duration of treatment is 21 days.
[f] Alternatives indicated in the 2016 WHO guidelines but not included in the EMLc for this indication are: erythromycin (oral): 50 mg/kg per day divided in 4 doses for 14 days.
[g] Alternatives indicated in the 2016 WHO guidelines but not included the EMLc for this indication are: tetracycline hydrochloride (eye ointment) 1%; povidone–iodine (water-based solution. Do not use alcohol-based solutions) 2.5%; silver nitrate (solution) 1%; chloramphenicol (eye ointment) 1%.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

20. Sexually transmitted infections – gonococcal infection

Note

In general this chapter applies to adults and young people older than 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.

Key messages

- *Neisseria gonorrhoeae* is a common curable sexually transmitted infection (STI) and resistance to antibiotics (including extensively resistant strains) is an increasing public health problem.
- Symptoms overlap with urogenital *Chlamydia trachomatis* infection and co-infection is frequent. Therefore, patients should be tested for both pathogens simultaneously, when available, and evaluated for other STIs (human immunodeficiency virus (HIV) infection, syphilis, trichomoniasis).
- Asymptomatic people should also be treated because they can transmit the infection to others.
- Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis for people at high risk of HIV infection) and sexual partners should be informed and treated.
- Reporting of this infection to health authorities is encouraged according to local regulations.

Other relevant WHO resources (please check regularly for updates)

- Sexually transmitted infections (STIs) – fact sheets *(189)*.
- Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae (201)*.
- WHO guidelines for the treatment of *Neisseria gonorrhoeae (89)*.
- WHO guidelines for the management of symptomatic sexually transmitted infections *(191)*.
- Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus *(192)*.
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 *(193)*.
- Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: 2021 *(202)*.

Gonococcal infection

Sexually transmitted infection • Page 1 of 3

In general this guidance applies to adults and young people aged over 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse

Definition

A sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoeae*

Pathogen

- *Neisseria gonorrhoeae* is a Gram-negative bacterium that can easily develop resistance to antibiotics leading to infections that are difficult to treat, which is an increasing public health problem worldwide
- Data on *Neisseria gonorrhoeae* resistance is available through GLASS (The WHO Global Antimicrobial Resistance Surveillance System) and GASP (The WHO Gonococcal AMR surveillance program)
https://www.who.int/data/gho/data/themes/topics/who-gonococcal-amr-surveillance-programme-who-gasp

Diagnosis

Clinical Presentation

- Some persons remain asymptomatic (women>men) though they can still transmit the infection
- If symptoms occur they overlap with those of chlamydial infection (co-infection possible and common)

Most common symptoms (usually occur a few days after infection):

- *In men*: acute urethritis with profuse mucopurulent urethral discharge and dysuria +/- testicular discomfort
- *In women*: mucopurulent vaginal discharge and dysuria +/- vaginitis with vaginal pain and inflammation and lower abdominal pain. Cervical discharge, cervical ectopy and friability and easy bleeding on contact may also occur
- *Additionally in both sexes*:
  - Symptoms of acute proctitis with pain, pruritus, anal discharge and bleeding
  - Pharyngitis and conjunctivitis are other possible presentations
  - Rarely infection can disseminate, typically leading to localized infection in one or more joints
- *In pregnant women*:
  - Infection can transmit to the child during vaginal delivery
- *In newborns*:
  - Acute ocular infection and pharyngitis can occur a few days after birth
  - Disseminated infection with septic arthritis (usually in multiple joints) may also occur

Microbiology Tests

- See WHO guidance "Laboratory diagnosis of sexually transmitted infections"
https://apps.who.int/iris/handle/10665/85343
- **Important**: all patients with suspected gonococcal infection should also be tested for chlamydial urogenital infection (as symptoms overlap) and other STIs (e.g. HIV, syphilis)

Reference standard:

- Nucleic acid amplification test (a test for both *N. gonorrhoeae* and *Chlamydia* is available)
  - Samples that can be used: urine (lower sensitivity and specificity in women), urethral, vulvovaginal, endocervical or anorectal samples collected with a swab

Other tests to consider:

- Culture + antimicrobial susceptibility testing: If symptoms persist despite adequate treatment and for surveillance of *Neisseria gonorrhoeae* resistance
- Microscopy (Gram stain)
  - Samples that can be used: urethral, endocervical, conjunctival samples collected with a swab
- Blood cultures: If disseminated infection is suspected

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Gonococcal infection

Sexually transmitted infection • Page 2 of 3

Prevention

Important elements of prevention include:

- Sexuality education
- Promoting consistent use of condoms
- Pre- and post-test counselling
- Safe sex and risk reduction counselling
- Interventions targeting high-risk groups

Important:

- Sexual partners should be informed of the disease and treated
- Reporting of this infection to health authorities is encouraged according to local regulations

Treatment (Section 1 of 2)

Treatment Recommendations

- Treatment is aligned with the WHO 2016 guidelines for the treatment of gonococcal infection (https://apps.who.int/iris/handle/10665/246114) and the WHO 2021 guidelines for the management of symptomatic sexually transmitted infections (https://apps.who.int/iris/handle/10665/34252) but only options listed in the 2021 EML are reported
- WHO is in the process of revising current treatment recommendations and dosages, please check the WHO website regularly for possible updates

Clinical Considerations

- Treatment is always indicated when infection is diagnosed, including in asymptomatic patients because they can transmit the infection to others
- Local resistance data should determine the most appropriate therapy and if data not available, dual therapy is preferred
- If symptoms do not resolve in approximately 5 days, resistant infection or alternative diagnosis should be suspected

Antibiotic Treatment Duration

Single Dose

Genital and Anorectal Infections

All dosages are for normal renal function

Dual Therapy

First Choice

WATCH Ceftriaxone 250 mg **IM**

---------- **COMBINED WITH** ----------

WATCH Azithromycin 1 g **ORAL**

Second Choice

WATCH Cefixime 400 mg **ORAL**

---------- **COMBINED WITH** ----------

WATCH Azithromycin 1 g **ORAL**

Single Therapy

Only use single therapy if local resistance data confirm susceptibility to the antibiotic

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

WATCH Cefixime 400 mg **ORAL**

---------- **OR** ----------

WATCH Ceftriaxone 250 mg **IM**

A single dose of 500 mg or 1 g ceftriaxone IM is recommended in some international guidelines

---------- **OR** ----------

ACCESS Spectinomycin 2 g **IM**

Gonococcal infection

Sexually transmitted infection • Page 3 of 3

Treatment (Section 2 of 2)

Antibiotic Treatment Duration

Single Dose

Retreatment after Treatment Failure

Consider treatment failure if symptoms persist after 5 days of adequate treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

WATCH Cefixime 800 mg **ORAL**

OR

WATCH Ceftriaxone 500 mg **IM**

OR

ACCESS Gentamicin 240 mg **IM**

OR

ACCESS Spectinomycin 2 g **IM**

Do not use for spectinomycin for oropharyngeal infections

COMBINED WITH

WATCH Azithromycin 2 g **ORAL**

Oropharyngeal Infections

All dosages are for normal renal function

Dual Therapy

First Choice

WATCH Ceftriaxone 250 mg **IM**

COMBINED WITH

WATCH Azithromycin 1 g **ORAL**

Second Choice

WATCH Cefixime 400 mg **ORAL**

COMBINED WITH

WATCH Azithromycin 1 g **ORAL**

Single Therapy

Only use single therapy if local resistance data confirm susceptibility to the antibiotic

WATCH Ceftriaxone 250 mg **IM**

A single dose of 500 mg or 1 g ceftriaxone IM is recommended in some international guidelines

Definition

Gonococcal infection is an STI caused by the bacterium *Neisseria gonorrhoeae*.

Pathogen

Neisseria gonorrhoeae, the organism causing gonorrhoea, is a Gram-negative bacterium.

The bacterium easily develops resistance to antibiotics, which has led to infections that are difficult to treat. As a result, resistance to antibiotics used for treatment (including third-generation cephalosporins) is a serious problem worldwide. Therefore, in 2012, WHO launched a global action plan to control the spread and impact of resistance in *Neisseria gonorrhoeae (201)*.

Data on *Neisseria gonorrhoeae* resistance are collected through the WHO Global Antimicrobial Resistance Surveillance System (GLASS) and the WHO Global Gonococcal Antimicrobial Surveillance Programme (GASP network) and are regularly published *(202–205)*.

Pathophysiology

Neisseria gonorrhoeae usually enters the mucosa (mostly of the genital tract) during sexual contact. Because of its many virulence factors, this bacterium can adapt to the local environment, evade immune response mechanisms and proliferate causing local inflammatory response and disease and, more rarely, systemic infection (i.e. gonococcal bacteraemia). If left untreated, or if it is inappropriately treated, complications may occur. In particular in women, pelvic inflammatory disease (i.e. an infection of the upper female reproductive tract) with inflammation of the uterine tubes (i.e. salpingitis), endometrium (i.e. endometritis) or abscess formation in the ovary/ovaries and tubes can occur. In men, complications include epididymitis and periurethritis with abscess formation. These complications can lead to infertility.

Disseminated gonococcal infection can occur as a result of bacteraemia secondary to mucosal infection (mostly of the genital tract) and can lead to arthritis, skin manifestations and other complications.

Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis which manifests as purulent ocular discharge and swollen eyelids. Untreated conjunctivitis may lead to scarring and blindness.

Epidemiology

Gonococcal infection is one of the most common STIs worldwide.

The 2021 WHO global progress report on HIV, viral hepatitis and STIs reported an estimated 82 million new gonococcal infections in 2020 among adults aged 15 to 49 years *(193)*.

The highest incidence of gonococcal infection is in the Africa and Western Pacific regions; this includes China and Australia among others *(206)*. Gonococcal infection increases the risk of HIV infection two- or three-fold.

Risk factors for gonococcal infection include HIV infection, young age, having multiple sexual partners or a new sexual partner, having partners with STIs, having had previous gonococcal infection and/or other STIs and several socioeconomic factors, such as low socioeconomic or educational level or substance abuse. Infection does not induce protective immunity therefore reinfection is possible. Resistance of *Neisseria gonorrhoeae* to antibiotics used to treat the infection is a concern; see the pathogen section for more information about resistance *(204)*.

Clinical presentation

Signs and symptoms of gonococcal infection vary in men and women and overlap with those of chlamydial infection. Some people with gonococcal infection may be asymptomatic even though they can still transmit the infection. When symptoms occur (usually a few days after being infected), the most common clinical presentation in men is acute urethritis characterized by profuse mucopurulent urethral discharge and dysuria; testicular discomfort can also be present. In women, mucopurulent vaginal discharge and dysuria are the most common symptoms. Several women may have lower abdominal pain because of ascending infection causing pelvic inflammatory disease. Gonorrhoea causes cervical infection that presents with cervical discharge, cervical ectopy and friability and easy bleeding on contact.

In both sexes (but in males more than females), symptoms of acute proctitis with pain, pruritus, discharge and bleeding of the rectum may occur. Pharyngitis (mostly manifesting as a mild sore throat) and conjunctivitis are other conditions that usually coexist with genital infection.

Rarely, the infection can disseminate (i.e. gonococcal bacteraemia) and this can typically lead to localized infection in one or more joints (i.e. gonococcal arthritis). Please refer to the chapter on septic arthritis for more information on this topic.

In pregnant women, the infection can be transmitted to the child during vaginal delivery. In newborns, gonococcal infection can present with acute ocular infection (i.e. conjunctivitis) or pharyngitis which manifest a few days after birth. Disseminated infection with septic arthritis (usually with multiple joints involved) can also occur in newborns.

Laboratory tests

Patient microbiology tests

Molecular testing has greatly improved the detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* among both symptomatic and asymptomatic men and women. Molecular testing has become the recommended gold standard technology to diagnose

and screen populations for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Table 20.1 indicates the types of specimens that can be used for this purpose.

Culture of *Neisseria gonorrhoeae* is still the standard method for performing antibiotic susceptibility testing. However, this organism is not easy to grow in the laboratory and requires special training and a special culture medium. For this reason, culture of *Neisseria gonorrhoeae* is not routinely performed as part of managing people with gonococcal infection in resource-limited settings.

Neisseria gonorrhoeae can also be identified by light microscopy of Gram-stained samples and a presumptive diagnosis can be made if intracellular Gram-negative diplococci are observed in polymorphonuclear leukocytes, best seen when there is a urethral discharge. Gram-stained smears from the cervix are also considered positive for the presumptive diagnosis of gonorrhoea in women if intracellular Gram-negative diplococci are observed in polymorphonuclear leukocytes. Gram stain of urethral samples among women has low yield and may not be cost-effective.

For more comprehensive information on the diagnosis of gonococcal infection, please refer to the most recent (2013) WHO guideline for the laboratory diagnosis of STIs *(192)*. Please check the WHO website regularly for possible updates. Patients with gonococcal infection are also usually evaluated for other STIs, such as chlamydial infection, hepatitis B, hepatitis C, HIV infection and syphilis.

Tests to consider when gonococcal infection is suspected are listed in Table 20.1. Additional tests for other STIs that could be considered when gonococcal infection is confirmed or suspected are shown in Table 20.2.

Table 20.1 – Microbiology tests to consider when gonococcal infection is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Qualitative test for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections (i.e. nucleic acid amplification test)[a,b] **This is the recommended reference standard**	To diagnose gonorrhoeal and/or chlamydial urogenital disease and extragenital infection	Health care facilities with clinical laboratories
Microscopy (Gram stain)[c]	To assess microbial morphology, and presence or absence of white blood cells	Health care facilities with clinical laboratories

continues

Table 20.1 *continued*

Diagnostic test	Purpose of the test	Settings where the test should be available
Culture[d] and antimicrobial susceptibility testing Consider if symptoms persist despite adequate treatment and for surveillance purposes.	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Blood cultures Consider if disseminated infection is suspected.	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.
[a] Usually gonococcal and chlamydial infections are tested at the same time since their clinical presentations are very similar.
[b] Possible specimens among women include a vulvovaginal specimen, which may be self-collected. An endocervical swab can be an alternative but requires a speculum. First-catch urine is another option, but the sensitivity and specificity tend to be lower in women. Among men, first-catch urine or urethral swabs are appropriate. Anorectal and pharyngeal samples are also adequate. Nucleic acid amplification tests also perform well for pharyngeal and anorectal samples.
[c] Possible specimens are: urethral swabs, endocervical swabs and conjunctival swabs. Note. Urine samples are not good specimens for microscopy.
[d] Possible specimens are: urethral swabs, endocervical swabs, vaginal swabs, rectal swabs, oropharyngeal swabs and conjunctival swabs. Note. Urine samples are not good specimens for culture. Culture is the standard method for performing antibiotic susceptibility testing.

Table 20.2 – Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected gonococcal infection as indicated in the WHO EDL *(6)*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Chlamydial urogenital infection	*Chlamydia trachomatis* NAAT	To diagnose chlamydial urogenital disease and extragenital infection	Health care facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories[a]

continues

Table 20.2 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people aged > 12 months	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Health care facilities with clinical laboratories
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people aged > 18 months	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)

continues

Table 20.2 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Syphilis	Antibodies to *Treponema pallidum*[b] (RDT)	To diagnose or help to diagnose *Treponema pallidum*	Community settings and health facilities without laboratories[a]
Syphilis and HIV (combined test)	Combined antibodies to *Treponema pallidum* and to HIV-1 and HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or *Treponema pallidum*	Community settings and health facilities without laboratories[a]
Trichomoniasis	Microscopy	To assess microbial morphology, and presence or absence of white blood cells	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; NAAT: nucleic acid amplification test; RDT: rapid diagnostic test.
[a] Community and health settings without laboratories are defined as community and health facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.
[b] Usually a non-treponemal test (e.g. rapid plasma reagin, Venereal Disease Research Laboratory test) is used for screening. Please refer to the chapter on syphilis for more details on testing.

Other tests

When gonococcal infection is suspected, laboratory tests other than microbiology are not usually needed. However, microscopy of vaginal or urethral secretions will usually show the presence of leukocytes (> 10 leukocytes/field).

Using microbiology surveillance data

Monitoring antibiotic resistance in *Neisseria gonorrhoeae* is recommended to inform local, national and global guidance.

Imaging

When gonococcal infection is suspected, imaging is not usually needed.

Antibiotic treatment

The recommendations on antibiotic treatment reported here are based on the most recent WHO guidelines for the treatment of gonorrhoea and on the management of symptomatic STIs *(89,191)*. Because of increasing antibiotic resistance to azithromycin in *Neisseria gonorrhoeae* and *Mycoplasma genitalium* and reduced susceptibility of *Neisseria gonorrhoeae* to cephalosporins, **WHO is currently revising treatment recommendations and dosages (please check the WHO website regularly for possible updates)**.

All people (including pregnant women) diagnosed with gonorrhoea should receive adequate antibiotic treatment. Antibiotic treatment options are shown in Table 20.3.

When choosing treatment, local resistance data should determine the choice of the most appropriate therapy. If data are not available, dual therapy (i.e. two antibiotics) should be given. If symptoms do not resolve within about 5 days of adequate antibiotic treatment, a resistant infection should be suspected, or an alternative diagnosis sought.

Table 20.3 – Antibiotic treatment for gonococcal infection as indicated in the 2016 WHO guidelines for the treatment of gonorrhoea *(89)*

Important

WHO is currently revising treatment recommendations and dosages (please check the WHO website regularly for possible updates).

Where more than one antibiotic is recommended for an infection, they are listed in alphabetical order and they should be considered equal treatment options, unless otherwise indicated.

Type of gonococcal infection	Treatment	Total treatment duration
Genital and anorectal infections (**dual therapy**[a])	**First choice** **Ceftriaxone** (IM): 250 mg **AND** **Azithromycin** (oral): 1 g **Second choice** **Cefixime** (oral): 400 mg **AND** **Azithromycin** (oral): 1 g	Single dose
Genital and anorectal infections (**single therapy**), if local resistance data confirm susceptibility to the antibiotic	**Cefixime** (oral): 400 mg **OR** **Ceftriaxone** (IM): 250 mg[b] **OR** **Spectinomycin** (IM): 2 g	Single dose

continues

Table 20.3 *continued*

Type of gonococcal infection	Treatment	Total treatment duration
Oropharyngeal infections[c] (**dual therapy**[a])	**First choice** **Ceftriaxone** (IM): 250 mg **AND** **Azithromycin** (oral): 1 g **Second choice** **Cefixime** (oral): 400 mg **AND** **Azithromycin** (oral): 1 g	Single dose
Oropharyngeal infections[c] (**single therapy**), if local resistance data confirm susceptibility to the antibiotic	**Ceftriaxone** (IM): 250 mg[b]	Single dose
Gonococcal ophthalmia neonatorum (i.e. gonococcal conjunctivitis)	**Ceftriaxone**[d] (IM): 50mg/kg	Single dose
Ocular prophylaxis[e] (topical treatment for the prevention of both chlamydial and gonococcal ophthalmia neonatorum)	**Erythromycin** (eye ointment): 0.5%	Antibiotic needs to be applied to both eyes soon after birth (single dose)
Retreatment after treatment failure Consider treatment failure if symptoms persist after 5 days of adequate treatment	**Cefixime** (oral): 800 mg **AND** **Azithromycin** (oral): 2 g **OR** **Ceftriaxone** (IM): 500 mg **AND** **Azithromycin** (oral): 2 g **OR** **Gentamicin** (IM): 240 mg **AND** **Azithromycin** (oral): 2 g **OR** **Spectinomycin**[c] (IM): 2 g **AND** **Azithromycin** (oral): 2 g	Single dose

IM: intramuscular.
Note. All dosages are for normal renal and hepatic function.
[a] Dual therapy should be given if no reliable local data on resistance are available.

continues

Table 20.3 *continued*

[b] A single dose of 500 mg or 1 g of ceftriaxone (IM) is recommended in some international guidelines *(207–209)*.
[c] Do not use spectinomycin to treat cases of oropharyngeal infection.
[d] Ceftriaxone should not be administered in neonates receiving calcium-containing intravenous fluids and it should be avoided in infants with hyperbilirubinaemia. Cefotaxime can be used as an alternative. Alternatives to ceftriaxone indicated in the 2016 WHO guidelines include kanamycin (IM) 25mg/kg or spectinomycin (IM) 25mg/kg *(89)*.
[e] Alternatives indicated in the 2016 WHO guidelines include tetracycline hydrochloride (eye ointment) 1%; povidone–iodine (water-based solution. Do not use alcohol-based solutions) 2.5%; silver nitrate (solution) 1%; chloramphenicol (eye ointment) 1%.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

No effective vaccine against *Neisseria gonorrhoeae* is available. Prevention is therefore one of the key elements included in the 2012 WHO global action plan to control the spread and impact of AMR in *Neisseria gonorrhoeae (201)*.

Important elements of prevention include counselling and behavioural approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling and promoting consistent use of condoms. Interventions targeting high-risk groups (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs) and offering HIV pre-exposure prophylaxis to people at high risk of HIV infection may be considered. Sexual partners should always be informed of the infection and treated. Reporting of this infection to health authorities according to local regulations should also be done.

21. Sexually transmitted infections – syphilis

Note

In general this chapter applies to adults and young people older than 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.

Key messages

- Syphilis has several stages of infection with different clinical presentations and remains common worldwide.
- All pregnant women should be screened for syphilis and treated if infected to prevent congenital syphilis in the child.
- Asymptomatic people should also be treated because they can transmit the infection to others, and all people with syphilis should also be evaluated for other sexually transmitted infections.
- Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis to people at high risk for HIV infection) and sexual partners should be informed and treated.
- Reporting of this infection to health authorities is encouraged according to local regulations.

Other relevant WHO resources (please check regularly for updates)

- Sexually transmitted infections (STIs) – fact sheets *(189)*.
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 *(193)*.
- WHO guidelines for the treatment of *Treponema pallidum* (syphilis) *(210)*.
- WHO guidelines for the management of symptomatic sexually transmitted infections *(191)*.
- Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus *(192)*.
- WHO guideline on syphilis screening and treatment for pregnant women *(211)*.

Definition

Syphilis is an STI caused by the bacterium *Treponema pallidum* subspecies *pallidum*. Syphilis is one of other treponematoses, that is, diseases caused by spirochaetes of the species *Treponema pallidum*. Other *Treponema pallidum* subspecies causing human diseases include subspecies *pertenue*, the causative pathogen of yaws *(212)*, subspecies *endemicum*, the causative pathogen of endemic syphilis or bejel, and subspecies *carateum*, the causative pathogen of pinta *(213)*. This chapter will only address disease caused by *Treponema pallidum* subspecies *pallidum* (syphilis). Information about other treponematoses is available on the WHO website *(212)*.

Syphilis can be classified as early or late based on the time since becoming infected. Usually infections of ≤ 2 years duration are defined as early and infections of > 2 years are defined as late. Furthermore, infections can be classified as primary, secondary or tertiary based on the clinical presentation *(210)*. There is usually a long latent phase with no clinical manifestations between secondary and tertiary infection; the tertiary phase only develops in untreated or inadequately treated infections. Overlap between these definitions exists, with early infection including primary and secondary syphilis and late infection including the latent phase and tertiary syphilis.

The latent phase can also be divided into two phases – early latent and late latent. Early latent syphilis is usually defined as infection of < 2 years, whereas late latent syphilis is defined as the presence of the disease of ≥ 2 years *(210)*. However, this distinction is difficult to apply because it is often impossible to establish the time of the initial infection.

Syphilis

Sexually transmitted infection • Page 1 of 2

In general this guidance applies to adults and young people aged over 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse

Pathogen

Treponema pallidum subspecies pallidum is a bacterium of the phylum Spirochaetes

- Slow growing, difficult to culture *in vitro*, thin

Definition

- A sexually transmitted infection (STI) caused by the bacterium *Treponema pallidum* subspecies *pallidum*
- The infection can be transmitted from the mother to her fetus because the pathogen can cross the placenta

Classification based on:

- Timing since acquisition
  - *Early*: ≤2 years (includes primary and secondary infections and the early latent phase)
  - *Late*: >2 years (includes the late latent phase and tertiary infections)
- Clinical presentation (see below)

Diagnosis

Clinical Presentation

Early syphilis:

- *Primary infection*: Often asymptomatic, localized non painful ulcerative lesion with indurated margins (usually on genitalia, mouth or rectum) +/- local lymphadenopathy
- *Secondary infection*:
  - Skin and mucosal manifestations over trunk and extremities including palms of hands and soles of feet
  - Rash is commonly maculopapular and non-irritant
  - Mucous membranes of mouth/perineum can show lesions
  - Fever (≥ 38.0 °C), generalized lymphadenopathy and malaise usually present
  - Meningitis, hepatitis and ocular involvement can occur

Late syphilis:

- *Tertiary infection*: Can affect different organ systems
  - Cardiovascular system: usually aortitis
  - Skin/soft tissues/bones: nodular lesions (gummas)
  - Central nervous system: often progressive dementia, psychiatric symptoms, problems with coordination of movements

Other Laboratory Tests

Primary syphilis: Usually not needed

Secondary or tertiary syphilis: May be required depending on the clinical presentation

Microbiology Tests

- See WHO guidance "Laboratory diagnosis of sexually transmitted infections" https://apps.who.int/iris/handle/10665/85343
- **Important**: all patients with suspected syphilis should also be tested for other STIs (e.g. HIV, gonococcal infection)

Direct detection methods:

- Can detect the pathogen in specimens from skin or tissue lesions

Serological tests:

- *Treponemal tests*: detect antibodies to treponemal antigens; they usually remain positive after infection even with successful treatment
  - Type of tests: **FTA-ABS**, **TPPA**, **TPHA**
- *Nontreponemal tests*: detect antibodies that react to lipids released in response to cellular damage caused by infection; usually become negative with successful treatment
  - Type of tests: **VDRL**, **RPR**
- All tests are negative initially in primary infection
- **Both treponemal and non-treponemal tests need to be positive to confirm the diagnosis**
- To increase access and same-day treatment, a rapid treponemal test followed (if positive) by a nontreponemal test is recommended; but starting with a non-treponemal test and confirming positive results with a treponemal test is also appropriate

Imaging

Usually not needed unless a complication of late syphilis is suspected

Syphilis

Sexually transmitted infection • Page 2 of 2

Prevention

Important elements of prevention include:

- Sexuality education
- Promoting consistent use of condoms
- Pre- and post-test counselling
- Safe sex and risk reduction counselling
- Interventions targeting high risk groups
- Access of pregnant women to early and adequate prenatal care to prevent congenital syphilis

Important:

- Sexual partners should be informed of the disease and treated
- Reporting of this infection to health authorities is encouraged according to local regulations

Treatment

Clinical Considerations

Treatment is aligned with the WHO 2016 guidelines for the treatment of *Treponema pallidum* (https://apps.who.int/iris/handle/10665/249572) and the WHO 2021 guidelines for the management of symptomatic sexually transmitted infections (https://apps.who.int/iris/handle/10665/342523) but only options listed in the 2021 EML are reported below

- Treatment is always indicated when infection is diagnosed, including in asymptomatic patients because they can transmit the infection to others
- In early syphilis (primary/secondary), partners should also be treated if exposed within 90 days
- Assess serological response by repeating non-treponemal test to detect a reduction in titer; a 4-fold reduction in titers confirms adequate response (repeat 3, 6 and 12 months after the end of treatment)

Antibiotic Treatment Duration

Since treatment duration varies according to the antibiotic used and the stage of the infection, please refer to the corresponding antibiotic section for treatment duration

Neurosyphilis

All dosages are for normal renal function

ACCESS Benzylpenicillin 2-4 million IU (1.2-2.4 g) q4h **IV**
Treatment duration: 14 days

---------- **OR** ----------

ACCESS Procaine benzylpenicillin 1.2 million IU (1.2 g) q24h **IM**
Treatment duration: 14 days

---------- **COMBINED WITH** ----------

Probenecid 500 mg q6h **ORAL**
Treatment duration: 14 days

Early Syphilis

All dosages are for normal renal function

First Choice

ACCESS Benzathine benzylpenicillin 2.4 million IU (≈ 1.8 g) **IM**
Treatment duration: single dose

Second Choice

ACCESS Procaine benzylpenicillin 1.2 million IU (1.2 g) q24h **IM**
Treatment duration: 10-14 days

Syphilis in Pregnancy

All dosages are for normal renal function

ACCESS Benzathine benzylpenicillin 2.4 million IU (≈ 1.8 g) **IM**
Treatment duration:
- Early Syphilis: Single dose
- Late or Unknown Stage Syphilis: One dose per week for 3 consecutive weeks (total of 3 administrations, the interval between doses should not exceed 14 days)

Late or Unknown Stage Syphilis

All dosages are for normal renal function

First Choice

ACCESS Benzathine benzylpenicillin 2.4 million IU (≈ 1.8 g) **IM**
Treatment duration: One dose per week for 3 consecutive weeks (total of 3 administrations, the interval between doses should not exceed 14 days)

Second Choice

ACCESS Procaine benzylpenicillin 1.2 million IU (1.2 g) q24h **IM**
Treatment duration: 20 days

Pathogen

Syphilis is caused by *Treponema pallidum* subspecies *pallidum*, a bacterium of the phylum Spirochaetes; other members of this phylum include *Leptospira* and *Borrelia*.

Treponema pallidum is characterized by slow growth, difficulty in culturing in vitro, and its thinness – 0.2 µm compared to about 0.5 µm for a bacterium like *Escherichia coli* – which makes it difficult to see with conventional microscopy.

Resistance to penicillin has not yet been reported and therefore it remains the antibiotic of choice for the treatment of syphilis. Resistance to azithromycin has been reported in some settings *(214)*.

Pathophysiology

Syphilis is usually acquired through sexual contact with infectious lesions on the mucosa or skin or, much more rarely, through the bloodstream. The infection can also be transmitted from the mother to her fetus because *Treponema pallidum* subspecies *pallidum* can cross the placenta and cause fetal death and congenital infection.

With sexual transmission, once *Treponema pallidum* subspecies *pallidum* enters the subcutaneous tissue, infection develops within 2–6 weeks (usually about 3 weeks) with formation of an ulcerative lesion that occurs at the site of inoculation. Usually, the immune system is able to control the early infection and, even if left untreated, the primary ulcerative lesion (i.e. chancre) resolves. However, dissemination of *Treponema pallidum* through the bloodstream can occur at the time of primary infection and this can result over time in secondary or tertiary syphilis in the absence of adequate treatment. In particular, tertiary syphilis has a long incubation period (up to years or decades after the initial infection) and develops in about a third of patients with untreated syphilis. In 2017, 370 000 prevalent cases of tertiary syphilis were reported worldwide but this number is probably an underestimation of the true burden of the disease *(44)*.

Congenital syphilis can occur as a result of vertical transmission of the pathogen from an infected mother to the fetus. The risk of transmission depends on a combination of factors, including maternal titres of non-treponemal tests (see Table 21.1 for an explanation about tests), timing, adequacy of maternal treatment and stage of maternal infection. The estimated total number of cases of congenital syphilis worldwide in 2016 was 661 000, or 473 per 100 000 live births *(215)*.

Epidemiology

Syphilis is a common curable STI and its incidence is increasing globally. WHO estimates there were 7 million new cases in 2020 *(193)*. Other bacterial STIs occur more frequently, for

example, in 2020 more than 82 million new cases of gonorrhoea and about 128 million new cases of chlamydial infection were reported *(193)*. However, syphilis has an important public health impact because of the potential serious consequences if left untreated, including maternal transmission to the fetus resulting in congenital syphilis and fetal death, and complications such as neurosyphilis and cardiovascular syphilis.

Moreover, as with other STIs, syphilis affects quality of life and increases the risk of transmitting or acquiring other STIs including HIV infection. This HIV risk is of particular concern because STIs characterized by the presence of ulcerative lesions have the highest risk of HIV transmission *(216)*.

The risk factors for syphilis include: having multiple sexual partners or a new sexual partner; having partners with STIs; having had a previous STI; and several socioeconomic factors, such as low socioeconomic or educational level, substance abuse and young age *(217,218)*. Lack of access to adequate prenatal care is an important risk factor for congenital syphilis.

Clinical presentation

Signs and symptoms of syphilis vary depending on the stage of the disease, early or late.

Early syphilis has the following signs and symptoms.

- Primary infection (localized disease). This is characterized by the presence of a localized non-painful ulcerative lesion (i.e. chancre) with indurated margins, usually associated with local lymphadenopathy. The lesion is usually located on the genitalia, mouth or rectum but other locations are possible depending on the site of inoculation. The lesion is often asymptomatic and can remain unnoticed, particularly among women. If left untreated, the lesion usually resolves within a few weeks without leaving a scar.
- Secondary infection (disseminated disease). This is characterized by skin and mucosal manifestations. Generally, a maculopapular non-irritant rash appears which is usually diffuse and extends bilaterally over the trunk and the extremities. A characteristic feature is the involvement of the palms of the hands and soles of the feet. The mucous membranes of the mouth and perineum can also show lesions (mostly flat lesions) that are highly infectious. Systemic manifestations (e.g. fever ≥ 38.0 °C, generalized lymphadenopathy and malaise) are usually present. Neurological manifestations (e.g. meningitis), hepatitis and ocular involvement can also occur in this phase.

Late syphilis has the following signs and symptoms.

- Tertiary syphilis (disseminated disease). This can occur as the result of an untreated early syphilis after a period of latency, with no clinical manifestations, that may last

years. Usually tertiary syphilis develops more rapidly in patients with HIV. In this phase, different organ systems can be affected, particularly: the cardiovascular system (typically with signs and symptoms of aortitis); the skin, soft tissues and bones (typically with granulomatous or nodular lesions also known as gummas); and the central nervous system (typically with symptoms of progressive dementia, psychiatric syndrome and tabes dorsalis, which is characterized by problems with coordination of movements, pain radiating from the spine and impaired response of the pupils to light).

Congenital syphilis infection during pregnancy can lead to spontaneous abortion or premature birth. Most babies with congenital syphilis are asymptomatic at birth but when symptoms are present, they usually develop days or weeks after birth. These symptoms often include anaemia, thrombocytopenia, rash (maculopapular, desquamative rash particularly over the palms, soles, mouth and anus), generalized lymphadenopathy, hepatomegaly and jaundice, nasal discharge (that may turn bloody), painful osteitis (mostly in long bones) and teeth abnormalities. The cerebrospinal fluid is abnormal, indicating neurological disease, in up to half of all babies. Of note, neurological consequences can be expressed later in life and this should always be considered with congenital syphilis.

Laboratory tests

For more comprehensive information on diagnosis of syphilis, please refer to the most recent (2013) WHO guideline for the laboratory diagnosis of STIs *(192)*. Please check the WHO website regularly for possible updates.

Patient microbiology tests

In patients with suspected syphilis, microbiology tests can support the diagnosis (Table 21.1). Certain microbiology tests are also used to screen asymptomatic pregnant women. For screening during pregnancy, please refer to the most recent (2017) WHO guideline on syphilis screening and treatment for pregnant women *(211)*.

Direct detection methods

These methods can be used to detect the pathogen in specimens obtained from skin or tissues lesions (Table 21.1). Direct detection methods include: dark-field microscopy where *Treponema pallidum* from lesions of primary syphilis can be observed (of note, a negative dark-field result does not exclude syphilis); and nucleic acid amplification tests to detect DNA sequences specific to *Treponema pallidum*. Direct detection is considered the gold standard but it is much less frequently used today because it is more time-consuming than serological tests.

Serological tests

Two types of serological test can be used, treponemal and non-treponemal.

- Treponemal tests detect antibodies to treponemal antigens and usually remain positive after infection even after successful treatment. These tests include: fluorescent treponemal antibody absorption test; *Treponema pallidum* particle agglutination assay; and *Treponema pallidum* haemagglutination assay. Treponemal rapid diagnostic tests for syphilis are available and prequalified by WHO.
- Non-treponemal tests detect antibodies that react to lipids, for example, cardiolipin released during cellular damage that occurs in response to *Treponema pallidum*. These are qualitative and quantitative tests that can also be used to monitor response to treatment because their titres tend to decline after adequate treatment and may become negative (i.e. non-reactive) over time. These tests include: rapid plasma reagin test and Venereal Disease Research Laboratory test.

Initially, a two-step approach is used to test for syphilis and both types of tests – treponemal and non-treponemal – need to be positive to confirm the diagnosis. In order to increase access to testing and ensure same-day treatment, WHO recommends the use of a rapid treponemal test followed (if positive) by a non-treponemal test.

However, starting with a non-treponemal test and confirmation of positive results with a treponemal test is also appropriate.

All serological tests for syphilis (non-treponemal and treponemal tests) are negative in the early phase of primary syphilis and take 1–4 weeks after the chancre appears to become reactive. Both treponemal and non-treponemal tests are reactive in secondary or tertiary syphilis.

Non-treponemal tests can rarely give false positive results, for example, during pregnancy or during an acute febrile illness. Figure 21.1 and Figure 21.2 and Table 21.2 can be used to help with the interpretation of the results of serological tests.

Additional tests for other STIs that could be considered when syphilis is confirmed or suspected are shown in Table 21.3.

Table 21.1 – Microbiology tests to consider when syphilis is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy of specimens obtained from skin and tissues lesions[a]	To assess microbial morphology	Health care facilities with clinical laboratories
Antibodies to *Treponema pallidum* (RDT)	To diagnose or help to diagnose *Treponema pallidum*	Community settings and health facilities without laboratories[b]
Combined antibodies to *Treponema pallidum* and to HIV-1 and HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or *Treponema pallidum*	Community settings and health facilities without laboratories[b]
Non-treponemal test: rapid plasma reagin	To screen for syphilis and monitor effectiveness of treatment	Health care facilities with clinical laboratories
Non-treponemal test: VDLR test[c]	To screen for syphilis and monitor effectiveness of treatment and also to screen for, diagnose and confirm neurosyphilis[c]	Health care facilities with clinical laboratories
Treponemal test: TPHA test[d]	To confirm syphilis and diagnose early and late syphilis	Health care facilities with clinical laboratories
Treponemal test: TPPA test[d]	To confirm syphilis and diagnose early and late syphilis	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; RDT: rapid diagnostic test; TPHA: *Treponema pallidum* haemagglutination; TPPA: *Treponema pallidum* particle agglutination; VDRL: Venereal Disease Research Laboratory.

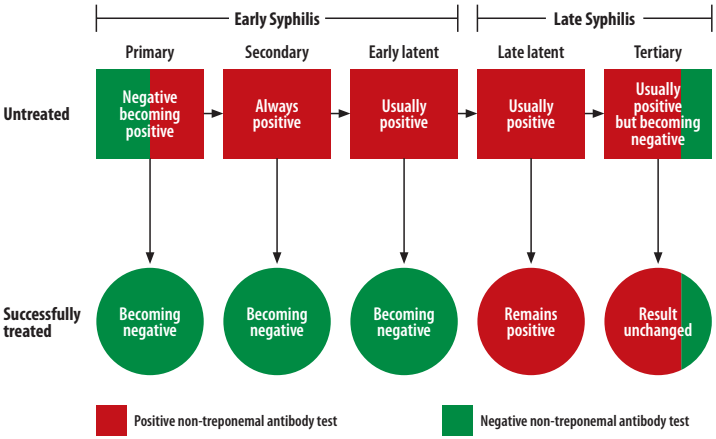
[a] Nucleic acid amplification tests (e.g. polymerase chain reaction) of specimens obtained from skin and tissues lesions could also be considered if available.

[b] Community and health settings without laboratories are defined as community and health facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

[c] If neurosyphilis is suspected (this can occur at any stage of infection including in the first few months), the VDRL test can also be used on the cerebrospinal fluid in the presence of a positive syphilis serology. The test has a high specificity (i.e. few false-positive results) but a low sensitivity (i.e. many false-negative results). Examination of the cerebrospinal fluid is recommended where there is clinical evidence of neurological involvement. It is also highly desirable in all patients with syphilis of more than 2 years duration or of uncertain duration in order to evaluate the possible presence of asymptomatic neurosyphilis *(219)*.

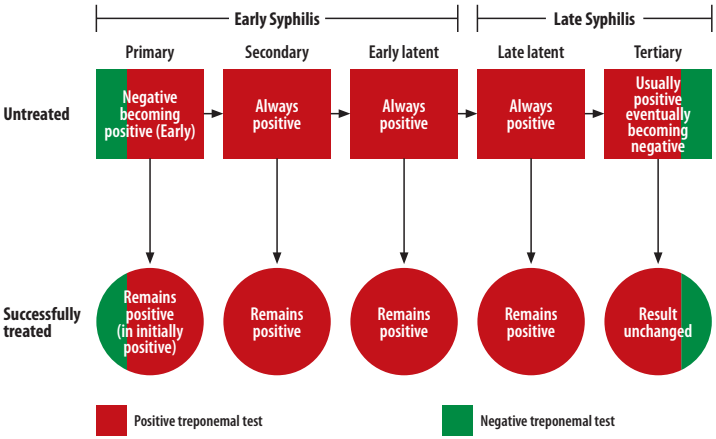
[d] Treponemal tests usually remain positive after the infection has been cleared.

Figure 21.1 – Reactivity of non-treponemal serological tests by stage of syphilis and effect of treatment



Source: *Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus*, 2013 *(192)*.

Figure 21.2 – Reactivity of treponemal serological tests by stage of syphilis and effect of treatment



Source: *Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus*, 2013 *(192)*.

Table 21.2 – Possible interpretation of combinations of non-treponemal and treponemal test results

Non-treponemal test (RPR or VDRL)	Treponemal test (FTA-ABS, TPPA, TPHA, RDT)	Interpretation
Positive	Positive	This supports the diagnosis of syphilis (the stage of disease and need for treatment should be determined on a case-by-case basis). Note. These cases should be notified to the local authority according to national guidance for disease notification.
Negative	Positive	Usually this can occur as a result of a successfully treated previous infection because treponemal tests tend to remain positive. Otherwise it could be a very early (or late) phase of the infection.
Positive	Negative	Usually this can be considered a false positive result (e.g. during pregnancy).
Negative	Negative	Usually the diagnosis of syphilis can be excluded.

FTA-ABS: fluorescent treponemal antibody absorption; RDT: rapid diagnostic test; RPR: rapid plasma reagin; TPHA: *Treponema pallidum* haemagglutination assay; TPPA: *Treponema pallidum* particle agglutination; VDRL: Venereal Disease Research Laboratory.

Table 21.3 – Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected syphilis as indicated in the WHO EDL *(6)*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Chlamydial urogenital infection and gonococcal infection	Qualitative test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections (NAAT)	To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection	Health care facilities with clinical laboratories

continues

Table 21.3 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories[a]
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay	To screen for acute and chronic hepatitis B virus infection in people older than 12 months	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Health care facilities with clinical laboratories
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people older than 18 months	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)

continues

Table 21.3 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Trichomoniasis	Microscopy	To assess microbial morphology, and presence or absence of white blood cells	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; NAAT: nucleic acid amplification test; RDT: rapid diagnostic test.
[a] Community and health settings without laboratories are defined as community and health facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Other tests

When primary syphilis is suspected, blood tests other than serology are not usually needed. However, in case of secondary or tertiary syphilis, laboratory tests may be required. If signs and symptoms of neurological disease (i.e. neurosyphilis) are present, a lumbar puncture to test the cerebrospinal fluid is indicated if available (Table 21.4).

Table 21.4 – Laboratory tests (other than microbiology) to consider when late syphilis is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Basic CSF profile: CSF leukocyte count[a], CSF differential leukocyte count and CSF protein[b] and glucose[c]	To aid in the diagnosis of neurosyphilis	Health care facilities with clinical laboratories

CSF: cerebrospinal fluid; EDL: Model List of Essential In Vitro Diagnostics.
[a] CSF leukocyte count: usually > 5 white blood cell/µL (> 0.005×10^9/L), or a higher cut-off > 20 cell/µL (> 0.02×10^9/L) in HIV-positive patients even though these are not specific findings of neurosyphilis.
[b] CSF protein levels: protein concentration is usually increased (> 45 mg/dL or > 0.45 g/L) but not a specific finding of neurosyphilis.
[c] CSF glucose levels: glucose concentrations are usually decreased but not a specific finding of neurosyphilis.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

When syphilis is suspected, imaging is not usually needed unless a complication of late syphilis is suspected.

Antibiotic treatment

All patients, including pregnant women, diagnosed with syphilis should receive a full course of antibiotic treatment. Serological response to treatment can be assessed by repeating a non-treponemal quantitative test – ideally the same type of non-treponemal test used at the time of diagnosis – to detect a reduction in titre. A four-fold reduction, or higher, in titres should be seen to confirm an adequate response to treatment for early syphilis. Usually assessments are repeated at 3, 6 and 12 months after the end of treatment.

In the case of early syphilis (primary or secondary), the partners of infected people should also be treated if they had sexual relations with the infected person in the 90 days before the person was diagnosed with syphilis. If more than 90 days have elapsed, serological testing is usually suggested and treatment is given accordingly.

The antibiotic treatment recommendations reported here (Table 21.5) are aligned with the most recent WHO guidelines for the treatment of syphilis and for the management of symptomatic STIs *(191,210)*.

Table 21.5 – Antibiotic treatment for syphilis by stage of the disease as indicated in the most recent WHO guidelines for the treatment of syphilis *(210)*

Please check the WHO website regularly for possible updates

Type of infection	Treatment	Total treatment duration
Early syphilis (adults and adolescents) Early syphilis includes primary, secondary and early latent syphilis of no more than 2 years duration	**First choice** **Benzathine benzylpenicillin** [a] (IM): 2.4 million IU (≈ 1.8 g)	Benzathine benzylpenicillin: single dose
	Second choice **Procaine benzylpenicillin** (IM): 1.2 million IU (1.2 g) given once a day	Procaine benzylpenicillin: 10–14 days

continues

Table 21.5 *continued*

Type of infection	Treatment	Total treatment duration
Late syphilis or unknown stage (adults and adolescents) This includes infection of more than 2 years duration without evidence of treponemal infection (i.e. asymptomatic infection)	**First choice** **Benzathine benzylpenicillin** [b] (IM): 2.4 million IU (≈ 1.8 g) **Second choice** **Procaine benzylpenicillin** (IM): 1.2 million IU (1.2 g) given once a day	Benzathine benzylpenicillin: one dose per week for 3 consecutive weeks (e.g. on days 1, 8 and 15) The interval between doses should not exceed 14 days Procaine benzylpenicillin: 20 days
Congenital syphilis Infants with confirmed disease or infants who are clinically normal but whose mother had untreated or inadequately treated syphilis[c] Inadequate treatment refers to treatment received < 30 days before delivery and/or treatment with a non-penicillin regimen	**Benzylpenicillin** (IV): 50 000–75 000 IU/kg/dose (30–45 mg/kg/dose) given every 12 hours **OR** **Procaine benzylpenicillin** (IM): 50 000 IU/kg (50 mg/kg) given once a day If IV access is available, benzylpenicillin is preferred over procaine benzylpenicillin.	10–15 days
Neurosyphilis[d]	**Benzylpenicillin** [e] (IV): 2–4 million IU (1.2–2.4 g) given every 4 hours **OR** **Procaine benzylpenicillin** [f] (IM): 1.2 million IU (1.2 g) given once a day **AND** Probenecid (oral): 500 mg given every 6 hours	14 days

continues

Table 21.5 *continued*

Type of infection	Treatment	Total treatment duration
Syphilis in pregnancy	**Early syphilis** **Benzathine benzylpenicillin** (IM): 2.4 million IU (≈ 1.8 g) Alternative options (not in the EML) in case of allergy to penicillin (or stock-outs): Ceftriaxone 1 g for 10–14 days Azithromycin (2 g single dose) or erythromycin (500 mg every 6 hours for 14 days) can also be used but neither of them crosses the placental barrier completely, therefore only the mother is treated, not the fetus.	**Early syphilis** Single dose
	Late syphilis or unknown stage **Benzathine benzylpenicillin** (IM): 2.4 million IU (≈ 1.8 g) Alternative option (not in the EML) in case of allergy to penicillin (or stock-outs): Erythromycin 500 mg every 6 hours for 30 days, but this does not treat the fetus since erythromycin does not cross the placental barrier completely, therefore only the mother is treated.	**Late syphilis or unknown stage** One dose per week for 3 consecutive weeks (e.g. on days 1, 8 and 15). The interval between doses should not exceed 14 days.

EML: Model List of Essential Medicines; IM: intramuscular; IU: international units; IV: intravenous;
Note. All dosages are for normal renal and hepatic function.

[a] Alternative options in case of allergy to penicillin or stock-outs are indicated in the 2016 WHO guidelines but these are not included in the EML for this indication. These alternatives are doxycycline (oral) 100 mg every 12 hours (except in pregnant women) for 14 days, or ceftriaxone 1 g (IM) for 10–14 days *(210)*. In special circumstances (i.e. when susceptibility is likely, based on local epidemiology) azithromycin 2 g (oral) as a single dose can be given. If penicillin cannot be used, doxycycline is the preferred choice (except in pregnant women) because of its lower cost and oral administration *(210)*.

[b] An alternative option, in case of allergy to penicillin or stock-outs, is indicated in the 2016 WHO guidelines but this option is not included in the EML for this indication. This option is doxycycline (oral) 100 mg every 12 hours (except in pregnant women) for 30 days *(210)*.

[c] If the mother was adequately treated and the infant is clinically normal, close monitoring of the infant is suggested. If treatment is provided, the 2016 WHO guidelines indicate benzathine benzylpenicillin (IM) 50 000 IU/kg (37.5 mg/kg) per day single dose as an option.

continues

Table 21.5 *continued*

[d] From the 2003 WHO guidelines on management of sexually transmitted infections *(219)*.
[e] Alternative options are indicated in the 2003 WHO guidelines for non-pregnant patients allergic to penicillin but they are not included in the EML. These options are: doxycycline (oral) 200 mg every 12 hours; and tetracycline (oral) 500 mg every 6 hours. Treatment duration is 30 days in both cases.
[f] Some authorities recommend adding benzathine benzylpenicillin 2.4 million IU (≈ 1.8 g) by IM injection, in three consecutive doses once weekly after completing this regimen, but there are no data to support this approach. Benzathine benzylpenicillin 2.4 million IU (≈ 1.8 g) by IM injection does not give adequate therapeutic levels in the cerebrospinal fluid *(210)*.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

Sexual transmission typically occurs only during primary, secondary and early latent infection. Mother-to-child transmission, however, has been documented to occur up to several years after the initial infection *(210)*.

Prevention of infection is a key strategy; no effective vaccine against *Treponema pallidum* is yet available therefore other preventive measures can be used.

The main elements of prevention include: comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling, and promoting consistent use of condoms. Interventions targeting groups who have a higher risk of infection – for example, men who have sex with men, transgender people, sex workers, people who inject drugs, indigenous communities and people in prison – should be considered. Offering HIV pre-exposure prophylaxis to people at high risk of HIV infection may be considered.

Access of pregnant women to early and adequate prenatal care, including screening at first visit and immediate treatment initiation if needed, are key to prevent congenital syphilis.

Sexual partners should always be informed of the infection and treated *(189)*. Reporting of this infection to health authorities according to local regulations should also be done.

22. Sexually transmitted infections – trichomoniasis

Note

In general this chapter applies to adults and young people older than 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.

Key messages

- Trichomoniasis is the most common curable sexually transmitted infection (STI) and in women it can manifest as a vaginal discharge; men are usually asymptomatic.
- Asymptomatic people should also be treated because they can transmit the infection to others and all people with trichomoniasis should also be evaluated for other STIs.
- Preventive services should be offered (e.g. condoms, brief sexuality education, human immunodeficiency virus (HIV) pre-exposure prophylaxis to people at high risk of HIV infection) and sexual partners should be informed and treated
- Reporting of this infection to health authorities is encouraged according to local regulations.

Other relevant WHO resources (please check regularly for updates)

- Sexually transmitted infections (STIs) – fact sheets *(189)*.
- WHO guidelines for the management of symptomatic sexually transmitted infections *(191)*.
- Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus *(192)*.
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 *(193)*.

Definition

Trichomoniasis is an STI caused by the protozoan *Trichomonas vaginalis*.

Trichomoniasis

Sexually transmitted infection

In general this guidance applies to adults and young people aged over 12 years. In children, specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse

Definition

A sexually transmitted infection (STI) caused by *Trichomonas vaginalis*

Diagnosis

Clinical Presentation

• Most persons have mild symptoms or remain asymptomatic (especially men) though they can still transmit the infection

Symptomatic infection:

• *In women*: acute onset of vaginal inflammation and discharge (frothy and with a bad smell), dysuria and pelvic pain

• *In men*: urethral discharge, dysuria and testicular discomfort or pain; rarely epididymitis and prostatitis can be present

Microbiology Tests

• See WHO guidance "Laboratory diagnosis of sexually transmitted infections" https://apps.who.int/iris/handle/10665/85343

• **Important**: all patients with suspected trichomoniasis should also be tested for other STIs (e.g. HIV, syphilis, gonococcal infection)

Tests to consider:

• Wet mount microscopy (easy and inexpensive but should be read within 10 minutes of sample collection)

• Nucleic acid amplification tests for *T. vaginalis* (very good sensitivity; preferred if available)

• Culture (good sensitivity but requires long incubation)

• Samples that can be used: Urethral, endocervical, and vaginal swabs

Other Laboratory Tests

Usually not needed

Imaging

Usually not needed

Pathogen

Trichomonas vaginalis is an anaerobe flagellated protozoan

Prevention

Important elements of prevention include:

• Sexuality education
• Promoting consistent use of condoms
• Pre- and post-test counselling
• Safe sex and risk reduction counselling
• Interventions targeting high-risk groups

Important:

• Sexual partners should be informed of the disease and treated
• Reporting of this infection to health authorities is encouraged according to local regulations

Treatment

Clinical Considerations

Treatment is aligned with the WHO 2021 guidelines for the management of symptomatic sexually transmitted infections (https://apps.who.int/iris/handle/10665/342523)

Treatment is always indicated when infection is diagnosed, including in asymptomatic persons because they can transmit the infection to others

Antibiotic Treatment Duration

Since treatment duration varies, please refer to the corresponding antibiotic section for treatment duration

• Evidence supports better cure rates with 7-day course (consider if treatment adherence is not an issue)

Antibiotic Treatment

All dosages are for normal renal function

ACCESS Metronidazole 2 g **ORAL**
Treatment duration: single dose

OR

ACCESS Metronidazole 400 or 500 mg q12h **ORAL**
Treatment duration: 7 days

Pathogen

Trichomoniasis is caused by *Trichomonas vaginalis*, an anaerobe flagellated protozoan.

Pathophysiology

Trichomonas vaginalis infects the mucosa of the urogenital tract during sexual contact and produces a local inflammatory response that causes vaginal or urethral discharge.

Epidemiology

Trichomoniasis is the most prevalent STI worldwide with an estimated 156 million new cases in 2020 as reported by WHO *(193)*.

The infection most commonly affects women older than 40 years. As with other STIs, the risk of acquiring or transmitting HIV is higher in cases of trichomoniasis and the infection is associated with adverse outcomes in pregnancy, such as preterm delivery, premature rupture of membranes and low birth weight *(220)*. If left untreated, trichomoniasis can persist for months or years and in pregnant women, it can be transmitted to the baby during delivery. Common risk factors for infection include multiple sex partners, a history of having other STIs (e.g. HIV infection) and substance abuse.

Clinical presentation

Most cases of trichomoniasis are asymptomatic, especially in men, or have mild symptoms. In women, symptoms include acute onset of vaginal inflammation and discharge (usually characterized by a bad smell and with a frothy appearance), dysuria and pelvic pain. In men, symptomatic infection usually presents with urethral discharge, dysuria, and testicular discomfort or pain. Epididymitis and prostatitis can also occur in a minority of cases.

Laboratory tests

For more comprehensive information on the diagnosis of trichomoniasis, please refer to the most recent (2013) WHO guideline on the laboratory diagnosis of STIs *(192)*. Please check the WHO website regularly for possible updates.

Patient microbiology tests

All people with trichomoniasis are also usually evaluated for other STIs, such as chlamydial infection, gonococcal infection, hepatitis B and hepatitis C, HIV infection and syphilis.

Tests to consider when trichomoniasis is suspected are indicated in Table 22.1.

Molecular assays such as nucleic acid amplification tests have the highest sensitivity of all diagnostic methods to detect *Trichomonas vaginalis* but they are not currently widely available as rapid point-of-care tests. However, if available, they should be used. Vaginal swabs are the samples of choice, but endocervical samples and urine can be used for some assays.

Historically, trichomoniasis has been diagnosed by performing wet mount microscopy. Although this is not the gold standard technique, a wet mount is frequently used because it is quick, inexpensive and easy to perform. However, to have a good chance of successfully identifying the motile trichomonads, the slide should be read within 10 minutes of collection of the sample since trichomonads quickly lose their motility. Non-motile cells cannot be diagnosed as trichomonads due to possible misidentification; for example, a non-motile trichomonad is difficult to differentiate from the nucleus of a vaginal epithelial cell.

Culture of *Trichomonas vaginalis*, which has a higher sensitivity than the wet mount microscopic examination, was the cornerstone for detecting this organism before the advent of point-of-care antigen tests and nucleic acid amplification tests. Although a culture medium is commercially available, cultures of samples from women with trichomoniasis are usually positive in the first 3 days of inoculation, but they have to be incubated for up to 7 days to rule out infection. Routine culture methods detecting *Trichomonas vaginalis* are no longer widely performed.

Additional tests for other STIs that could be considered when trichomoniasis is confirmed or suspected are shown in Table 22.2.

Table 22.1 – Microbiology tests to consider when trichomoniasis is suspected as indicated in the WHO EDL *(6)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy[a,b]	To assess microbial morphology and presence or absence of white blood cells	Health care facilities with clinical laboratories
Culture[b]	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

EDL: Model List of Essential In Vitro Diagnostics.

[a] If available, nucleic acid amplification tests for *Trichomonas vaginalis* could be considered, especially if the microscopy examination is negative. Nucleic acid tests for trichomoniasis are not listed in the third version of the EDL.

[b] Possible specimens are urethral swabs, endocervical swabs and vaginal swabs.

Table 22.2 – Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected trichomoniasis as indicated in the WHO EDL *(6)*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Chlamydial urogenital infection and gonococcal infection	Qualitative test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections (NAAT)	To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection	Health care facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories[a]
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people > 12 months	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Health care facilities with clinical laboratories

continues

Table 22.2 *continued*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people > 18 months	Community settings and health facilities without laboratories[a] (RDT) Health care facilities with clinical laboratories (immunoassay)
Syphilis	Antibodies to *Treponema pallidum*[b] (RDT)	To diagnose or help to diagnose *Treponema pallidum*	Community settings and health facilities without laboratories[a]
Syphilis and HIV combined test	Combined antibodies to *Treponema pallidum* and HIV-1/HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or *Treponema pallidum*	Community settings and health facilities without laboratories[a]

EDL: Model List of Essential In Vitro Diagnostics; HIV: human immunodeficiency virus; NAAT: nucleic acid amplification test; RDT: rapid diagnostic test.
[a] Community and health settings without laboratories are facilities such as health posts and centres, doctors' offices, outreach clinics, ambulatory care and home-based and self-testing. These tests are also assumed to be available at health care facilities with laboratories.
[b] Usually a non-treponemal test, such as rapid plasma reagin, Venereal Disease Research Laboratory test, is used for screening. Please refer to the chapter on syphilis for more details on testing.

Other tests

When trichomoniasis is suspected, laboratory tests (other than microbiology) are not usually needed.

Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

When trichomoniasis is suspected, imaging is not usually needed.

Antibiotic treatment

Antibiotic treatment is always indicated when trichomoniasis is diagnosed (Table 22.3), including in asymptomatic patients, to stop transmission. Sexual partners should also be tested and treated if infected.

Table 22.3 – Antibiotic treatment for trichomoniasis as indicated in the 2021 WHO guidelines for the management of symptomatic sexually transmitted infections *(191)*

Please check the WHO website regularly for possible updates

Treatment	Total treatment duration
Metronidazole (oral): 2 g	Single dose
OR	
Metronidazole (oral): 400 or 500 mg given every 12 hours[a]	7 days

Note. All dosages are for normal renal and hepatic function.
[a] If compliance is not a problem, consider giving 500 mg (oral) every 12 hours for 7 days. Evidence supports better cure rates with a 7-day course of treatment compared with a single dose *(221)*.
Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in orange and RESERVE antibiotics in red.

Prevention

No effective vaccine against *Trichomonas vaginalis* is available. Prevention of infection is therefore a key strategy. Important elements of prevention include counselling and behavioural approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling, and promoting consistent use of condoms. Interventions targeting high-risk groups (e.g. men who have sex with men, transgender people, sex workers and people who inject drugs) may be considered. Offering HIV pre-exposure prophylaxis to people at high risk of HIV infection may be considered.

Sexual partners should always be informed of the infection and treated *(189)*. Reporting of this infection to health authorities according to local regulations should also be done.

23. Lower urinary tract infection

Note

The focus of this chapter is community-acquired acute cystitis.

Key messages

- Urinary tract infections (UTIs) are more common in women and increase with age and frequency of sexual activity.
- Most cases are caused by *Escherichia coli*.
- Urine culture should be considered in children and in people at higher risk of complicated infections (e.g. men, pregnant women) or in the case of recurrent infections.
- Oral nitrofurantoin for 5 days is the main recommended treatment for lower UTIs.
- A positive urine culture in asymptomatic patients is not an indication for antibiotic treatment in the great majority of cases.

Other relevant WHO resources (please check regularly for updates)

- Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2013 *(31)*.

Definition

Lower UTIs are acute infections in which only the lower part of the urinary tract is affected, such as the bladder (e.g. cystitis). These infections are often classified as either complicated or uncomplicated based on the presence of risk factors that make them more difficult to treat.

Complications can occur with lower UTIs because of certain patient-related risk factors. While there is no universally accepted definition of what constitutes a complicated UTI, lower UTIs in individuals with certain conditions of the urinary tract (e.g. anatomical anomalies and kidney stones) are generally complicated. Infections in pregnant women are also usually included in this category. Examples of factors that may increase the risk of a complicated lower UTI are shown in Box 23.1 but should not be considered a complete list.

Box 23.1 – Factors that may increase the risk of a complicated lower urinary tract infection

- Obstruction at any site of the urinary tract
- Foreign body (e.g. urinary catheters and stents)
- Incomplete voiding
- Vesicoureteral reflux
- Recent history of instrumentation
- Male sex
- Pregnancy
- Diabetes
- Immunosuppression

Notes. The list gives some examples but is not aimed to be complete. No widely accepted definition of a complicated urinary tract infection currently exists. Some experts suggest that the list above is too long and may result in diagnosing too many patients with a complicated infection. The presence of one or more of these risk factors does not mean that the infection is complicated and in need of a different treatment approach.

Source: *Guidelines on urological infections of the European Association of Urology (222)*.

Lower urinary tract infection

Urinary tract infection • Page 1 of 2

Definition

• Infection of the lower part of the urinary tract (e.g. the bladder-cystitis)

• Urinary tract infections (UTI) in individuals with structural anomalies of the urinary tract or who are immunocompromised and in pregnant women are generally considered at greater risk of complicated evolution (complicated UTI)

Most Likely Pathogens

Bacteria:

• **Most common**:

- Enterobacterales (mostly *Escherichia coli* including multidrug-resistant strains such as those producing ESBL)

• **More rarely**:

- Coagulase-negative Staphylococci: *S. saprophyticus* (mostly in young women)
- *Streptococcus agalactiae* (group B *Streptococcus*)
- *Enterococcus* spp.
- *Pseudomonas aeruginosa* or *Acinetobacter baumannii* (including multidrug-resistant strains such as those producing ESBL especially in patients with recent antibiotic exposure)

Diagnosis

Clinical Presentation

Acute (< 1 week) dysuria, increased urinary urgency and frequency, lower abdominal pain or discomfort and sometimes gross hematuria

• In women, a vaginal source of the symptoms (vaginal discharge or irritation) should be excluded first

• In elderly patients with pre-existing urinary symptoms the most reliable symptoms of infection are acute urinary changes compared to the baseline

Microbiology Tests

In symptomatic patients:

• Urine culture if risk of complicated UTI and/or recurrent UTI (to confirm the diagnosis and adapt empiric treatment)

Important:

• A positive urine culture in an asymptomatic patient indicates bacterial colonization and does not require treatment except in pregnant women or in patients undergoing urological procedures in which bleeding is anticipated

• The absence of urine leucocytes has a good negative predictive value but the positive predictive value of leucocyturia is suboptimal

Other Laboratory Tests

In symptomatic patients:

• Urinalysis (dipstick or microscopy) to detect bacteriuria and/or indirect signs of infection (positive leucocyte esterase and nitrites)

• Blood tests usually not needed

Imaging

Usually not needed unless need to investigate possible underlying abnormalities of the urinary tract

Lower urinary tract infection

Urinary tract infection • Page 2 of 2

Treatment

Clinical Considerations

Antibiotic treatment recommended if compatible clinical presentation AND a positive test (positive urine leucocytes/leucocyte esterase or positive urine culture)

- If tests could not be performed, treat based on clinical presentation
- Clinical improvement should be evident within 48-72h
- Antibiotics shorten duration of symptoms by 1-2 days

Antibiotic Treatment Duration

Duration varies according to the antibiotic used - see corresponding antibiotic section

Note: in general consider longer treatments for pregnant women (usually 5 days) and men (usually 7 days)

Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS

Amoxicillin+clavulanic acid 500 mg+125 mg q8h **ORAL**
Treatment duration: 3-5 days

Active against some ESBL-producing isolates

OR

ACCESS

Nitrofurantoin **ORAL**
- 100 mg q12h (modified release formulation)
- 50 mg q6h (immediate release formulation)

Treatment duration: 5 days

Nitrofurantoin is the preferred treatment option for acute lower UTI and is active against most ESBL-producing isolates

OR

ACCESS

Sulfamethoxazole+trimethoprim 800 mg+160 mg q12h **ORAL**
Treatment duration: 3 days

Resistance is high in many settings and NOT active against most ESBL-producing isolates

OR

ACCESS

Trimethoprim 200 mg q12h **ORAL**
Treatment duration: 3 days

Resistance is high in many settings and NOT active against most ESBL-producing isolates

Lower urinary tract infection

Urinary tract infection • Page 1 of 2

Definition

• Infection of the lower part of the urinary tract (e.g. the bladder-cystitis)

• Urinary tract infections (UTI) in children with structural anomalies of the urinary tract (e.g. vesicoureteral reflux or other congenital anomalies) or who are immunocompromised are generally considered at greater risk of complicated evolution (complicated UTI)

Most Likely Pathogens

Bacteria:

• **Most common**:

- Enterobacterales (mostly *Escherichia coli* including multidrug-resistant strains such as those producing ESBL)

• **More rarely**:

- *Streptococcus agalactiae* (group B *Streptococcus*)
- *Enterococcus* spp.
- *Pseudomona aeruginosa* or *Acinetobacter baumannii* (including multidrug-resistant strains such as those producing ESBL especially in patients with recent antibiotic exposure)

Diagnosis

Clinical Presentation

• Acute (< 1 week) dysuria, increased urinary urgency and frequency, incontinence/wetting, lower abdominal pain or discomfort and sometimes hematuria

• Generally no systemic signs/symptoms (e.g. fever)

• In girls, a vaginal source of the symptoms (vaginal discharge or irritation) should be excluded first

Microbiology Tests

In symptomatic patients:

• Urine culture (always in children) to confirm the diagnosis and adapt empiric treatment

Important:

• A positive urine culture in an asymptomatic patient indicates bacterial colonization and does not require treatment except in patients undergoing urological procedures in which bleeding is anticipated

• The absence of urine leucocytes has a good negative predictive value but the positive predictive value of leucocyturia is suboptimal

Other Laboratory Tests

In symptomatic patients:

• Urinalysis (dipstick or microscopy) to detect bacteriuria and/or indirect signs of infection (positive leucocyte esterase and nitrites)

• Blood tests usually not needed

Imaging

Usually not needed unless need to investigate possible underlying abnormalities of the urinary tract

Lower urinary tract infection

Urinary tract infection • Page 2 of 2

Treatment

Clinical Considerations

Antibiotic treatment recommended if compatible clinical presentation AND a positive test (positive urine leucocytes/leucocyte esterase or positive urine culture)

- If tests could not be performed, treat based on clinical presentation
- Clinical improvement should be evident within 48-72h
- Antibiotics shorten duration of symptoms by ~2 days

Antibiotic Treatment Duration

Duration varies according to the antibiotic used - see corresponding antibiotic section

Antibiotic Treatment

All dosages are for normal renal function

Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

ACCESS

Amoxicillin+clavulanic acid 80-90 mg/kg/day of amoxicillin component **ORAL**

- **Oral weight bands**:

3-<6 kg	250 mg of amox/dose q12h
6-<10 kg	375 mg of amox/dose q12h
10-<15 kg	500 mg of amox/dose q12h
15-<20 kg	750 mg of amox/dose q12h
≥20 kg	500 mg of amox/dose q8h or 1 g of amox/dose q12h

Treatment duration: 3-5 days

Amox = amoxicillin
Active against some ESBL-producing isolates
Must refrigerate oral liquid after reconstitution

OR

ACCESS

Nitrofurantoin 2 mg/kg/dose q12h OR 1 mg/kg/dose q6h (immediate-release formulation) **ORAL**

Treatment duration: 5 days

Nitrofurantoin is the preferred treatment option for acute lower UTI and is active against most ESBL-producing isolates

OR

ACCESS

Sulfamethoxazole+trimethoprim 20 mg/kg + 4 mg/kg q12h **ORAL**

- **Oral weight bands**:

3-<6 kg	100 mg+20 mg q12h
6-<10 kg	200 mg+40 mg q12h
10-<30 kg	400 mg+80 mg q12h
≥30 kg	800 mg+160 mg q12h

Treatment duration: 3 days

Resistance is high in many settings and NOT active against most ESBL-producing isolates

OR

ACCESS

Trimethoprim 4 mg/kg q12h **ORAL**

- **Oral weight bands**:

3-<6 kg	20 mg q12h
6-<10 kg	40 mg q12h
10-<30 kg	80 mg q12h
≥30 kg	200 mg q12h

Treatment duration: 3 days

Resistance is high in many settings and NOT active against most ESBL-producing isolates