Microbiology Nuts & Bolts

Key Concepts of Microbiology & Infection

3rd Edition

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About the Author

The author has been described as a gifted teacher and educator, who has an exceptional level of microbiology and infectious diseases knowledge, with an even greater ability to translate that knowledge so that others can also understand this often complicated subject. His award-winning teaching is the highlight of many medical students' clinical attachments and as a result of his dedication to the subject, many junior colleagues have been motivated and inspired to enter a career in Microbiology.

He qualified from Southampton University Medical School in 1997 and has worked in diverse areas of medicine, general surgery, emergency medicine and paediatrics. Now, as a Consultant Clinical Microbiologist in a United Kingdom NHS hospital, he spends his days diagnosing, treating and managing infections as well as teaching others how to do this safely and effectively.

Microbiology textbooks often considered by students to be dull and contain long lists of boring bacterial names; they appear to have little relevance to clinical medicine. The author recognised there was a need for a clinically-orientated no-nonsense microbiology book, so he decided to get on and write one. The feedback has been amazing, with both the first and second editions of Nuts & Bolts regularly making the list of top 3 microbiology textbooks on Amazon.co.uk. The website and accompanying Bug Blog are read worldwide by thousands of interested people every week and it is clear that many of you out there really value "Nuts & Bolts".

The author is ever grateful for your continuing support.

www.microbiologynutsandbolts.co.uk

Introduction

Microbiology Nuts & Bolts helps doctors and healthcare staff to confidently identify the microorganisms causing an infection and understand how to treat them. The book is set out by condition rather than microorganism allowing for quick reference in a clinical setting. Readers regularly comment just how amazing it is that so much information has been packed into such a small book. It is not an all-encompassing reference text and is deliberately not referenced extensively in order to keep its presentation simple. It is concise enough to be of use on a daily basis, be it on a ward or in a clinic, yet detailed enough to promote a thorough understanding of microorganisms, their management and the treatment of patients. It has received fantastic feedback in reviews by the Royal College of Physicians, the Royal College of Pathologists, the Royal Pharmaceutical Society, the Hospital Infection Society, the British Society for Antimicrobial Chemotherapy, the Institute of Biomedical Science and the Society for Applied Microbiology.

The book is divided into six parts: Basic Concepts, Microbiology, Infection Control, Clinical Scenarios, Antibiotics and Emergencies. It is best to read Basic Concepts and Microbiology first, as this gives the building blocks to understanding infection. After that, the Clinical Scenarios and Antibiotics sections aid diagnosis and management of specific infections.

Emergencies have been separated into their own section to ensure they can be found quickly. Flowcharts help guide initial emergency treatment, which often needs to be implemented immediately in order to save lives, although they are not a replacement for experienced senior support. Infection Control does not go into depth regarding policies and politics but gives practical advice about preventing the spread of infections and what to do when you have too many patients for the side rooms available.

The previous editions were well received by doctors and healthcare staff and as always their valuable feedback has been instrumental in shaping this, the latest edition. Existing sections have been fully updated and new sections have been added for acute bronchitis, necrotising pancreatitis and Lyme disease as well as new antibiotics and updates for the management of sexually transmitted infections and infection control precautions for viral haemorrhagic fevers. The Emergencies section has undergone extensive revision to take into account changes in UK national guidelines for the management of sepsis, meningitis, encephalitis and malaria. The size has also changed to accommodate larger text but we hope it still remains small enough to be your go to pocket book.

We have been asked many times why is there no App for Microbiology Nuts & Bolts? The short answer is that Apps are great at giving answers but less able to "teach", leading to healthcare staff blindly following algorithms and proformas instead of understanding the fundamental principles of medicine...so no, there is no App!

The ultimate aim of the book is to empower doctors and healthcare staff to manage patients with infections better; if it achieves this then it is a success.

P.S. Don't forget to write a review on Amazon and like us on FaceBook where you'll find the latest edition of the Bug Blog.

First published: 2013. Second edition: 2014. Third edition: 2019.
ISBN-13: 978-1-9160071-0-9

Hard work, artwork and front cover: J Garner
Editor Chief in Charge: J Garner

A clinically focused, no-nonsense pocket book to the key elements of microbiology and infection. A must-have guide to stop common and often unnecessary mistakes that occur in everyday medicine and antibiotic prescribing.

Dedication
To Jenny and the cat club who are still helping and hindering in equal measure and using inappropriate terms in an untimely manner such as "that should be straight-forward" and "it will be simple"!

Disclaimer
The author and the publisher have made every effort to ensure that the information is as accurate and up-to-date as possible (2019). Therefore, except for any liability which cannot be excluded by law, neither the publisher nor the author accept liability for damage of any nature (including damage to property, personal injury or death) arising directly or indirectly from the information in this book.

If you like this book, recommend it to someone else. If you don't, then tell us why at...

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Basic Concepts

What is Infection? Infection vs. Colonisation vs. Contamination

Infection is the presence of microorganisms causing damage to body tissues, usually in the presence of acute inflammation (pain, swelling, redness, heat and loss of function). For example *Staphylococcus aureus* on intact skin does not cause a problem; it is the normal flora for skin. However, if you cut your skin, *Staphylococcus aureus* can cause infection in the cut with associated inflammation and tissue damage.

Microorganisms can also cause damage in the absence of inflammation but it is unusual, e.g. in neutropaenic patients with angio-invasive fungal infections causing tissue infarction.

Colonisation describes when bacteria grow on body sites exposed to the environment, without causing infection. This is a normal process. These bacteria may form part of the normal flora of the individual; however colonisation is not necessarily normal flora. Occasionally, bacteria which are not normally regarded as part of the normal flora can also colonise body areas e.g. *Pseudomonas* spp. in a wound is not normal flora of the skin or a wound but it is not actually causing tissue damage or infection; it is just growing in the warm wet conditions of the wound. *Pseudomonas* spp. are the normal flora of warm wet places. Likewise, some prosthetic devices can also become colonised with bacteria without causing infection e.g. urinary catheters.

Colonisation does not normally harm the patient and does not usually need treating with antibiotics e.g. *Neisseria meningitidis* can be found in up to 30% of the healthy population in their oropharynx. However, infection can result in harm and often needs treatment with antibiotics e.g. if *Neisseria meningitidis* enters the bloodstream from the oropharynx to cause septicaemia, then it needs urgent treatment.

Examples of colonisation

Body Site or Prosthetic Device	**Bacterial Colonisation**
Pressure sores	• Skin flora e.g. *Staphylococcus* spp. • Enteric flora e.g. *Enterococcus* spp., *Escherichia coli*, *Pseudomonas* spp.
Breaks in the skin e.g. wounds	• Skin flora e.g. *Staphylococcus* spp. • Enteric flora e.g. *Enterococcus* spp., *Escherichia coli*, *Pseudomonas* spp.
Upper respiratory tract	• Mixed enteric flora in patients given antibiotics or who have been in healthcare settings for more than 4 days e.g. *Enterococcus* spp., *Escherichia coli*, *Pseudomonas* spp.
Urinary catheter	• Enteric flora e.g. *Enterococcus* spp., *Escherichia coli*, *Pseudomonas* spp.
Endotracheal tube **OR** Tracheostomy tube in a ventilated patient	• Mixed enteric flora in patients given antibiotics or who have been in healthcare settings for more than 4 days e.g. *Enterococcus* spp., *Escherichia coli*, *Pseudomonas* spp.

Warning
In the absence of good clinical information on request forms (see section – Microbiology, Why Bother Completing Request Forms?) microbiology laboratories are unable to distinguish between colonisation and infection and so will just report the presence of bacteria. It is then up to the clinician to decide if these bacteria are causing infection.

Better filled in request forms lead to better clinical advice from microbiology services.

Contamination is the presence of a microorganism that has been introduced into a microbiology sample from an external source e.g. poor technique when taking the sample, a swab touching a surface before being used, sneezing over a patient whilst they provide a sputum sample. Contamination can also occur when a sample is not collected correctly and the patients "normal flora" (microorganisms growing in their normal environment) gets into the sample e.g. urine taken incorrectly can contact perineal skin and pick up the "normal microorganisms" which then grow in the laboratory (the presence of epithelial cells in the urine sample indicates definite contact with skin and therefore a risk of contamination).

What is Normal Flora and why is it Important?

Normal flora is the community of microorganisms that live on another living organism (human or animal) or inanimate object without causing disease. The human body is not sterile; we become colonised with bacteria from the moment we are born. We are covered with, and contain within our intestines, approximately one hundred trillion (10^{14}) bacteria that form the normal flora of our bodies. This normal flora helps prevent us being colonised with dangerous bacteria, which might lead to infection.

Microbiome is the term for a community of normal microorganisms.
Dysbiosis is the term for the disruption of the microbiome, removing normal microorganisms or the growth of abnormal microorganisms.

Many circumstances can change normal flora. For example, the normal flora of the human body begins to change after admission to a hospital or long-term care facility. The process usually begins around day 4 of admission; this is why after 4 days of admission the antibiotics for hospital acquired infections change. It is not because the severity of the illness is different.

Knowledge of the normal flora of the human body allows:

- Prediction of the pathogens causing infection as bacteria tend to grow in specific body sites e.g. *Streptococcus pneumoniae* from the upper respiratory tract causing pneumonia or *Staphylococcus aureus* from the skin causing intravenous cannula infections
- Investigation for underlying abnormalities in specific areas of the body when bacteria are isolated from normally sterile sites e.g. *Escherichia coli* isolation from blood cultures indicates probable intra-abdominal pathology as *E. coli* is part of the normal gastrointestinal flora, or growth of an Alpha-haemolytic *Streptococcus* sp. in blood cultures may indicate infective endocarditis as a result of poor dentition as Alpha-haemolytic *Streptococcus* spp. are part of the normal mouth flora

Nothing is 100% accurate but knowing where bacteria normally live can help work out when they are in the wrong place. This allows predictions of the likely causes of disease and hence the choice of suitable antibiotics for empirical therapy. Knowing which factors affect normal flora allows predictions to be made as to what the flora will become under the influence of those factors, e.g. exposure to antibiotics removes sensitive bacteria, so if a patient with a cut hand, and a sensitive *Staphylococcus aureus* (MSSA) in their normal flora, is given Flucloxacillin for the cut, a void will be left behind which could be filled by a Flucloxacillin resistant bacterium such as Meticillin resistant *Staphylococcus aureus* (MRSA).

Myth
Bacteria have no place in our environment. **FALSE** - Bacteria are part of the normal environment. Almost everything has its own normal flora. Hospitals, the community, soil, animals, air conditioning units and swimming pools all have their own "normal flora". However, certain things like surgical instruments and synovial fluid should be sterile. If something contains its normal flora it is normal; if it grows something else's normal flora e.g. synovial fluid grows skin flora, it is abnormal. Knowing where normal flora comes from allows you to identify the likely cause of infection or know where to investigate.

Circumstances Affecting Normal Flora

Certain circumstances allow microorganisms the opportunity to become part of a person's normal flora. It is usually a combination of factors: right person, in the right place at the right time... (or wrong place at the wrong time if you are the person).

Right Person

The right personal circumstances to allow colonisation.

- Patients are more easily colonised because their diseases, treatments or medical procedures often remove or bypass the normal mechanisms for preventing colonisation e.g. cannulae breach the skin barrier, antacid drugs reduce gastric acid production, steroids prevent white blood cells from functioning properly and cystic fibrosis patients do not clear mucus from their lungs effectively due to changes in the mucociliary escalator
- Contact with companion animals. Companion animals often share normal flora with their owners. The normal flora of a cat owner will often contain *Pasteurella multocida*; part of a cat's normal URT flora
- Lifestyle choices (smoking, alcohol misuse, drug abuse or obesity) can alter normal flora damaging tissue, breaching barriers, acting as an immunosuppressant, or creating microorganism-loving environments

Right Place

The right environmental circumstances to allow colonisation.

- Hospitals admit patients with infections caused by microorganisms that can be readily transferred to other people, e.g. each gram of stool from a patient with *Norovirus* contains 1 billion infectious particles
- Antibiotic resistant bacteria are more common in hospitals as antibiotics are frequently used to treat patients with infections. This creates a selective pressure, removing sensitive bacteria and leaving resistant bacteria behind to settle in the environment e.g. Flucloxacillin given for skin infections may select out MRSA
- The hospital environment can become seeded with bacteria which remain in the environment after a patient has been discharged, e.g. *Clostridium difficile* produces spores which are difficult to kill and can survive for up to 6 months in an environment without proper cleaning

Right Time

The right moment to colonise.

- Exposure to antibiotics removes sensitive bacteria from normal flora; leaving a void other bacteria will fill. Coming into contact with a microorganism whilst on, or having recently taken, an antibiotic allows the opportunity for the new microorganism to establish itself as part of the normal flora
- Bacteria in the food chain can become part of a person's normal flora after eating contaminated food e.g. GRE in chickens and ESBL-positive *Escherichia coli* in "pre-washed" salads. These microorganisms do not necessarily make the person ill at the time of acquisition but can later cause infection if they get into the wrong body site, e.g. ESBL-positive *Escherichia coli* causing a UTI

Bacterial Flora in a Normal Person in the Community

Below are body sites and their common normal flora; isolating these microorganisms from their normal body site is normal and does not indicate infection. Knowing where microorganisms are normally found helps identify a cause if they migrate from their normal body site into another body site. The microorganisms listed below are also most likely to cause disease if they migrate to another body site. For example, *Escherichia coli* from the gastrointestinal tract gets into the urogenital tract causing a UTI.

Upper Respiratory Tract

- *Staphylococcus* spp.
- *Streptococcus* spp.
  - *Streptococcus pneumoniae*
  - Alpha-haemolytic *Streptococcus* spp.
- *Haemophilus* spp.
- Anaerobes

Skin

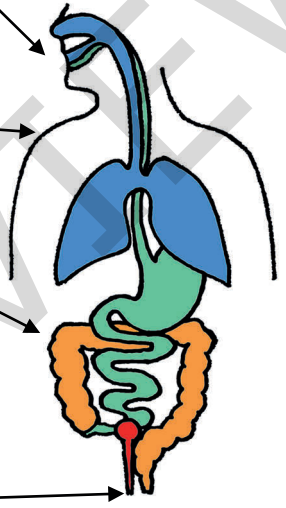
- *Staphylococcus* spp.
- Coryneform bacteria or "Diphtheroids"
- *Cutibacterium* spp.

Gastrointestinal Tract

- Anaerobes
- *Enterococcus* spp.
- Enterobacteriaceae
  - *Escherichia coli*
  - *Klebsiella* spp.
- *Streptococcus* spp.
  - *Streptococcus anginosus* group
- *Lactobacillus* spp.
- *Candida* spp.

Genital Tract

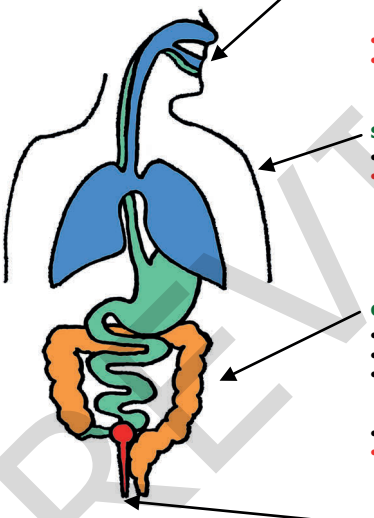
- *Lactobacillus* spp.
- *Streptococcus* spp.
  - *Streptococcus agalactiae*



In the community, normal flora is generally sensitive to antibiotics.

Bacterial Flora in a Normal Person in a Hospital or Long-term Care Facility

Below are body sites and their common normal flora for a hospital patient or a person in a long-term care facility. They are different to community normal flora because of exposure to different microorganisms, physiological changes, immunosuppressants and selective pressures. Isolating these microorganisms from their normal body site in hospitals or long-term care facilities is normal and does not indicate infection.



Upper Respiratory Tract
- *Staphylococcus* spp.
- Anaerobes
- Enterobacteriaceae
  - *Escherichia coli*
  - *Klebsiella* spp.
- *Candida* spp.
- *Pseudomonas* spp.

Skin
- *Staphylococcus* spp.
- Enterobacteriaceae
  - *Escherichia coli*
  - *Klebsiella* spp.

Gastrointestinal Tract
- Anaerobes
- *Enterococcus* spp.
- Enterobacteriaceae
  - *Escherichia coli*
  - *Klebsiella* spp.
- *Candida* spp.
- *Pseudomonas* spp.

Genital Tract
- *Candida* spp.

In hospital environments most of the normal flora remains sensitive to antibiotics but added to these are normal flora that are resistant to antibiotics and environmental factors, such as drying, alcohol hand scrubs or detergents (these more resistant microorganisms are shown in red)

Diagnosing Infection: History

It may sound obvious but in order to manage a patient with an infection safely and effectively you first have to work out what is wrong with them. This is done through the dynamic process of formulating a **differential diagnosis**. The process begins the moment the patient is referred (e.g. you are told the patient has a cough; you narrow questioning to the respiratory system and a differential diagnosis that includes diseases like pneumonia, lung cancer, COPD etc.). By taking a **history**, **examination** and requesting targeted **investigations** you narrow down the differential diagnosis until you get to a single diagnosis.

A **differential diagnosis** is a list of potential diseases or infections that a patient might have. The simplest and most effective method of formulating a differential diagnosis is:

- **Immediately life-threatening** conditions e.g. meningitis, encephalitis, necrotising fasciitis
- **Common** conditions e.g. UTI, pneumonia, cellulitis, heart failure
- **Uncommon** conditions e.g. infective endocarditis

In the **history**, the key infection-related aspects to concentrate on are:

History	Examples of Significance
The patient's specific symptoms	• Cough indicating chest or upper respiratory tract • Right upper quadrant pain indicating possible cholangitis
A chronological timeline of when and how symptoms developed	• Chicken Pox followed by haemorrhagic skin lesions pointing towards invasive Group A Beta-haemolytic *Streptococcus* and necrotising fasciitis
Contact with people with infections or symptoms	• Tuberculosis contact
A list of recent travel (countries and regions)	• Malaria endemic regions
The patient's vaccination history	• Primary childhood courses as well as travel-related vaccines
The patient's current and former occupations	• Healthcare staff and blood-borne viruses • Plumber and exposure to *Legionella pneumophila*
The patient's pastimes and hobbies	• Water sports and exposure to rats in leptospirosis
Any pets or contact with animals	• Zoonotic infections e.g. *Pasteurella multocida* and cat bites, *Chlamydophila psittaci* and parrots
A sexual history	• Sexually transmitted diseases and blood-borne viruses
The patient's ethnic origin	• Exposure to relatives with tropical infections
The patient's country of birth	• Chronic tropical infections • Exposure to relatives with tropical infections

Microbiology

How to Take Microbiology Specimens

Aseptic Technique

Aseptic technique is a procedure that is designed to minimise contamination. Microbiology samples should be taken aseptically to prevent contamination with bacteria e.g. if you take blood cultures without aseptic technique it is likely that the result will be a skin contaminant rather than the cause of the infection.

Examples of techniques to minimise the risk of contamination:

- Blood cultures and CSF - clean the skin with 2% Chlorhexidine and wear gloves
- Midstream urine specimen (MSU) - part the labia or retract the foreskin, void the first part of the urine stream (10-20mls at least) and then collect the next portion (approx. 10-20mls)
- Wound swabs - remove slough (which is dead and detached tissue and is not a sign of infection), debride the wound to reveal the fresh tissue beneath, swab the fresh tissue
- Sputum - ask patients to cough sputum immediately into the specimen container rather than holding it in the mouth whilst looking for a container

Sample Before Treatment

If safe to do so, take microbiology samples before starting antibiotics otherwise those antibiotics may inhibit the growth of bacteria, causing negative cultures.

Blood Cultures First

Always take blood cultures before any other blood samples because other blood sample collection bottles are not necessarily sterile and can therefore contaminate the blood culture collection kit. This will lead to contaminated blood cultures, known as pseudobacteraemia.

Aerobic Bottle First

Take the aerobic bottle before the anaerobic bottle in case there is not enough blood for both bottles e.g. if the needle comes out of the patient's arm. You are more likely to diagnose infection from the aerobic blood culture bottle because more pathogenic bacteria grow in this type of bottle than the anaerobic bottle.

Cerebrospinal Fluid

Do not forget to take a sample for peripheral blood glucose, at the same time as CSF protein and CSF glucose. The glucose levels need to be compared and therefore done at the same time. As glucose levels vary, if peripheral blood glucose is forgotten you will not be able to take the sample later as the comparison will not be valid. The comparison allows a distinction to be made between bacterial meningitis and other causes of meningitis (see section – Emergencies, Meningitis).

Avoid a Quick Swab

If possible send pus or tissue rather than swabs because pus and tissue can be Gram stained allowing recognition of bacteria or fungi that are present but which have failed to grow on culture.

Hints and Tips

What's the difference between cultures and Gram stains? **Microscopy** includes any investigation using a microscope, including the Gram stain. **Culture** is whatever grows after incubation e.g. on the agar plate. They are not necessarily the same; antibiotics can inhibit growth in culture, microorganisms may not grow fast enough or may have specific growth requirements that prevent them being cultured even though they can be seen on microscopy. Therefore microscopy may give a more complete view whereas culture may not. Culture, however, will give the microorganisms names and provide antibiotic **sensitivities**. Microscopy, Culture and Sensitivities are often abbreviated to MC&S.

For example: At the time of appendicectomy the patient is on Cefuroxime and Metronidazole. The intra-abdominal pus sample is sent to the laboratory, the result later shows:

Result

Specimen	Pus
Appearance	-
Microscopy	Gram-positive cocci in chains Gram-negative bacilli Yeasts
Culture	Enterococcus faecium - Amoxicillin resistant - Vancomycin sensitive

The microscopy shows a mixture of bowel flora, but the *Enterococcus faecium* is the only bacterium that grows on culture because it is inherently resistant to Cefuroxime and Metronidazole. The yeast may not have had sufficient time to grow on culture. It would be a mistake to only treat the *Enterococcus faecium* as the microscopy clearly shows the presence of other bowel flora.

How to Interpret Microbiology Results - Bacteriology

There are methods to systematically read chest X-rays (see Appendix 1), and a similar approach should be taken to laboratory results. They are multipart results and reading the parts in isolation means you will misinterpret the significance of the result. In order to correctly interpret a bacteriology report all three parts (if given) need to be considered in this order:

Appearance

- A description of the appearance of the sample e.g. purulent, bloodstained, turbid, clear
- Is there evidence of inflammation or disease e.g. purulent sputum, pus or liquid stool
- Is there evidence of contact with a non-sterile site or absence of disease e.g. salivary sputum, formed stool

Microscopy

- A list of the different appearances of microorganism present e.g. the report states a Gram-positive coccus in chains seen on the Gram film
- Is there evidence of contact with a non-sterile site or absence of disease e.g. epithelial cells in urine
- Is it consistent with the diagnosis e.g. the patient has symptoms of cough, SOB and fever; a possible diagnosis is pneumonia and pneumonia can be caused by a Gram-positive coccus in chains

Warning
BEWARE neutropaenic patients may be unable to mount a white blood cell response. They can grow bacteria and have significant infections in the absence of inflammation.

Culture and sensitivity

- A list of the microorganisms which have grown
- Is it consistent with the diagnosis e.g. *Streptococcus pneumoniae* is cultured from a patient with pneumonia
- A list of antibiotics used to treat the bacteria that were cultured; it is not usually necessary to give every sensitive antibiotic listed.
  - The list of antibiotics allows choices based around potential allergies to antibiotics
  - You may have to use combinations of antibiotics to treat mixed infections e.g. *Escherichia coli* and *Bacteroides* spp. with Cefuroxime and Metronidazole

Common Mistake
Some doctors assume that if bacteria are grown from a patient's specimen then antibiotics should be given. **This is a mistake.** Growth of bacteria in the absence of inflammation (i.e. normal microscopy or no white blood cells), or growth of bacteria in the presence of other factors (e.g. epithelial cells in urine) is an indication of probable contamination or colonisation, not infection. Do not over interpret the significance of these results.
REMEMBER Bacteria are normal in certain places as colonisers or normal flora.

Occasionally other tests are performed and reported separately as they do not fit the usual sequence of Appearance, Microscopy and Culture. They are performed when the clinical details alert the laboratory to the need for further or specific testing.

- **Antigen detection**
  - Clinical details state CAP e.g. the laboratory conducts the tests for urine Pneumococcal and Legionella antigens
  - Clinical details state an outbreak of diarrhoea and vomiting e.g. the laboratory conducts the tests for *Norovirus* and *Rotavirus* in stool
- **Molecular detection of nucleic acid or Polymerase Chain Reaction (PCR)**
  - Clinical details state meningitis e.g. the laboratory conducts the tests for *Neisseria meningitidis* and *Streptococcus pneumoniae* PCR on EDTA blood or CSF
- **Toxin detection**
  - Clinical details state diarrhoea after starting Ciprofloxacin e.g. the laboratory conducts the tests for *Clostridium difficile* toxin in stool

Basic Bacterial Identification by Microscopy

There are too many microorganisms to remember easily so they need to be separated into groups with similar features. Microbiologists use a number of terms to describe the different appearances of bacteria; Gram-positive or Gram-negative, coccus or bacillus etc. For example, the Microbiologist might telephone with a result, saying "the cause is a Gram-negative bacillus growing both aerobically and anaerobically". This may appear to be pointless jargon but using a simple system of firstly identifying the staining method, then the shape of the microorganism and finally the microorganism's growth requirements, a doctor can begin to eliminate microorganisms, like in a game of Cluedo®, in order to identify the most likely cause of the infection.

If a microorganism is Gram-negative, it cannot be any of the Gram-positives or acid-fast bacilli and therefore these can be discounted. If the microorganism is bacillus-shaped then all of the cocci can be discounted. If the microorganism is then described as growing anaerobically, the aerobes can be discounted; and if it is also described as growing aerobically as well as anaerobically the anaerobes can also be discounted. This identifies the microorganism as a Gram-negative bacillus growing as a facultative anaerobe e.g. an Enterobacteriaceae, *Haemophilus* spp., *Eikenella* spp., *Pasteurella* spp. or *Capnocytophaga* spp. The clinical history can then narrow the list further because if the patient has CAP it is probably a *Haemophilus* spp., if they have a cat bite it is probably a *Pasteurella* spp., and if they have pyelonephritis it will be one of the Enterobacteriaceae.

Identifying the staining method

Ziehl-Neelsen Stain	Acid-fast	Stains red using the ZN method, bacteria have mycolic acid in their cell wall
Gram Stain	Gram-positive	Stains purple with Gram's method, bacteria have a thick cell wall and no cell membrane
	Gram-negative	Stains red with Gram's method, bacteria have a cell membrane outside a thin cell wall

Identifying the shape

Coccus	Shaped like a sphere
Bacillus	Shaped like a rod

Identifying the growth requirements

Aerobic	Grows in the presence of oxygen
Anaerobic	Grows in the absence of oxygen
Facultative Anaerobe	Able to grow in the presence or absence of oxygen
Microaerophilic	Grows in the presence of oxygen at lower concentrations than in air

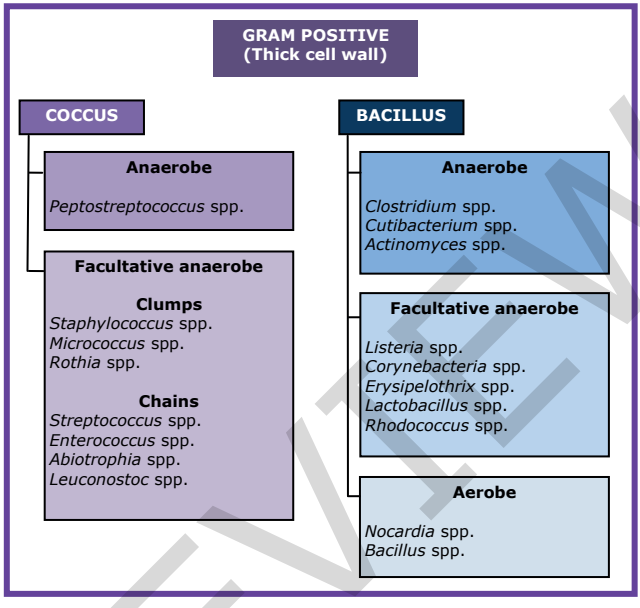
Knowledge of bacterial identification from the Gram film appearance helps predict the cause of an infection from the microscopy result up to 48 hours before the culture result is available. By using both the Basic Bacterial Identification diagrams and the Table of Bacterial Causes of Infection (following pages) you can identify the likely bacteria from the Gram film appearance on the microscopy result. For example:

- The patient clinically has meningitis; the Gram film of the CSF shows Gram-positive cocci in chains. Meningitis is caused by *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Haemophilus influenzae* and *Mycobacterium tuberculosis*. We know it is Gram-positive therefore ruling out *Neisseria meningitidis* and *Haemophilus influenzae*, which are Gram-negative, and *Mycobacterium tuberculosis*, which is an acid-fast bacillus. The microscopy also states coccus, which rules out *Listeria monocytogenes* as this is a bacillus. This leaves *Streptococcus pneumoniae*, a chain-forming Gram-positive coccus

- The patient clinically has septic arthritis; the Gram film of the synovial fluid shows Gram-positive cocci in clumps. Septic arthritis is caused by *Staphylococcus aureus*, Beta-haemolytic *Streptococcus* (Groups A, B, C, G), *Escherichia coli* and other Enterobacteriaceae. As it is Gram-positive this rules out *Escherichia coli* and other Enterobacteriaceae, which are Gram-negative. The microscopy also states clumps, which rules out *Streptococcus* spp. as these form chains. This leaves *Staphylococcus aureus*, a clump-forming Gram-positive coccus

- The patient clinically has peritonitis; the Gram film of the peritoneal fluid shows Gram-positive cocci in chains, Gram-positive bacilli and Gram-negative bacilli. Peritonitis is caused by bowel flora including: *Enterococcus* spp., *Clostridium* spp., *Bacteroides* spp., *Escherichia coli* and other Enterobacteriaceae. The mixed Gram film appearance shows the presence of the entire bowel flora. This indicates the patient has probably perforated their bowel rather than developed spontaneous bacterial peritonitis. Even this result is helpful as it indicates there is a hole in the bowel. The patient needs surgery not just antibiotics, as no antibiotic tablet is large enough to plug the hole! Antibiotics will only help if the hole is surgically repaired

Basic Bacterial Identification



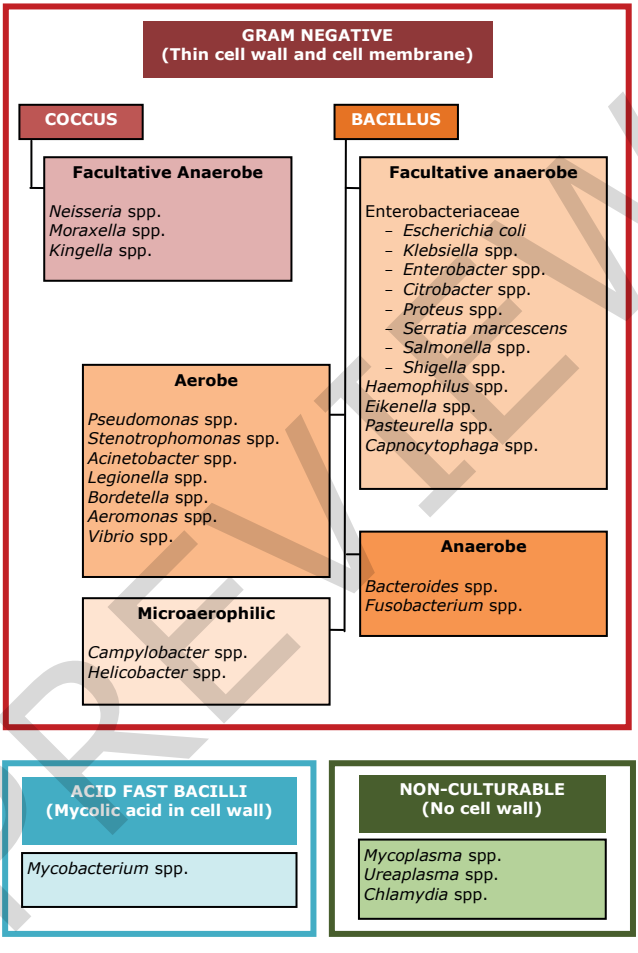

GRAM NEGATIVE
(Thin cell wall and cell membrane)
COCCUS
BACILLUS
Facultative Anaerobe
Neisseria spp.
Moraxella spp.
Kingella spp.
Facultative anaerobe
Enterobacteriaceae
– Escherichia coli
– Klebsiella spp.
– Enterobacter spp.
– Citrobacter spp.
– Proteus spp.
– Serratia marcescens
– Salmonella spp.
– Shigella spp.
Haemophilus spp.
Eikenella spp.
Pasteurella spp.
Capnocytophaga spp.
Aerobe
Pseudomonas spp.
Stenotrophomonas spp.
Acinetobacter spp.
Legionella spp.
Bordetella spp.
Aeromonas spp.
Vibrio spp.
Anaerobe
Bacteroides spp.
Fusobacterium spp.
Microaerophilic
Campylobacter spp.
Helicobacter spp.
ACID FAST BACILLI
(Mycolic acid in cell wall)
Mycobacterium spp.
NON-CULTURABLE
(No cell wall)
Mycoplasma spp.
Ureaplasma spp.
Chlamydia spp.

Table of Bacterial Causes of Infection

✓ = Common Cause – = Not a Common cause

Clinical Scenarios	Gram-positive Bacteria								Anaero-	
	Staphylococcus aureus (MSSA)	Staphylococcus aureus (MRSA)	Coagulase Negative Staphylococcus	Beta-haemolytic Streptococcus (A, B, C, G)	Enterococcus faecalis	Enterococcus faecium	Streptococcus pneumoniae	Listeria monocytogenes	Clostridium perfringens	Clostridium difficile
Respiratory Infections										
Community Acquired Pneumonia (CAP)	✓1	–	–	–	–	–	✓	–	–	–
Hospital Acquired Pneumonia (HAP)	✓	✓	–	–	–	–	✓	–	–	–
Ventilator Associated Pneumonia (VAP)	✓	✓	–	–	–	–	✓	–	–	–
Aspiration Pneumonia	✓	–	–	–	–	–	✓	–	–	–
Exacerbation of COPD	✓	–	–	–	–	–	✓	–	–	–
Acute Bronchitis	–	–	–	–	–	–	–	–	–	–
Head and Neck Infections										
Otitis Media	–	–	–	–	–	–	✓	–	–	–
Otitis Externa	✓	–	–	✓	–	–	–	–	–	–
Orbital Cellulitis	✓	–	–	✓	–	–	✓	–	–	–
Sinusitis	✓	–	–	✓	–	–	✓	–	–	–
Urogenital Infections										
Urinary Tract Infection (UTI)	–	–	–	–	–	–	–	–	–	–
Prostatitis	–	–	–	–	–	–	–	–	–	–
STDs	–	–	–	–	–	–	–	–	–	–
Skin, Soft Tissue, Bone and Joint Infections										
Cellulitis	✓	✓	–	✓	–	–	–	–	–	–
Cellulitis in Diabetes & Vascular Insufficiency	✓	✓	–	✓	–	–	–	–	✓	–
Bites	✓	–	–	✓	–	–	–	–	✓	–
Burns, Skin Grafts, Post-Operative	✓	✓	–	✓	–	–	–	–	✓	–
Intravenous Device Associated Infection	✓	✓	–	–	–	–	–	–	–	–
Osteomyelitis	✓	✓	–	✓	–	–	–	–	–	–
Septic Arthritis	✓	✓	–	✓	–	–	–	–	–	–

? = Uncommon Cause **OR** only under specific circumstances (see notes)

Gram-negative Bacteria											
bes									**Non-Culturable**		
Bacteroides fragilis	Neisseria meningitidis	Neisseria gonorrhoeae	Haemophilus influenzae	Escherichia coli	ESBL-positive Escherichia coli	Enterobacteriaceae	Pseudomonas aeruginosa	Moraxella catarrhalis	Legionella pneumophila	Mycoplasma pneumoniae	Chlamydia spp.
–	–	–	✓	–	–	–	–	–	✓	✓	✓
–	–	–	✓	?2	?2	✓	✓	–	–	–	–
–	–	–	✓	✓	✓	✓	✓	–	–	–	–
✓	–	–	✓	✓	✓	✓	–	–	–	–	–
–	–	–	✓	–	–	–	–	✓	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	✓	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
✓	–	–	✓	–	–	–	–	–	–	–	–
–	–	–	–	✓	✓	✓	?3	–	–	–	–
–	–	–	–	✓	✓	✓	?3	–	–	–	–
–	–	✓	–	–	–	–	–	–	–	–	✓
–	–	–	–	–	–	–	–	–	–	–	–
✓	–	–	–	✓	–	✓	✓	–	–	–	–
✓	–	–	✓	–	–	–	–	–	–	–	–
✓	–	–	–	✓	–	✓	✓	–	–	–	–
–	–	–	–	–	–	?4	?4	–	–	–	–
–	–	–	–	?5	–	?5	–	–	–	–	–
–	–	–	–	?5	–	?5	–	–	–	–	–

Table of Bacterial Causes of Infection Cont.

✓ = Common Cause – = Not a Common cause

Clinical Scenarios	Gram-positive Bacteria								Anaero-	
	Staphylococcus aureus (MSSA)	Staphylococcus aureus (MRSA)	Coagulase Negative Staphylococcus	Beta-haemolytic Streptococcus A, B, C, G)	Enterococcus faecalis	Enterococcus faecium	Streptococcus pneumoniae	Listeria monocytogenes	Clostridium perfringens	Clostridium difficile
Gastrointestinal Infections										
Peritonitis	–	–	–	–	✓	✓	–	–	✓	–
Cholecystitis & Cholangitis	–	–	–	–	✓	✓	–	–	✓	–
Necrotising Pancreatitis	–	–	–	–	✓	✓	–	–	✓	–
Other Infections										
Infective Endocarditis	✓	–	✓	–	✓	✓	–	–	–	–
Emergencies										
Sepsis	✓	✓	–	✓	–	–	✓	✓	–	–
Neonatal Sepsis	–	–	–	✓7	–	–	–	–	–	–
Neutropaenic Sepsis	✓	✓	–	–	–	–	–	–	–	–
Meningitis	–	–	–	–	–	–	✓	–	–	–
Neonatal Meningitis	–	–	–	✓7	–	–	–	✓	–	–
Epiglottitis	–	–	–	✓	–	–	–	–	–	–
Epidural Abscess	✓	–	–	–	–	–	–	–	–	–
Necrotising Fasciitis	–	–	–	✓	–	–	–	–	✓	–
Toxic Shock Syndrome	✓	–	–	✓	–	–	–	–	–	–

1. *Staphylococcus aureus* is an uncommon cause of CAP except after Influenza or out-of-hospital cardiac arrest
2. *Escherichia coli* occasionally causes HAP in particularly debilitated patients
3. *Pseudomonas aeruginosa* can cause UTIs and prostatitis in patients with anatomically abnormal urinary tracts or catheters
4. Enterobacteriaceae and *Pseudomonas aeruginosa* can cause central venous catheter infections, particularly in the immunodeficient

? = Uncommon Cause **OR** only under specific circumstances (see notes)

Gram-negative Bacteria											
bes									**Non-Culturable**		
Bacteroides fragilis	Neisseria meningitidis	Neisseria gonorrhoeae	Haemophilus influenzae	Escherichia coli	ESBL-positive Escherichia coli	Enterobacteriaceae	Pseudomonas aeruginosa	Moraxella catarrhalis	Legionella pneumophila	Mycoplasma pneumoniae	Chlamydia spp.
✓	–	–	–	✓	?6	✓	?6	–	–	–	–
✓	–	–	–	✓	?6	✓	?6	–	–	–	–
✓	–	–	–	✓	?6	✓	?6	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
–	✓	–	–	✓	–	✓	✓	–	–	–	–
–	–	–	–	✓	–	?8	–	–	–	–	–
–	–	–	–	✓	–	✓	✓	–	–	–	–
–	✓	–	✓	–	–	–	–	–	–	–	–
–	–	–	–	✓	–	?8	–	–	–	–	–
–	–	–	✓	–	–	–	–	–	–	–	–
–	–	–	–	✓	–	✓	–	–	–	–	–
–	–	–	–	–	–	✓	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–

5. *Escherichia coli* and Enterobacteriaceae can cause osteomyelitis and septic arthritis in the elderly, particularly following haematogenous seeding from UTIs
6. ESBL-positive *Escherichia coli* and *Pseudomonas aeruginosa* are more common in intra-abdominal infections following surgery
7. Group B Beta-haemolytic *Streptococcus* is the most common cause of neonatal sepsis and meningitis
8. Enterobacteriaceae such as *Klebsiella* spp., *Salmonella* spp. and *Serratia marcescens* are unusual but severe causes of neonatal sepsis and meningitis

How to Interpret Microbiology Results – Serology and Virology

Serology is the investigation of a component of blood i.e. serum, to look for evidence of infection, past infection, immunity to infection or susceptibility to infection. Bacteriology looks for living microorganism whereas serology is not reliant on the microorganism being alive. Antigen and antibody tests are performed on serum, removed after the blood has clotted, whereas PCR requires the whole blood sample.

Reasons to send samples to a serology or molecular laboratory are:

- The organism cannot be cultured e.g. a virus or the non-culturable bacteria e.g. *Mycoplasma* spp., *Chlamydia* spp. or *Treponema pallidum*
- The patient may be on an antibiotic that prevents the microorganism from being cultured e.g. patient with meningitis is correctly given Benzylpenicillin by the GP before admission into hospital, which will stop *N. meningitidis* from growing but PCR will still detect bacteria
- To assess the risk of a patient acquiring an infection after exposure to the infectious microorganism e.g. testing for *Varicella Zoster Virus* antibody in a pregnant woman exposed to Chicken Pox
- To assess whether a patient has had an infection in the past or been immunised against that infection e.g. a patient exposed to blood contaminated with *Hepatitis B Virus* has evidence of antibodies against the virus and so cannot acquire it from this needlestick injury
- To detect a microorganism that might be too small to see on microscopy e.g. viruses

In general, there are three types of serology report:

- **Antigen detection**
  - Either molecules from infected cells or fragments of infecting microorganisms
  - Detects acute infection
  - Cheap, usually a rapid result on the same day as sample received
- **Antibody detection**
  - Indicating the individual's response to infection
  - IgM indicates acute or recent infection
  - IgG indicates past infection or immunity
  - Cheap, usually a rapid result on the same day as sample received
- **Molecular detection of nucleic acid or Polymerase Chain Reaction (PCR)**
  - Detects microorganism genes by multiplying undetectable amounts of DNA or RNA to a level that can be detected
  - Detects acute infection e.g. *Enterovirus* PCR in CSF, but can also detect reactivated past infections e.g. CMV in HIV-positive patients
  - Can be affected by contamination as small amounts of microorganism genes can give positive results if they get into the sample after it has been taken
  - Expensive and requires specialist laboratory staff

Combination antibody results e.g. *Epstein Barr Virus* serology
Some infections are diagnosed using combinations of antibody tests e.g. EBV. Viral capsid antigen (VCA) IgM and IgG are present at the onset of symptoms; IgM starts to disappear after 3 months whilst IgG persists for life. Epstein-Barr nuclear antigen (EBNA) IgG starts to appear 6-12 weeks after onset of symptoms when the virus begins to become latent.

The results can be interpreted as follows:

Antibody response	Interpretation	Antibody response	Interpretation
VCA IgM -ve VCA IgG -ve EBNA IgG -ve	Susceptible to infection	VCA IgM -ve VCA IgG +ve EBNA IgG -ve	Evidence of possible recent EBV infection (repeat in 1-2 weeks to look for EBNA IgG)
VCA IgM +ve VCA IgG +ve EBNA IgG -ve	Evidence of acute EBV infection	VCA IgM -ve VCA IgG +ve EBNA IgG +ve	Evidence of past EBV infection

Examples of Serology / Virology Requests, Results and Interpretations

Clinical Details on the request form:
3 month old with bronchiolitis
Result

Specimen	Nasopharyngeal Aspirate (NPA)
Result	Respiratory Syncytial Virus (RSV) antigen detected

How is this Interpreted?
The child is shown to have the most common cause of bronchiolitis: RSV. An antigen test has been used as it is cheap and quick, giving the paediatricians a rapid answer for why the child is unwell. Treatment is usually supportive only, although in certain patients Ribavirin is used under the guidance of a Consultant Paediatrician.

Clinical Details on the request form:
Healthcare staff member post-immunisation against *Hepatitis B Virus*
Result

Specimen	Blood
Result	Anti-HBs antibody positive >100mIU/ml

How is this Interpreted?
The healthcare staff member has responded well to the vaccination course. An antibody test has been used because evidence of immunity is being sought not evidence of infection (as in antigen tests). The healthcare staff member is now immune to *Hepatitis B Virus* and protected from this virus should they sustain a needlestick injury.

Clinical Details on the request form:
Acute confusion, fever and seizures
Result

Specimen	Cerebrospinal Fluid (CSF)
Result	Herpes Simplex Virus DNA detected by PCR

How is this Interpreted?
The patient has clinical features of possible encephalitis and the detection of HSV by PCR confirms HSV encephalitis. A molecular test has been used as it detects the presence of a virus and therefore infection. PCR is an expensive test but there is no antigen test available to detect viruses in CSF. HSV encephalitis requires treatment with at least 2 weeks of IV Aciclovir. It is a serious and potentially life-threatening infection.

Infection Control

Summary of Isolation Priority and Infection Control Precautions

"Help! I have 3 patients and only 2 side rooms" is a common problem for an oncall Microbiologist. Below is the priority for use of side rooms for the most common scenarios.

Microorganism	Priority	Isolation
Viral Haemorrhagic Fever	1	See section – Infection Control, Viral Haemorrhagic Fever: Control Measures
Influenza	2	Up to 7 days after onset, 14 days if immunodeficient
Open Pulmonary Tuberculosis	3	Until 2 weeks of completed antibiotic treatment **OR** until discharge
Measles	4	Until 5 days after onset of rash
Varicella Zoster Virus (VZV) Chicken Pox and Shingles	5	Until vesicles dry and crusted over
Meningitis	6	Bacterial meningitis only Until 24 hours after antibiotics started
Clostridium difficile Associated Disease (CDAD)	7	Until diarrhoea resolved for 48 hours
Diarrhoea and Vomiting	8	Until diarrhoea and vomiting resolved for 48 hours
Antibiotic Resistant Gram-negative Bacteria	9	Until discharge unless higher priority case requires isolation
MRSA	10	Until discharge unless higher priority case requires isolation
Glycopeptide resistant *Enterococcus* (GRE)	11	Until discharge unless higher priority case requires isolation
Group A Beta-haemolytic *Streptococcus*	12	Until 24 hours after antibiotics started
Cellulitis	13	Until 24 hours after antibiotics started

If there are more patients than side rooms discuss the situation with the hospital Bed Manager, rather than a Microbiologist, as they will be able to help with up-to-date bed allocation and prioritisation.

PPE	Additional Information
See section – Infection Control, Viral Haemorrhagic Fever: Control Measures	**Viral haemorrhagic fever takes priority over everything!**
Universal precautions	Surgical face mask, gloves and apron required if within 1 metre of patient **OR** when patient receiving nebulised medication. Gloves, gowns and FFP3 face protection for aerosol-generating procedures
Universal precautions FFP2 face mask for aerosol-generating procedures	FFP3 face mask if caring for patient with open pulmonary MDR-TB in negative pressure room
Universal precautions	Staff caring for patient must be immune
Universal precautions	Staff caring for patient must be immune
Universal precautions Face mask required for aerosol-generating procedures	
Universal precautions	Separate toilet facilities Hand hygiene with soap and water
Universal precautions	Separate toilet facilities Hand hygiene with soap and water
Universal precautions	
Universal precautions	
Universal precautions	
Universal precautions	
Universal precautions	

Clostridium difficile Associated Disease (CDAD)

The bacterium *Clostridium difficile* was reclassified in 2016 to *Clostridioides difficile* but as this has not yet become mainstream this book will continue to use the old name. It is the most common cause of antibiotic associated diarrhoea. It spreads very readily in the hospital environment unless infection control measures are put in place. Clinical features of *Clostridium difficile* Associated Disease (CDAD) range from asymptomatic carriage through to diarrhoea, toxic megacolon and death.

Mode of Transmission

- Faecal-oral spread
- *Clostridium difficile* can survive for long periods of time in the environment as spores which, if not removed, can then infect new patients

Incubation Period

- Unknown
- Symptoms can occur at any time after prescribing antibiotics, however usually 5-10 days

Period of Communicability

- Patients should remain in isolation until 48 hours after symptoms resolve

Best Practice Control Measures

Careful antibiotic prescribing	Where possible avoid the use of antibiotics which are regarded as particularly predisposing to CDAD – the "**4Cs**" • **C**ephalosporins • **C**iprofloxacin and other quinolones • **C**lindamycin • **C**o-amoxiclav Reduced Ciprofloxacin usage was the main driver for decreasing CDAD in the UK
Hand hygiene	With soap and water, alcohol gel is **NOT** effective
PPE	See section – Infection Control, Personal Protective Equipment Remove **ALL** PPE before leaving room
Isolation	Side room preferably with own toilet facility
Environmental decontamination	Deep cleaning of the clinical area daily and after patient is discharged
Patient care	Accurate recording of symptoms Stool sample for *Clostridium difficile* toxin testing Do not prescribe anti-motility agents If patients require investigations in other departments, inform those departments of patient's condition in advance Patient should be last on a list and deep cleaning commence after patient's departure

Myth
Antibiotics cause CDAD. **FALSE** - Antibiotics do not cause CDAD they only predispose to CDAD. If a patient does not come into contact with *Clostridium difficile* bacteria the patient will not get CDAD even if they have many predisposing factors (e.g. over 65 years old, cancer, bowel surgery, previous antibiotics, nasojejunal tubes, Proton Pump Inhibitors, hospitalisation or living in a long-term care facility). Eradicating *Clostridium difficile* from the environment by good cleaning practices is of fundamental importance in the control of CDAD.

The attitude that certain antibiotics should be avoided at all cost so as to avoid CDAD **is potentially dangerous**. The correct antibiotic for the infection should be given whilst being aware of the risk of predisposing to CDAD. For example, an elderly patient with urosepsis who is allergic to Penicillin, the doctors don't want to use Ciprofloxacin as it predisposes to CDAD and don't like using Gentamicin because it can cause renal failure. As a result they choose a seemingly random antibiotic such as Teicoplanin...Why? This is like putting diesel in a petrol car...it is simply wrong. The antibiotic needs to be active against the causative microorganism and able to penetrate the infected site.

Teicoplanin is probably the worst possible choice because it has no activity against the common causes of urosepsis and therefore the patient may die as a result of avoiding the use of Ciprofloxacin for fear of causing CDAD infection. Interestingly, doctors don't worry about prescribing Ceftriaxone for meningitis even though this antibiotic also predisposes to CDAD.

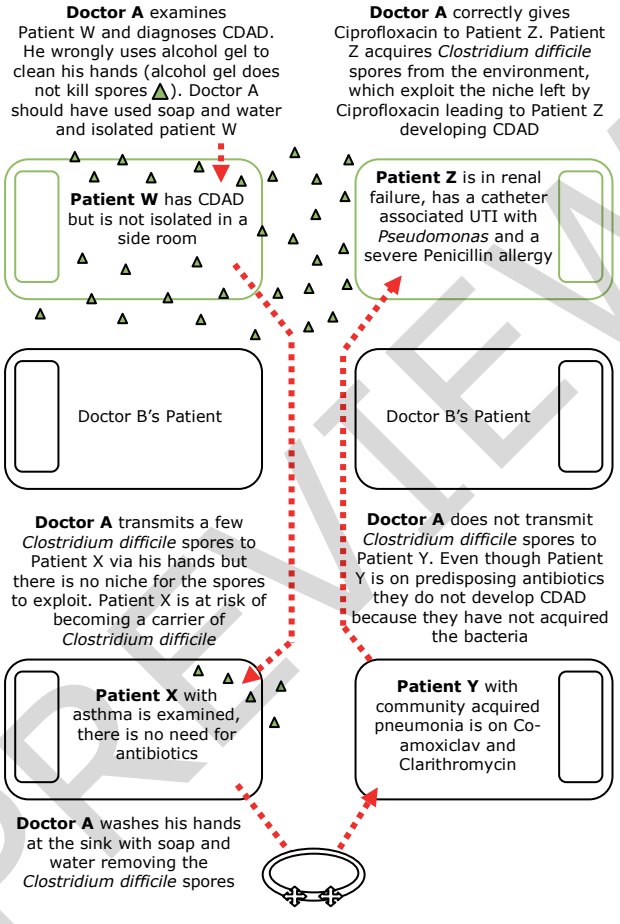
Don't select the wrong antibiotic for the infection the patient currently has because you are worried they may acquire another infection in the future.

Warning
In order to try and reduce the incidence of CDAD, hospitals are restricting the use of high risk predisposing antibiotics. As a result there is an increasing reliance on a small pool of antibiotics to treat a broad range of infections. The heavy use of these antibiotics is leading to increasing bacterial resistance. For example, an empirical guideline that uses a lot of Beta-lactam-Beta-lactamase inhibitor combinations (Co-amoxiclav and Piptazobactam) leads to increased numbers of infections with AmpC and ESBL-positive bacteria.

The increased rates of resistant bacteria mean an over reliance on carbapenem antibiotics (e.g. Meropenem); this has led to a rapid rise in carbapenemase producing Enterobacteriaceae. Not only are there no new antibiotics becoming available to treat these resistant bacteria, carbapenems also predispose to CDAD. Ultimately CDAD rates will increase while our ability to treat resistant infections decreases.

The current strategy of restricting antibiotics is storing up a problem for the future. Restrictive antibiotic guidelines put a strong selective pressure on bacteria that are far better at evolving than humans. Controlling CDAD in the environment may be a better long-term solution even though this proves harder to implement.

How *Clostridium difficile* can Spread in a Ward Environment



The development of CDAD is often multi-factorial and there are many predisposing factors but ultimately the patient has to acquire the bacterium *Clostridium difficile* before they can develop CDAD or become a carrier of *Clostridium difficile*.

The root cause for CDAD in Patient Z is failure to isolate Patient W in a side room NOT the antibiotic Ciprofloxacin

Multiple Antibiotic Resistant Gram-negative Bacteria

Increasing antibiotic resistance in Gram-negative bacteria is making initial antibiotic choice more difficult and therefore mortality is rising. Currently there are few new anti-Gram-negative antibiotics being developed by the pharmaceutical industry.

There are 3 main groups of multiple antibiotic resistant Gram-negative bacteria:

- Enterobacteriaceae with ESBL, AmpC or carbapenemase enzymes – including *Escherichia coli*, *Klebsiella* spp., *Enterobacter cloacae*, *Citrobacter freundii*, *Morganella morganii*, *Serratia marcescens*
- *Acinetobacter* spp. – resistant to aminoglycoside antibiotics as well as occasionally carbapenems and Colistin
- *Pseudomonas* spp. – resistant to combinations of Ceftazidime, Piptazobactam, carbapenems, aminoglycosides and quinolones

Mode of Transmission

- Transmission can occur via hands or via faecal-oral colonisation.

Incubation Period

- Many Gram-negative bacteria are able to colonise people. Once the microorganism is part of the patient's normal flora it can potentially cause infection and be spread to others at any time. The majority of infections with Gram-negative bacteria follow previous colonisation.

Period of Communicability

- Potential cross-infection can occur at any time whilst the patient remains colonised with the resistant bacteria. However, risk is highest with environmental contamination e.g. during outbreaks of diarrhoea.

Best Practice Control Measures

Careful antibiotic prescribing	Certain antibiotics have been implicated in the selection of antibiotic resistant Gram-negative bacteria e.g. Ciprofloxacin and the Beta-lactam-Beta-lactamase inhibitor combination antibiotics such as Co-amoxiclav and Piptazobactam
Hand hygiene	With soap and water or alcohol hand gel
PPE	See section – Infection Control, Personal Protective Equipment Remove **ALL** PPE before leaving room
Isolation	Side room preferably with own toilet facility
Environmental decontamination	Deep cleaning of the clinical area daily and after patient is discharged

Carbapenemases

Strains of *Klebsiella* spp. and *Escherichia coli* are now regularly isolated which are resistant to the carbapenem antibiotics. A carbapenemase is any Beta-lactamase enzyme that:

- Can breakdown carbapenem antibiotics
- Gives resistance to **ALL** of the Beta-lactam antibiotics such as the penicillins and cephalosporins
- Is often associated with other genes giving resistance to other antibiotics such as the quinolones and aminoglycosides

Carbapenemases are important because the carbapenems (Ertapenem, Meropenem, Imipenem and Doripenem) are often seen as the last line of antibiotics in the fight against infections with Gram-negative bacteria. Carbapenem resistance is not associated with a specific infection but rather with a diverse clinical spectrum of diseases. Infections due to bacteria with these enzymes have a very high mortality in excess of 50%.

The genes which encode these enzymes are usually located on a mobile genetic element such as a plasmid and therefore have the potential to spread between bacterial species. The most important currently are known as the "Big Five":

- *Klebsiella pneumoniae* carbapenemase (KPC)
- New Delhi metallo-beta-lactamase (NDM)
- Verona integron-encoded metallo-beta-lactamase (VIM)
- Imipenemase metallo-beta-lactamase (IMP)
- Oxacillin carbapenemases (OXA)

Treatment of Patients with Infections

Most carbapenemase-producing bacteria remain susceptible to: Polymyxins e.g. Colistin, Tigecycline, Nitrofurantoin and Fosfomycin. The current recommendations for the treatment of patients with severe infections caused by carbapenemase producing bacteria are combinations of antibiotics: Colistin **PLUS** carbapenem, Colistin **PLUS** Tigecycline or Colistin **PLUS** aminoglycoside.

Patient Screening

On admission to hospital, patients will be classified as either:

1) NOT infected or colonised (no further action required)
2) CONFIRMED (infection or colonisation)
3) SUSPECTED (infection or colonisation)

How to Screen for Carbapenemase–Producing Bacteria

- Rectal charcoal swab with visible faecal material **OR** stool sample
- **PLUS** charcoal swab from any wound and device-related site if hospitalised within the previous 12 months in a country with a high prevalence of carbapenemase producing bacteria

CONFIRMED

- Patients who have a positive microbiological culture for carbapenemase producing bacteria from a clinical specimen or screening test at any stage during their admission to any hospital

SUSPECTED

- Patients who have been an inpatient in a hospital abroad
- **OR** been an inpatient in a UK hospital known to have had problems with spread of carbapenemase-producing Enterobacteriaceae
- **OR** previously been colonised or had an infection with a carbapenemase producing Enterobacteriaceae
- **OR** had close contact with a person who has been colonised or had an infection with a carbapenemase producing Enterobacteriaceae

Best Practice Control Measures for CONFIRMED or SUSPECTED

Screening	Send weekly screening samples
Careful antibiotic prescribing	If patient has an infection seek specialist advice from a Microbiologist or Infectious Diseases Physician
Hand hygiene	With soap and water or alcohol hand gel
Personal Protective Equipment	See section – Infection Control, Personal Protective Equipment Remove **ALL** PPE before leaving room
Isolation	Side room preferably with own toilet facility for duration of hospital stay
Environmental decontamination	Deep cleaning of the clinical area daily and after patient discharge

Patients with **CONFIRMED** infections or colonisation who have 3 negative screening samples should **ONLY** be moved out of isolation if there is a serious risk to their health from remaining in isolation. This is because the screening tests are not perfect and even if negative now previously positive patients can become positive again, especially if given antibiotics. If in doubt discuss with the Infection Control Team.

Contact Screening and Management

If a patient has not been isolated in a side room and is found to have a carbapenemase-producing bacterium then all contacts within the bays or wards in which they have been should also be screened. This **DOES NOT** include household contacts or members of hospital staff.

All contacts should be isolated or cohorted together whilst awaiting results of screening samples if possible. If initial screening tests are negative they should have repeat screening samples sent on day 2 and day 4 and if they remain negative in all three samples they can then be managed as normal and the isolation or cohorting relaxed.

If a contact tests positive then they should be managed as a **CONFIRMED** infection or colonisation **AND** all of their contacts should be screened.

No further management is recommended after the patient is discharged from hospital although nursing care facilities would be recommended to consider the risk of transmission within their environments.

The patient and their General Practitioner should be made aware of the patient's status so that if they are re-admitted to hospital the hospital is made aware of their status.

Warning

In 2015, 25% of pork and poultry meat on sale in China were found to contain Enterobacteriaceae resistant to Colistin. The Colistin resistance was encoded by a gene in a plasmid (which can transfer to other bacteria) called MCR-1. With MCR-1 mother nature now has all she needs to create bacteria, such as *E. coli,* which are resistant to **ALL** antibiotics currently used to treat infections. Complete resistance occurred in a patient from the USA who had surgery in India in 2017.

New Antibiotics for Treating Resistant Gram-negative Bacteria

New antibiotics for the treatment of antibiotic resistant Gram-negative bacteria can be split into:

- **Combinations** of existing beta-lactams with beta-lactamase inhibitors e.g. Ceftolozane + Tazobactam, Ceftazidime + Avibactam, Meropenem + Vaborbactam, Imipenem + Relebactam and Aztreonam + Avibactam
- **New versions** of old antibiotics that aren't beta-lactams e.g. Eravacycline, Plazomicin and Cefiderocol.

Spectrum of activity of "new" antibiotics

✓= active ?= partial/unreliable activity **-** = inactive

Antibiotic	Enterobacteriaceae (e.g. *E. coli*, *Klebsiella* spp.)					*Pseudomonas* spp.		*Acinetobacter* spp.
	ESBL	AmpC	KPC	OXA-48	NDM	Efflux	AmpC	
Ceftolozane + Tazobactam	✓	?	-	?	-	✓	✓	-
Ceftazidime + Avibactam	✓	✓	✓	✓	-	?	✓	-
Meropenem + Vaborbactam	✓	✓	✓	-	-	-	✓	?
Imipenem + Relebactam	✓	✓	✓	-	-	✓	✓	?
Aztreonam + Avibactam	✓	✓	✓	✓	✓	-	?	-
Eravacycline	✓	✓	✓	✓	✓	-	-	✓
Plazomicin	✓	✓	✓	✓	-	?	?	?
Cefiderocol	✓	✓	✓	✓	✓	✓	✓	✓

Note: As of November 2018 only Ceftolozane + Tazobactam and Ceftazidime + Avibactam are routinely available in the UK.

Clinical Scenarios

Cholecystitis and Cholangitis

Acute cholecystitis is inflammation of the gallbladder, usually secondary to cystic duct obstruction.

Acute cholangitis is inflammation of the biliary tree due to obstruction of the common bile duct.

Clinical Features

Cholecystitis	• Fever • Nausea • Right upper quadrant or epigastric pain and tenderness
Cholangitis	• Charcot's Triad – fever + right upper quadrant pain + jaundice (present in 85% of patients) • Right upper quadrant or epigastric pain and tenderness • Sepsis

Causes

Cholecystitis and Cholangitis	Often mixed microorganisms: • Enterobacteriaceae e.g. *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp. • *Enterococcus* spp. • Anaerobes e.g. *Bacteroides* spp., *Clostridium* spp., *Fusobacterium* spp.

Investigations

- Blood cultures
  - Positive in 50% of cases
  - Cholecystitis and cholangitis are usually polymicrobial. Even if a single predominant bacterium is grown, it is important to treat this as a mixed infection
- Bile for culture and sensitivity
- Abdominal ultrasound scans are diagnostic in 90% of cases

Treatment

Patients may require surgical decompression of the biliary tree, especially with cholangitis.

1st line	IV Amoxicillin **PLUS** IV Gentamicin **PLUS** IV Metronidazole
2nd line (if 1st line contraindicated)	IV Teicoplanin **OR** IV Vancomycin **PLUS** IV Gentamicin **PLUS** IV Metronidazole

Total Duration
5-7 days

Dosing
See section - Antibiotics, Empirical Antibiotic Guidelines.

Prognosis and Complications
Complications occur in 10-15% of patients with cholecystitis:
- Gallbladder empyema
- Emphysematous cholecystitis
- Gallbladder perforation leading to peritonitis
- Pericholecystic abscess
- Intra-abdominal abscess
- Cholangitis (following cholecystitis)
- Liver abscess
- Pancreatitis
- Bacteraemia

Prophylaxis and Prevention
No role for antibiotics to prevent recurrence.

Peritonitis

Primary Peritonitis is inflammation of the peritoneum due to infection unrelated to other intra-abdominal abnormalities. Bacteria spread from the gastrointestinal tract via the lymphatics, blood or occasionally via translocation across the gut mucosal wall. In women, spread can also be via the fallopian tubes. Patients with cirrhosis and/or ascites are most at risk.

Secondary peritonitis is inflammation of the peritoneum as a result of a breach in a mucosal barrier leading to gastrointestinal or genitourinary flora entering the peritoneal cavity. The common reasons for secondary peritonitis are perforation of an intra-abdominal viscus e.g. appendicitis or following surgery.

Clinical Features

- Abdominal tenderness and/or guarding
- Hyperthermia **OR** hypothermia
- Increased respiratory rate
- Fever
- Increased heart rate
- Hypotension

Causes

Primary Peritonitis	
Common	• Enteric bacteria (70% of patients) e.g. *Escherichia coli*, *Klebsiella* spp., *Enterococcus* spp., *Streptococcus* spp.
Uncommon	• *Mycobacterium tuberculosis* • *Streptococcus pneumoniae* (associated with HIV infection) • *Neisseria gonorrhoeae* • *Chlamydia trachomatis*

Secondary Peritonitis	
Common	• Usually polymicrobial including Enterobacteriaceae, *Enterococcus* spp., *Streptococcus* spp., anaerobes and occasionally *Candida* spp.

Investigations

- Peritoneal fluid for microscopy, culture and sensitivity
- Gram stain is positive in 40% of cases
- White blood cell count >250/μL is significantly raised and suggests infection (sensitivity 86%, specificity 98%)
- Blood cultures
  - Positive in 1/3 patients
- Peritonitis is usually polymicrobial. Even if a single predominant bacterium is grown, it is important to treat this as a mixed infection

Treatment

All patients with peritoneal fluid white blood cell counts >250/μL or positive Gram stains should be treated empirically until culture results are known. If the patient has perforated an intra-abdominal viscus then the main treatment is surgery.

Primary peritonitis	
1st line	IV Co-amoxiclav **PLUS** IV Gentamicin
2nd line (if 1st line contraindicated)	IV Teicoplanin **OR** IV Vancomycin **PLUS** IV Gentamicin **PLUS** IV Metronidazole

Secondary peritonitis	
1st line	IV Piptazobactam **PLUS** IV Gentamicin
2nd line (if 1st line contraindicated)	IV Teicoplanin **OR** IV Vancomycin **PLUS** IV Gentamicin **PLUS** IV Metronidazole

Total Duration
5-7 days

Dosing
See section - Antibiotics, Empirical Antibiotic Guidelines.

Prognosis and Complications
Mortality depends on underlying co-morbidities but can be as high as 60% if there is established infection and organ failure secondary to sepsis.

Prophylaxis and Prevention
In primary peritonitis, antibiotic prophylaxis decreases the frequency of infection in patients with cirrhosis and ascites who have had a previous episode of peritonitis.

1st line	PO Co-trimoxazole
2nd line (if 1st line contraindicated)	PO Ciprofloxacin

In secondary peritonitis, antibiotics should be given to cover clean-contaminated or contaminated surgery. Contaminated surgery has a post-operative infection rate of 30-40%; antibiotics reduce this to 4-8%. Clean-contaminated surgery is where the surgeon will be entering a non-sterile site such as the bowel e.g. appendicectomy. Contaminated surgery is where there are faeces in the peritoneum or a penetrating injury.

Warning
Perforation of an intra-abdominal viscus can give rise to a form of necrotising fasciitis called "synergistic gangrene". This is a severe soft tissue infection cause by mixed bacteria and is a surgical emergency (see section – Emergencies, Necrotising Fasciitis).

Antibiotics

The Daily Review of Antibiotic Therapy

Patients on antibiotics should be reviewed every day to ensure they are responding to treatment and that they are not getting any side effects.

Questions to ask:

Is the patient getting better?	• Are they improving subjectively i.e. feeling better? • Are they improving objectively i.e. blood test results such as white blood cell count, CRP improving? • Is the diagnosis still correct? • If the patient is not feeling better follow the method for failing to respond to antibiotics (see section – Antibiotics, Reasons for Failing Antibiotic Therapy)
Can the patient be converted from IV to oral antibiotics?	See section – Antibiotics, Intravenous to Oral Switching of Antibiotics
Can the antibiotics be narrowed down to a specific treatment?	• Review the microbiology results • Empirical antibiotics cover all common causes of a particular type of infection, they are not specific • Narrowing down antibiotics reduces side effects and risks of complications such as CDAD
Are antibiotic levels required?	• Have levels been taken? • Are they within acceptable ranges (see section – Antibiotics, Therapeutic Drug Monitoring)
Is the patient's renal and liver function stable?	• If not, then dosage of antibiotic may require adjusting (see section – Antibiotics, Antibiotic Dosing in Adult Renal Impairment)
Is the patient experiencing side effects?	• If side effects are severe the antibiotic may require changing (see section – Antibiotics, for individual antibiotic agents) • Consult the BNF • Do not forget to ask about symptoms of CDAD for patients on Cephalosporins, Ciprofloxacin, Clindamycin and Co-amoxiclav
Have any other drugs been started that might interact with the antibiotics?	See section – Antibiotics, for individual antibiotic agents • Consult the BNF
Can the antibiotics be stopped?	• Is there an indication? • Is there a stop date? • Has the patient received the correct duration of antibiotics for the infection? • Is the patient better? Not necessarily the same as back to normal, which may take longer

How is Antibiotic Resistance Detected in the Laboratory?

Antibiotic resistance is determined using four methods in the laboratory:

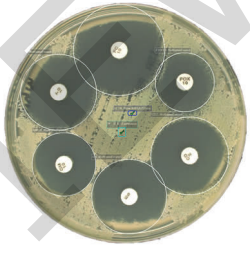
- Implication of resistance from bacterial species identification
- Disc diffusion using, for example, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) method
- Measurement of the minimum inhibitory concentration (MIC)
- Measurement of the minimum bactericidal concentration (MBC)

Bacterial Species Identification

Each bacterium has a different pattern of sensitivity and resistance to the array of antibiotics available. Once bacteria have been identified (Gram stain, ZN stain etc.) resistance patterns can be implied as certain bacteria are known to be consistently resistant to certain antibiotics (see section – Antibiotics, What is Antibiotic Resistance?)

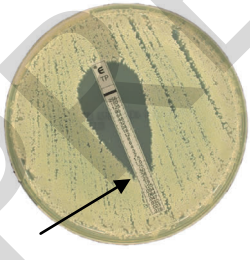
Disc Diffusion

Antibiotic-impregnated filter paper discs are placed on specific agar plates, which have been inoculated with the bacteria to be tested. If the bacteria are sensitive to the antibiotic they will not be able to grow in a zone around the antibiotic, called the zone of inhibition. Resistant bacteria will be able to grow close to the disc. Because resistance is usually relative it is necessary to measure the zone diameter to see if it is large enough to correspond to physiologically achievable concentrations of antibiotic. EUCAST publish regular updates to their method including the zone sizes for bacteria and antibiotic combinations. This method takes 24-48 hours.



Disc diffusion testing of antibiotic sensitivity

Minimum Inhibitory Concentration (MIC)



Etest for determining MIC

The MIC is the least amount of antibiotic required to prevent a bacterium from multiplying. The bacterium may still be alive. It is only usually performed in specific clinical scenarios under the instruction of a Microbiologist, e.g. infective endocarditis. The most common method employed in most UK laboratories is the Etest method whereby a strip impregnated with an antibiotic gradient is placed on an inoculated agar plate. The MIC is determined by how far up the strip the bacterium can grow. Low concentrations (bottom of strip) allow growth whereas higher concentrations (top of strip) inhibit the growth. The MIC is the point at which the growth meets the strip. This method takes 24-48 hours.

Minimum Bactericidal Concentration (MBC)

The MBC is the least amount of antibiotic required to kill a bacterium. It is very rarely performed. It is difficult to do and labour intensive. Different dilutions of antibiotic are prepared in liquid culture media from low concentration to high concentration. The bacterium is then inoculated into these tubes. After 24-48 hours the tubes where the bacterium is growing become cloudy (green tubes in the diagram below); some tubes show no bacterial growth (clear tubes in the diagram below).

This test allows the laboratory to initially determine the MIC (the lowest concentration of antibiotic required to prevent a bacterium from multiplying). The first clear tube shows inhibition of growth and corresponds to the MIC.

The MBC is determined by plating out the liquid cultures to agar. The first cloudy tube is known to have the bacterium growing and is used as a positive control, while the clear tubes have either inhibited or killed bacteria in them. The agar does not contain antibiotic therefore any living bacteria will now not be inhibited and start to grow (e.g. tube A). Tube B is the MBC; the bacterium in the tube has not grown on the agar because it has been killed by the concentration of antibiotic that was in tube B.

Calculation of Minimum Bactericidal Concentration (MBC)

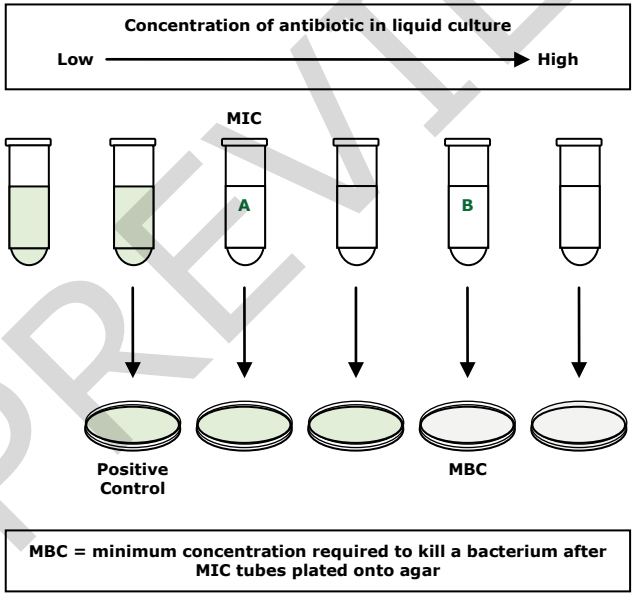


Table of Antibiotic Spectrum of Activity

✓ = Usually sensitive – = usually resistant **OR** inappropriate therapy

Antibiotic	Gram-positive Bacteria								Anaero-	
	Staphylococcus aureus (MSSA)	Staphylococcus aureus (MRSA)	Coagulase Negative Staphylococcus	Beta-haemolytic Streptococcus (A, B, C, G)	Enterococcus faecalis	Enterococcus faecium	Streptococcus pneumoniae	Listeria monocytogenes	Clostridium perfringens	Clostridium difficile
Penicillins										
Benzylpenicillin	–	–	–	✓	✓	–	✓	✓	✓	–
Amoxicillin / Ampicillin	–	–	–	✓	✓	–	✓	✓	✓	–
Co-amoxiclav	✓	–	–	✓	✓	–	✓	–	✓	–
Flucloxacillin	✓	–	?	✓	–	–	✓	–	–	–
Temocillin	–	–	–	–	–	–	–	–	–	–
Pivmecillinam Hydrochloride	–	–	–	–	–	–	–	–	–	–
Piptazobactam	✓	–	–	✓	✓	–	✓	–	✓	–
Cephalosporins										
Cefradine	✓	–	?	✓	–	–	✓	–	–	–
Cefalexin	✓	–	?	✓	–	–	✓	–	–	–
Cefuroxime	✓	–	?	✓	–	–	✓	–	–	–
Ceftriaxone / Cefotaxime	✓	–	–	✓	–	–	✓	–	–	–
Ceftazidime	–	–	–	–	–	–	–	–	–	–
Ceftazidime + Avibactam	–	–	–	–	–	–	–	–	–	–
Ceftolozane + Tazobactam	–	–	–	–	–	–	–	–	–	–
Ceftaroline	✓	✓	✓	✓	–	–	✓	–	✓	–
Carbapenems										
Ertapenem	✓	–	–	✓	✓	–	✓	–	✓	–
Meropenem	✓	–	–	✓	✓	–	✓	✓	✓	–
Diaminopyramidines										
Trimethoprim	?	?	–	–	–	–	–	–	–	–
Macrolides and Lincosamides										
Erythromycin	✓	?	–	✓	–	–	✓	–	–	–
Clarithromycin	✓	?	–	✓	–	–	✓	–	–	–
Azithromycin	✓	–	–	✓	–	–	✓	–	–	–
Clindamycin	✓	?	–	✓	–	–	✓	–	✓	–

? = Variable sensitivity **P** = Prophylaxis only

Gram-negative Bacteria											
bes									**Non-Culturable**		
Bacteroides fragilis	Neisseria meningitidis	Neisseria gonorrhoeae	Haemophilus influenzae	Escherichia coli	ESBL-positive Escherichia coli	Enterobacteriaceae	Pseudomonas aeruginosa	Moraxella catarrhalis	Legionella pneumophila	Mycoplasma pneumoniae	Chlamydia spp.
–	✓	?	–	–	–	–	–	–	–	–	–
–	✓	?	?	?	–	–	–	–	–	–	–
✓	–	?	✓	✓	–	?1	–	✓	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	✓	✓	✓	✓	–	✓	–	–	–
–	–	–	–	✓	✓	✓	–	–	–	–	–
✓	–	–	✓	✓	–	✓1	✓	✓	–	–	–
–	–	–	–	✓	–	–	–	–	–	–	–
–	–	–	–	✓	–	–	–	–	–	–	–
–	–	–	✓	✓	–	?	–	✓	–	–	–
–	✓	✓	✓	✓	–	✓2	–	✓	–	–	–
–	–	–	✓	✓	–	✓2	✓	✓	–	–	–
–	–	–	✓	✓6	✓6	✓6	✓6	✓	–	–	–
–	–	–	✓	✓	✓	–	✓	✓	–	–	–
–	–	–	✓	✓	–	✓2	–	✓	–	–	–
✓	–	–	✓	✓	✓	✓	–	✓	–	–	–
✓	✓	–	✓	✓	✓	✓	✓	✓	–	–	–
–	–	–	?	✓	–	✓	–	–	–	–	–
–	–	–	–	–	–	–	–	✓	✓	✓	✓
–	–	–	–	–	–	–	–	✓	✓	✓	✓
–	–	–	–	–	–	–	–	✓	✓	✓	✓
✓	–	–	–	–	–	–	–	✓	–	–	–

Table of Antibiotic Spectrum of Activity Cont.

✓ = Usually sensitive – = usually resistant **OR** inappropriate therapy

Antibiotic	Gram-positive Bacteria								Anaero-	
	Staphylococcus aureus (MSSA)	Staphylococcus aureus (MRSA)	Coagulase Negative Staphylococcus	Beta-haemolytic Streptococcus (A, B, C, G)	Enterococcus faecalis	Enterococcus faecium	Streptococcus pneumoniae	Listeria monocytogenes	Clostridium perfringens	Clostridium difficile
Aminoglycosides										
Gentamicin	✓	✓	–	–	–	–	–	–	–	–
Amikacin	✓	✓	–	–	–	–	–	–	–	–
Quinolones										
Ciprofloxacin	✓	–	–	–	–	–	–	–	–	–
Levofloxacin	✓	–	–	✓	–	–	✓	–	–	–
Glycopeptides and Lipopeptides										
Vancomycin IV	✓	✓	✓	✓	✓	✓	✓	✓	✓	–
Vancomycin PO	–	–	–	–	–	–	–	–	–	✓
Teicoplanin	✓	✓	✓	✓	✓	✓	✓	✓	✓	–
Daptomycin	✓	✓	✓	✓	✓	✓	✓	–	✓	–
Nitroimidazoles										
Metronidazole	–	–	–	–	–	–	–	–	✓	✓
Tetracyclines and Glycylcyclines										
Doxycycline	✓	✓	–	?	–	–	✓	–	–	–
Tigecycline	✓	✓	✓	✓	✓	✓	✓	–	–	–
Oxazolidinones										
Linezolid	✓	✓	✓	✓	✓	✓	✓	✓	✓	–
Other										
Co-trimoxazole	✓	✓	?	✓	–	–	✓	✓	–	–
Rifampicin	✓5	✓5	✓5	✓5	–	–	✓5	–	–	–
Fusidic Acid	✓5	✓5	✓5	–	–	–	–	–	–	–
Colistin	–	–	–	–	–	–	–	–	–	–
Chloramphenicol	?	?	?	?	–	–	✓	–	–	–
Fidaxomicin	–	–	–	–	–	–	–	–	–	✓
Fosfomycin	✓	✓	✓	?	✓	✓	✓	–	✓	–

1. May not be active against bacteria producing AmpC e.g. *Enterobacter cloacae*, *Serratia marcescens*, *Citrobacter freundii*, *Morganella* spp.
2. Not active against bacteria producing AmpC e.g. *Enterobacter cloacae*, *Serratia marcescens*, *Citrobacter freundii*, *Morganella* spp.
3. Most ESBL-positive *Escherichia coli* clones are resistant to Gentamicin and Ciprofloxacin, but this is unpredictable

? = Variable sensitivity **P** = Prophylaxis only

Gram-negative Bacteria											
bes									**Non-Culturable**		
Bacteroides fragilis	Neisseria meningitidis	Neisseria gonorrhoeae	Haemophilus influenzae	Escherichia coli	ESBL-positive Escherichia coli	Enterobacteriaceae	Pseudomonas aeruginosa	Moraxella catarrhalis	Legionella pneumophila	Mycoplasma pneumoniae	Chlamydia spp.
–	–	–	–	✓	? 3	✓	✓	–	–	–	–
–	–	–	–	✓	✓	✓	✓	–	–	–	–
–	P	?	✓	✓	? 3	✓	✓	✓	✓	✓	✓
–	–	–	✓	✓	?3	✓	✓	✓	✓	✓	✓
–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
✓	–	–	–	–	–	–	–	–	–	–	–
–	–	?	✓	–	–	–	–	✓	✓	✓	✓
–	–	–	✓	✓4	✓4	? 4	–	✓	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	✓	?	?	?	–	✓	–	–	–
–	P	–	✓	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
✓	–	–	–	✓	✓	✓?	✓	-	–	–	–
–	✓	–	✓	?	?	?	–	?	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	✓	✓	✓	✓	✓	✓	–	–	–

4. Not active in the urinary tract or against Proteus spp.
5. Should not be used as single therapy, should only be used as adjuncts to other antibiotics
6. Including most CPE positive bacteria except NDM

Gentamicin, Amikacin and Tobramycin

Gentamicin, Amikacin and Tobramycin are aminoglycoside antibiotics.

Mechanism of Action

- Bactericidal
- Antibiotic binds to the ribosome causing a shape change that interferes with mRNA translation thereby preventing protein synthesis
- Aminoglycosides are taken up into bacterial cells by an energy-dependent mechanism (not concentration-dependent) which results in very high intracellular levels. This is responsible for the "post-antibiotic effect" seen with these drugs (continued potent antibacterial activity despite sub-therapeutic levels in blood), because the level in the bacteria remains therapeutic

Mechanisms of Resistance

- Reduced entry of antibiotic into anaerobic bacteria because these lack an energy-dependent transport mechanism
- Mutation of the active site therefore antibiotic does not bind
- Production of aminoglycoside modifying enzymes which break down the antibiotic before it reaches the active site. This is usually specific to each individual antibiotic so other aminoglycosides often remain active
- Antibiotic is removed from the bacteria by an efflux pump before it is able to act, often leading to resistance to all aminoglycosides

Hints and Tips
Complete antibiotic class resistance is very unusual in aminoglycosides. It is common for bacteria to be resistant to Gentamicin but sensitive to Amikacin. In this situation Amikacin is a good antibiotic to use instead of Gentamicin for septic patients when there is concern about potential antibiotic resistance e.g. previous courses of Gentamicin or known colonisation with a Gentamicin-resistant Enterobacteriaceae.

Pharmacology and Pharmacodynamics

- Intravenous and topical only
- Aminoglycosides display concentration-dependent killing, i.e. more bacteria are killed at higher peak concentrations. Once daily dosing gives higher peak concentrations and is therefore preferable to conventional TDS dosing
- 99% excreted unchanged in urine
- Bile level achieves 30% of serum levels
- Aminoglycosides are often used in combination with cell wall active agents (e.g. Beta-lactams) as this leads to synergy, i.e. the combination of the antibiotics is more effective than the sum of both agents used alone

Spectrum of Activity of Gentamicin, Amikacin and Tobramycin

Gram-positive	• *Staphylococcus aureus* (including MRSA)
Gram-negative	• Enterobacteriaceae e.g. *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Salmonella* spp. • *Pseudomonas* spp.
Mycobacteria	• *Mycobacterium tuberculosis* (including MDR)

Cautions and Contraindications

- See BNF for full details
- Renal failure (reduce dose in severe renal failure or **DO NOT** use)
- Pregnancy (avoid unless benefit outweighs risk)
- Myasthenia gravis (aminoglycosides are contraindicated in myasthenia gravis as they can precipitate a myasthenic crisis)
- Drugs
  - Increased ototoxicity when used in conjunction with Furosemide
  - Increased renal toxicity if used with other nephrotoxic agents e.g. Colistin, Vancomycin, Ciclosporin, Tacrolimus

Common Mistake

Some doctors withhold Gentamicin in septic patients with renal failure because of concern it will make the renal failure worse. **This is a mistake.** Gentamicin is an essential part of sepsis treatment in many empirical guidelines. Withholding it means patients may die from sepsis due to worries about the potential for worsening renal failure.

If in doubt give a stat dose of Gentamicin and review.

Side Effects

- Nephrotoxic
- Ototoxic
- Side effects tend to be related to concentration in blood therefore doses should be calculated for ideal body weight in renal failure (**NOT** actual body weight) and serum levels must be monitored.

Ideal body weight (IBW) calculation:

- Male IBW = 50 + (2.3 x height in inches above 60 inches)
- Female IBW = 45 + (2.3 x height in inches above 60 inches)

Monitoring

- Monitor serum levels on the 3rd - 4th dose, then weekly or more frequently if renal function changes
- For peak and trough levels (see section – Antibiotics, Therapeutic Drug Monitoring)
- Warn patients to report hearing and balance disturbances, and review daily for symptoms
- At least twice weekly monitoring of urea and electrolytes

Hints and Tips

Renal failure with Gentamicin occurs in 10% of patients but is rarely severe and usually recovers in <21 days of stopping Gentamicin.

Gentamicin induced renal failure is more common in:

- Prolonged courses of Gentamicin (≥7 days)
- Comorbidities (old age, diabetes mellitus, leukaemia)
- Reduced intravascular volume
- Drug interactions (e.g. Furosemide, non-steroidal anti-inflammatory drugs NSAIDS, Ciclosporin, Vancomycin)
- High serum Gentamicin concentrations

The risk of renal failure with Gentamicin can be reduced by:

- Using the correct dose for the individual patient
- Correcting fluid and electrolyte disturbances
- Limiting treatment to <7 days
- Avoiding co-administration with other nephrotoxic drugs

Emergencies

Sepsis

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is sepsis with circulatory, cellular or metabolic dysfunction, and has a high mortality.

Sepsis and septic shock are clinical diagnoses not laboratory diagnoses:
- **Sepsis** - infection with evidence of a systemic response to that infection e.g. hypoxia, oliguria, confusion
- **Septic shock** - sepsis associated with organ dysfunction, hypoperfusion or hypotension

Sepsis and septic shock are medical emergencies and early recognition and treatment improve survival.

Risk Factors for Sepsis
- Age <1 year or >75 years
- Frailty or comorbidities e.g. diabetes, renal failure, liver failure
- Trauma, surgery or other invasive procedure within 6 weeks
- Immunosuppression
- Intravascular device
- Breaches to skin integrity e.g. cuts, burns, blisters
- Current or recent pregnancy (within 6 weeks)

Clinical Features

Potential source of infection OR NEWS ≥4?

- Pneumonia
- Empyema
- UTI
- Acute abdomen
- Meningitis
- Infective endocarditis
- CVC infection
- Skin/soft tissue infection
- Bone/joint infection
- Wound infection
- Other

New signs or symptoms of infection? TWO or more of the following:

- Temperature >38.3°C
- Heart Rate >90bpm
- WBC <4x10^9/L
- Altered mental state
- Temperature <36°C
- Respiratory Rate >20 bpm
- WBC >12x10^9/L
- Blood glucose >7.7mmol/L

Evidence of organ dysfunction remote to the site of infection? ONE of the following or SOFA ≥2 (see opposite):

- Lactate >2mmol/L
- Systolic blood pressure <90mmHg **OR** Mean arterial pressure <65mmHg
- Systolic blood pressure >40mmHg below baseline
- Creatinine >175mmol/L **OR** urine output 0.5ml/kg/hour for more than 2 hours
- Bilateral pulmonary infiltrates **PLUS** O_2 required to keep O_2 saturations >92%
- Bilateral pulmonary infiltrates **PLUS** PaO_2/FiO_2 ratio <300*
- Bilirubin >34 mmol/L
- Coagulopathy INR >1.5 **OR** APTT >60 seconds
- Platelet count <100x10^9/L

If YES to questions 1 +2 + 3 = criteria for SEPSIS

Note: *PaO_2 measured in mmHg (1kPa = 7.5mmHg), FiO_2 as % converted into a decimal e.g. 32% = 0.32

Adapted from: Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock www.survivingsepsis.org

Sequential Organ Failure Assessment Score (SOFA)

	Score				
Parameter	**0**	**1**	**2**	**3**	**4**
PaO_2/FiO_2 mmHg	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Platelets X 10^9/L	≥150	<150	<100	<50	<20
Bilirubin µmol/L	<20	20-32	33-101	102-204	>204
Cardiovascular status*	MABP ≥70 mmHg	MABP <70 mmHg	Dopamine <5 **OR** Dobutamine any dose	Dopamine 5.1-15 **OR** Epinephrine **OR** Norepinephrine ≤0.1	Dopamine <5 **OR** Epinephrine **OR** Norepinephrine >0.1
Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Creatinine µmol/L or Urine output ml/day	110	110-170	171-299	300-440 <500	>440 <200

Note: *Inotrope doses are in µg/kg/min

Warning
If vasopressors (e.g. Norepinephrine) are required to keep MABP ≥65mmHg **AND** Lactate >2mmol/L despite fluid resuscitation then the patient has **SEPTIC SHOCK**

Hints and Tips
Use the abbreviated qSOFA (quick Sepsis-Related Organ Failure Assessment) to quickly assess sepsis severity, if ≥2 there is an increased risk of death or prolonged ICU stay. Take action!
- Respiratory rate ≥22/min
- Altered mental status
- Systolic blood pressure ≤100mmHg

Causes

Common	• *Staphylococcus aureus* • Group A Beta-haemolytic *Streptococcus* • Enterobacteriaceae e.g. *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., • *Pseudomonas* spp. • *Neisseria meningitidis*

Investigations
- Blood cultures
- Urine for microscopy, culture and sensitivity if able
- Do not unduly delay treatment as mortality increases

Treatment

Antibiotics should be given within 1 hour of the diagnosis of sepsis (see section – Emergencies, Adult Sepsis "Golden-Hour" Management Flowchart)

Adults	
1st line	IV Piptazobactam **PLUS** IV Gentamicin
2nd line (if 1st line contraindicated)	IV Teicoplanin **OR** IV Vancomycin **PLUS** IV Gentamicin **PLUS** IV Metronidazole
If previous ESBL or AmpC positive bacteria	IV Meropenem **PLUS** IV Gentamicin
If MRSA positive	**ADD** IV Teicoplanin **OR** IV Vancomycin

In addition to antibiotics a source of sepsis should be identified and managed as soon as possible e.g. removal of infected CVC, drainage of abscess, repair of perforated abdominal viscus.

For Children (see section – Emergencies, Initial Management of Meningococcal Sepsis in Children)

Children	
1st line	IV Cefotaxime **PLUS** IV Gentamicin
2nd line (if 1st line contraindicated)	IV Chloramphenicol **PLUS** IV Gentamicin

Total Duration

7-10 days

Unless a causative microorganism or focus of infection requires longer treatment e.g. *Staphylococcus aureus* bacteraemia, listeriosis or meningitis (see section – Antibiotics, Adult Empirical Antibiotic Guidelines)

Dosing

See section - Antibiotics, Empirical Antibiotic Guidelines Emergencies.

Warning - Prognosis and Complications

Mortality in sepsis increases if adequate antibiotic treatment is delayed:

- Septic shock - mortality increases by 7% per hour for the first 6 hours that treatment is not adequate
- Sepsis without shock – mortality increases 1-1.5% per hour for the first 6 hours that treatment is not adequate

Adult Sepsis "Golden-Hour" Management Flowchart