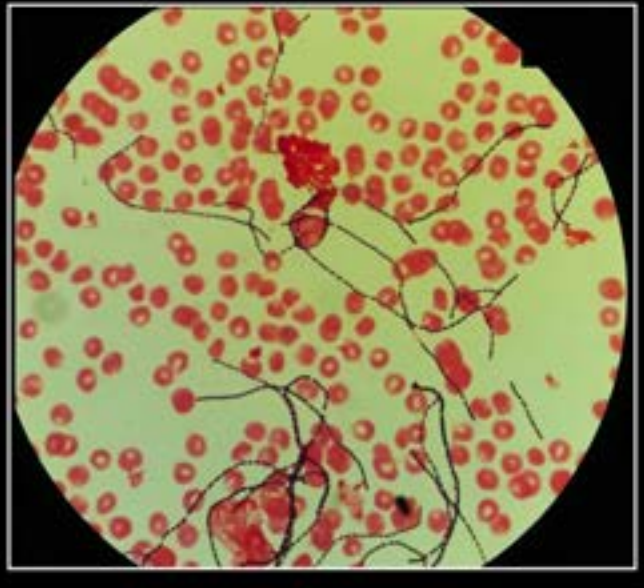
Practical Clinical Microbiology and Infectious Diseases

A Hands-On Guide

EDITED BY
Firza Alexander Gronthoud



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Edited by

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Preface

There are already many valuable medical textbooks available covering various aspects of clinical microbiology and infectious diseases. Although important fundamental concepts such as epidemiology, pathogenesis and clinical manifestations are being taught, reading these textbooks might not necessarily prepare the medical professional on how to deal with frequent issues that arise during the various stages of infection management, with common examples being interpreting and acting on laboratory results and adverse events related to antibiotic use such as drug toxicities and allergies, as well as preventing infections from difficult-to-treat organisms.

This book addresses this issue by drawing on the real-life clinical experiences of its authors, targeting those healthcare professionals working in the field of infection management, such as doctors training in clinical microbiology and infectious diseases or those who already have obtained their specialty degree or any medical professional interested in the management of infection.

The aim of this handbook is to concisely offer practical guidance on how to translate theoretical apply theory into clinical practice, as well as to provide guidance on how to deal with day-to-day scenarios and clinical problems encountered when managing infections.

Learning the tricks of the trade from experienced infection specialists supports the specialty trainee (and any medical professional interested in infection) to develop confidence and competence in dealing with common but sometimes challenging and complex clinical scenarios and ultimately improving patient safety and experience.

We hope that this handbook is a useful source and quick access reference.

Firza Alexander Gronthoud, MD, DTM&H

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I dedicate this book to my parents and my sister. Everything I have achieved in life would not have been possible without their unconditional love, support and guidance. They have always been there for me during my entire personal and professional life. They taught me humbleness, discipline, manners, respect, compassion and kindness and so much more which has been instrumental in all my successes in life. I am truly blessed and eternal grateful to them.

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Editor

Firza Alexander Gronthoud, MD, DTM&H, obtained his primary medical degree in 2009 at Maastricht University (the Netherlands). He completed his specialty training in 2015 in medical microbiology and virology at the Amsterdam Medical Centre. During this period, he spent one year in Medan, Indonesia, as part of an international research collaboration between the Netherlands and Indonesia. In 2015, he moved to the United Kingdom to take up his first consultant post at Manchester University Hospital NHS Foundation Trust. In 2017, he completed the diploma course in tropical medicine and hygiene at the London School of Hygiene and Tropical Medicine. Dr. Gronthoud currently works as a consultant microbiologist at the Royal Marsden Hospital NHS Foundation Trust and is pursuing an MSc in clinical microbiology and infectious diseases at Edinburgh University (Scotland).

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Section I

Principles of Infection Management

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1.1 Pillars of Infection Management

Firza Alexander Gronthoud

CLINICAL CONSIDERATIONS

Antibacterial agents (antibiotics) are used to treat bacterial infections, antiviral agents are used to treat viral infections, antiparasitic agents are used to treat infections caused by parasites and antifungal agents are used to treat infections caused by yeasts and moulds (commonly grouped as fungi). Together, these agents are also referred to as antimicrobials. There is widespread (mis)use of antimicrobials for both preventing and treating infections. An unintended consequence of antimicrobial treatment is the emergence of antimicrobial-resistant organisms as well as increased risk of drug toxicity, length of hospital stay, increased morbidity and mortality and increased costs. It is therefore worthwhile to consider the following.

Varying Degrees of Antibiotic Resistance

- *Multidrug resistant (MDR)*: Resistant to at least one antibiotic in three or more classes
- *Extensively drug resistant (XDR)*: Resistant to at least one antibiotic in all but two or fewer classes
- *Pan-drug resistant (PDR)*: Resistant to all antibiotics in all classes

Finding the Balance

High burden of infections (infection pressure) leads to increased use of antibiotics. Antibiotics exert pressure (antibiotic pressure) on the gut microbiota (commensal flora) which can lead to emergence and spread of antibiotic-resistant organisms to healthcare workers, patients and the environment. Gut commensal flora can resist colonization with drug-resistant organisms through secretion of antimicrobial products, competition for nutrients and help with maintenance of gut barrier integrity. This is called colonization resistance. High antibiotic pressure reduces colonization resistance and increases rates of patients colonized with drug-resistant organisms (colonization pressure). Increased colonization pressure further drives spread of MDR organisms (MDROs) and increased rates of infections caused by MDROs. This, in turn, leads to a vicious circle with increased use of broad-spectrum antibiotics, leading to increased antibiotic pressure on the gut, reduced colonization resistance and increased colonization pressure.

CLINICAL PEARL

Colonization resistance is also affected by drugs other than antimicrobials.

- Proton-pump inhibitors decrease intestinal pH, promoting colonization with MDRO and *Clostridioides difficile*.
- Metformine promotes the presence of butyrate-producing bacteria. Butyrate contributes to maintenance of gut barrier functions and has immunomodulatory and anti-inflammatory properties, thus contributing to colonization resistance.
- Antipsychotics have been shown to possess antibacterial effects.

Goals of Infection Management

- Diagnose and treat infections and prevent spread of infections to others.
- Reduce antibiotic pressure, colonization pressure, infection pressure and antibiotic resistance and keep the human microbiota healthy and maintaining its colonization resistance.

Pillars of Infection Management

The three pillars of infection management are diagnosis, treatment and prevention and control of infectious diseases and requires close collaboration among the microbiology laboratory staff, consultant microbiologist, consultant infectious diseases specialist, antimicrobial pharmacist and infection control nurses, supported by the executive board of the hospital.

CLINICAL APPROACH

To implement and execute the three pillars of infection management, it is essential to have diagnostic stewardship, antimicrobial stewardship and infection prevention and control initiatives in the hospital.

Diagnostic Stewardship

Accurate and fast microbiology results directly impact antimicrobial stewardship through early rationalization of antibiotics, shortening duration of treatment and facilitating intravenous to oral stepdown. It also allows for timely implementation of effective infection control precautions.

Key principles are taking the right samples at the right time, ensuring samples are collected according to hospital policies with optimized laboratory processes in place to ensure high-quality results with a short turnaround time and avoiding releasing meaningless results which can mislead clinicians and lead to inappropriate use of antimicrobials.

Antimicrobial Stewardship

Inappropriate antibiotic use may lead to increased adverse effects, secondary infections, drug interactions, additional costs, prolonged lengths of hospital stays and hospital readmissions.

The goal of antimicrobial stewardship is to ensure appropriate use of antimicrobial agents, improve patient outcome and reduce risk of both adverse drug events and emergence of antimicrobial resistance. Safety and effectiveness of antimicrobials including glycopeptides, aminoglycosides and certain azoles require therapeutic drug monitoring to ensure adequate blood levels.

Infection Prevention and Control

The absence of new, effective anti-Gram-negative antibiotics makes infection prevention and control the most important counter-measure against multidrug-resistant Gram-negative pathogens. Infection prevention and control can prevent additional infections and the spread of resistant pathogens and thereby reduce the need to use antibiotics.

These three pillars of infection management will be discussed in more details in Chapters 1.2–1.4.

Every patient is unique and may have individual infection risk factors influenced by personal lifestyle and underlying comorbidities. Effective implementation of the three pillars of infection management should be tailored to each individual by using a holistic but individualized approach.

This often involves a multidisciplinary team approach whereby individual infection risk factors are assessed and managed. Examples include smoking, alcohol use, diabetes, nutrition, wound care, intravascular and bladder catheter care and vaccination.

Finally, it is essential to maintain a healthy gut microbiota as there is a strong relationship between gut microbiota and the immune system, and an association with cancer and autoimmune disorders has been demonstrated.

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1.2 Diagnostic Stewardship

Firza Alexander Gronthoud

CLINICAL CONSIDERATIONS

More than half of all medical decisions are based on laboratory results. Approximately 25% have a negative impact on patient outcomes, raising the need to reduce laboratory error to as close to zero as possible. Fast, accurate microbiology results lead to quicker appropriate treatment decisions and timely implementation of infection control precautions.

Choosing the right test and collecting the right specimen using the correct method, reducing turnaround time and correctly interpreting results requires specialist knowledge, often not taught in medical school or higher medical training.

Similar to an antimicrobial stewardship programme to ensure correct use of antibiotics, there is a need for a diagnostic stewardship programme to prevent improper use of the clinical laboratory and optimize the quality of infection management. It is therefore worthwhile to consider the following.

Negative Consequences of Improper Use of the Microbiology Laboratory

- Long transport time or inefficient laboratory processes can prolong long turnaround time of results, leading to unnecessary prolongation of broad-spectrum antimicrobials.
- Not distinguishing between colonization and infection can lead to inappropriate use of antimicrobials.
- Ordering the wrong test at the wrong time or collecting specimens incorrectly can yield false-negative or false-positive results.
- Failing to retrieve or ignoring a test result.

Disadvantages of Not Performing Microbiology Tests

- Prescribing antibiotics without knowing the cause of infection can lead to unnecessary use of broad-spectrum antibiotics or the use of antibiotics not active against the organism causing the infection.
- It can also lead to use of antibiotics when there is no infection at all.
- Increased risk of treatment failure or relapse of infection can lead to more antibiotic courses.

The Role of the Microbiology Laboratory

- Report significant results and avoid risk of misinterpretation of nonsignificant results.
- Provide advice about best use of the laboratory and recommend antimicrobial treatment regimens through education and guidelines.
- Antimicrobial-resistance surveillance informs local antimicrobial guidelines and feeds into regional, national and international surveillance.
- Screening for multidrug-resistant organisms to aid timely implementation of infection control precautions.

Role of Clinicians in Diagnostic Stewardship

- To understand the advantages, disadvantages and clinical value of tests in different settings.
- To provide clinical information to ensure appropriate microbiological tests are performed on the sample.
- Accurate result interpretation to avoid inappropriate use of antimicrobials.

CLINICAL PEARL

The Dipstick

- Overuse of urine dipsticks in the diagnosis of urinary tract infections. Major cause of unnecessary antibiotic treatment.
- Asymptomatic bacteriuria is very common in the elderly and a positive dipstick test does not necessarily mean that the patient needs treatment.

Impact of Rapid Accurate Microbiology Diagnosis

- Shortens duration of treatment
- Early de-escalation from broad-spectrum to narrow-spectrum agents
- IV to oral stepdown
- Rapid detection of alert organisms and multidrug-resistant organisms
- Reduces risk of toxic side effects
- Reduces risk of emergence of antimicrobial resistance
- Reduces total antimicrobial consumption and costs
- Improves patient outcomes and reduces length of hospital stay

Turnaround Time

Long turnaround times lead to delays in diagnosis and unnecessary use of antimicrobials or use of ineffective antimicrobial treatments. Factors that can influence turnaround times of diagnosis include:

- Culture: Most tests for bacterial infection still rely on prolonged incubation to grow bacteria on culture media.
- Serological tests rely on the detection of antibodies to the infection, and these may not appear for at least 10–14 days after the onset of the infection.
- Transport time.

Diagnostic stewardship aims to improve all aspects of the laboratory diagnosis of infections. Diagnostic stewardship is an effective and important mechanism in the capacity-building and quality-improvement process in the healthcare system. It also helps to optimize resource utilization and to improve surveillance data. Stages in the diagnostic process that are covered within diagnostic stewardship are:

- Indication for test and specimen selection
- Provision of relevant clinical information
- Correct storage and transportation of specimens to the laboratory
- Booking in and processing specimens

- Selection of appropriate tests
- Reporting and interpretation of results
- Guiding patient management

CLINICAL APPROACH

Key interventions of diagnostic stewardship are as follows.

Education of Clinical Staff to Improve the Diagnostic Value of Requested Tests

Teaching sessions, development of guidelines and hospital wide campaigns can raise awareness of appropriate use of the microbiology laboratory and can upskill members of the staff. Some topics that could be covered in teaching sessions are:

- Ability of a test to differentiate between health and disease.
- Does the test result play a significant role in the management and/or outcome of the patient, i.e. to rule out infection or distinguish between bacterial and viral infection.
- Overview of the various microbiology tests (i.e. PCR, culture, serology) and their advantages and disadvantages.
- Basic understanding of the meaning of microbiology results and promoting correct interpretation of results.

Guidelines can offer guidance on appropriate collection and transport of specimens:

- Transport time should be less than two hours to prevent bacterial overgrowth.
- Most specimens should be stored between 2 and 8°C; exceptions include mycology samples, blood cultures and cerebrospinal fluid.
- Avoid blood culture contamination through aseptic techniques. Volume of blood is more important than timing (i.e. waiting until a patient spikes a fever).
- Urine: Send midstream urine. To avoid diagnosing a colonized catheter rather than infection, replace catheter first and then send new urine sample. Use boric acid containers.
- A positive dipstick or cloudy and offensive-smelling urine in the absence of urinary symptoms is not an indication for sending a urine culture or antimicrobial therapy.
- Wound swabs and sinus tracts often grow colonizing bacteria not involved in the infection. Irrigating the wound with saline, squeezing the edge of the wound until pus is discharged and sending pus for culture increases diagnostic yield.
- Avoid sending catheter urine or drain fluid which has been in the collecting bag for hours.
- If admitted more than 48 hours ago, then only test for *Clostridioides difficile* after other causes of diarrhoea have been excluded. (Appropriate testing for *C. difficile* is discussed in more detail in Chapter 5.9.)
- Stool cultures in afebrile outpatients with acute onset of watery diarrhoea is highly unlikely to yield positive results for a bacterial pathogen.
- Examination of stool for ova and parasites should be obtained only in patients with diarrhoea for more than 2 days plus an appropriate travel history or if there is a strong suspicion of *Giardia* or *Cryptosporidium* infection.
- Sterile fluids (pleural fluid, joint aspirate, peritoneal fluid): If a large volume can be obtained, it should be inoculated into blood culture bottles containing nutrient media. A small portion should also be sent to the laboratory in a sterile tube so that appropriate stains (e.g. Gram, acid-fast) can be prepared and direct culture can be performed.

- Therapeutic drug monitoring: Taking trough levels too early has a detrimental effect as clinicians may withhold the dose or reduce the dose, leading to treatment failure and worse patient outcome.
- Only send line tips if there is a suspicion of infection.
- Guidance on requesting serology: If the serum is taken too early, no antibodies will be detected, and serology test will be negative. Conversely, if the sample is taken too late, serology test may not be able to distinguish between past or active infection.
- With many arboviral infections, such as dengue, the period of viraemia may only be detectable in the first days of infection. After this period, it may be more useful to perform serology.

CLINICAL PEARL

It is common practice for clinicians to take a blood culture when a patient is febrile. Clinical signs of sepsis are a response to the release of endotoxins or exotoxins from the organisms, occurring as long as one hour after the organisms entered the blood. Thus, few to no organisms may be in the blood when the patient becomes febrile. For this reason, it is recommended that two to three blood samples should be collected at random times during a 24-hour period (Murray et al., 2013).

Improving Laboratory Processes and Better Use of Resources

- Complying with national and international guidance on laboratory test methods, i.e. UK Standard Methods for Investigation, United States ASM/IDSA guideline.
- Participating in laboratory accreditation requirements to assess compliance with the ISO15189 standard.
- For most bacterial culture requests, repeat testing should be rejected as it can lead to confusing results. Conversely, for some types of infections (viral, rickettsiosis, Lyme), repeat serologic testing is necessary to detect a rise in antibody titre which is seen in the acute infection.
- Adding comments to assist in interpreting results or advising on when to repeat the test.
- Improving turnaround time of results to guide earlier clinical decision-making:
  - Extending laboratory opening hours
  - Seven day per week working and reporting to meet deadlines of ward rounds or patient review
  - Substituting slow bacterial culture methods with rapid molecular techniques
- Introducing technological advances:
  - Lab automation to enable higher laboratory throughput of specimens at lower cost; they can also have positive benefit for stewardship activities. As well as improving laboratory turnaround times, automation can provide greater consistency of culture among samples and, in some cases, improve the yield of organisms from cultured samples.
  - Rapid bacterial identification with matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS); can be performed on both colonies or directly on clinical samples, i.e. blood cultures.
  - Rapid identification with MALDI-TOF without susceptibility testing but may not necessarily translate into empirical antimicrobial therapy changes.
  - Commercial or in-house molecular methods such as polymerase chain reaction (PCR) can not only detect the most common causes of respiratory tract, central nervous system, gastrointestinal and bloodstream infections but also detect antimicrobial-resistance genes.

- Presence of resistance genes may not necessarily correlate with *in vivo* susceptibility. For now, phenotypic susceptibility testing remains the gold standard.
- Molecular tests can also be used for rapid screening for multidrug-resistant organisms. Bacterial culture is slower but can provide extensive antimicrobial susceptibility testing.

Restrictive Reporting of Antimicrobial Susceptibility Testing

- Reporting of susceptibility results should prevent inappropriate antimicrobial prescribing
- Influence clinician prescribing behaviour such as building experience and confidence that (combinations of) small spectrum antimicrobials are as effective as broad spectrum antimicrobials including carbapenems.

Better Use of Hospital IT

Building in rules in the electronic patient record to:

- Reject samples
- Advise on the best test
- Advise on when to repeat tests

Audits

Regular audits should be performed to evaluate the effect of each of the above interventions. Examples of metrics that can be used:

- Rate of specimen rejection
- Blood culture contamination rate
- Turnaround time of results
- Time from presentation of symptoms to diagnosis
- Rate of antimicrobial treatment modifications based on microbiology results
- Time to implementation of infection control precautions
- Duration of isolation
- Antimicrobial consumption

Communication and Collaboration with Other Disciplines

- Optimal patient care depends on good communication between clinical staff at point-of-care, microbiology laboratories and surveillance staff.
- Standard operating procedures could stipulate how rapidly provisional results will be communicated, the on-call availability of laboratory staff and include provision for regular meetings to discuss results for individual care, to facilitate the development and adaptation of local treatment guidelines and to address performance and challenges.
- Joint ward rounds, with the presence of both clinicians and microbiologists, provide further opportunities for improving communication and patient management.
- Multidisciplinary team meetings facilitate and improve collaboration and build mutual understanding between clinical, laboratory and surveillance staff.

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1.3 Antimicrobial Stewardship

Firza Alexander Gronthoud

CLINICAL CONSIDERATIONS

Up to 50% of antimicrobial use in hospitals is inappropriate, leading to increased length of antimicrobial duration, increased length of stay, emergence of antimicrobial resistance and increased risk of drug toxicity. Antimicrobial stewardship is a multidisciplinary team effort and initiatives should be tailored to each healthcare institution owing to different practices, cultures and healthcare systems and processes in place. It is therefore worthwhile to consider the following:

The Goal of Antimicrobial Stewardship

The primary goal of antimicrobial stewardship is to ensure that for each patient, the right antimicrobial is given at the right time using the right dose and route and reducing the risk of drug toxicity and emergence of antimicrobial resistance.

Secondary Goals

- Improve patient outcome by improving infection cure rates and reducing mortality and morbidity
- Improve patient safety
  - Prevent colonization with multidrug-resistant organisms and infection with *Clostridioides difficile*
  - Reduce length of hospital stay and antimicrobial consumption
- Reduce healthcare costs

Common Causes of Inappropriate Use of Antibiotics

- Treating respiratory or gastrointestinal viral infections
- Treating asymptomatic bacteriuria in patients who are not pregnant or who are not undergoing urological procedures
- Not reviewing antimicrobial therapy when microbiology results are available
- Mismatch antimicrobial spectrum of activity and microorganisms (potentially) involved in the infection
- Not following local guidelines
- Intravenous route when oral can be used
- Incorrect duration and incorrect dose and frequency
- Not reviewing drug allergy status
- Not reviewing prescriptions for drug-drug interaction
- Prolonged use of surgical prophylaxis >24 hours
- In the ICU setting, failure to de-escalate or excessive duration of therapy

Collateral Damage of Antibiotics

- Emergence and spread of antimicrobial resistance
- Reduced colonization resistance (See Chapter 1.1 ‘Pillars of Infection Management’)
- Changes in metabolic capacity of microbiota causing overall health consequences

CLINICAL PEARL

Carriage of resistant bacteria in our microbiota can persist for many months, and the risk of prolonged carriage is increased by further antibiotic use.

Drivers of (Mis)Use of Antibiotics

- Lack of knowledge and education
- Lack of or inadequate diagnostics tests leads to uncertainty regarding presence of infection (see Chapter 1.2)
- Fear of a life-threatening infection
- Local culture and historical practice

Clinical Consequences of Antimicrobial Resistance

- Longer time to resolution of symptoms
- Prolonged courses of antimicrobial therapy
- Increased use of broad-spectrum antibiotics
- Increased length of stay with risk of healthcare-acquired infections

Utility of PK/PD Targets

- Suboptimal antimicrobial concentrations promote development of multidrug resistance. Improving outcomes from infection requires understanding of the interactions between the drug, host and infecting pathogen.
- Application of pharmacokinetic and pharmacodynamic drug targets can optimize antimicrobial killing and prevent emergence of antimicrobial resistance (see Chapter 3.8).

Reducing Risk of Adverse Drug Events

- Timely de-escalation to narrow-spectrum antimicrobials reduces risk of resistance or development of *C. difficile* infection.
- Renal dose adjustments will ensure patients are not over- or under-dosed, which may increase their risk for adverse effects, infection relapse or development of resistance.

Potential Barriers to Implementing Antimicrobial Stewardship Initiatives

- Executive teams with different priorities
- Opposition from prescribers
- Lack of trained staff (microbiology, infectious diseases, pharmacy and nurses)
- Outdated IT technology making it difficult to (1) monitor antimicrobial use and costs, and (2) obtain local antimicrobial susceptibility data
- Outdated guidelines

CLINICAL APPROACH

Rational use of Antimicrobials

Antimicrobial stewardship is every prescriber's responsibility, and for each antimicrobial prescription, the following items need to be considered:

- Which organisms could be involved in this infection?
- Risk factors for drug-resistant bacteria (hospital admissions in past 3 months, previous antimicrobial courses)
- Take cultures before starting antimicrobials
- Tissue penetration
- Take into account renal and hepatic function
- In cases of positive microbiology cultures: distinguishing between infection or colonization can prevent unnessecary antibiotic prescriptions
- Limiting the use of broad-spectrum drugs when a narrower antimicrobial spectrum suffices
- Shortening duration of therapy when prolonged antibiotic courses do not provide benefit
- Avoiding drug-drug interactions
- Appropriate dose
- Therapeutic drug monitoring
- Intravenous or oral route
- Use empirical therapy first; narrow the spectrum later
- Use a proper dose first up; no point under-dosing patients
- Where possible, use monotherapy (it reduces cost and toxicity)
- If the microbiology suggests reduced susceptibility, think: Are the antibiotics working clinically? Is there direct bedside evidence that they are working? If the answer is yes, then you should continue them in spite of laboratory evidence. *In vitro* sensitivity does not predict *in vivo* effect. It might be good to liaise with the infection specialist to ensure the right dose is given.
- Limit 'prophylactic' use to appropriate situations
- Consider non-infective causes of inflammation (it's not always sepsis)

These are quite a few considerations and may seem daunting for the clinical team who are also dealing with other non-infectious problems. Fortunately, the antimicrobial stewardship team can provide support and guidance to clinicians through:

- Providing guidance on appropriate investigations and sampling, initiation of empiric therapy, streamlining to directed therapy
- Reviewing prescriptions for antimicrobial agents
- Providing advice on optimization of antimicrobial therapy, i.e. therapeutic drug monitoring and modifying doses in renal or hepatic impairment
- Reviewing drug interactions with existing medications
- Promoting IV to oral stepdown when appropriate
- Gathering data and feeding back to clinicians and executive board: point prevalence surveys, audit data, quality improvement data collection, primary care prescribing data
- Updating local guidelines, taking into account local resistance profiles
- Managing an outpatient parenteral antimicrobial therapy service
- Ensuring compliance with national quality standards or quality initiatives
- Providing education through a formal teaching session or ad hoc education on ward rounds (Education is an essential tool to influence prescribing behaviour and upskill members of staff to further enhance and increase acceptance of stewardship strategies.)

The antimicrobial stewardship team can choose from various approaches when performing the above activities:

- *Restrictive*: Formulary restrictions, pre-approval by a senior member of an antimicrobial stewardship team doctor (i.e. infection specialist or a specified expert on the ICU team) and automatic stop orders.

- *Collaborative or enhancement*: Education of prescribers, implementation of treatment guidelines, creating awareness of adverse drug events, use of PK/PD concepts and prospective audit and feedback to providers.
- *Structural*: Use of computerized antibiotic decision support systems, faster diagnostic methods for antimicrobial resistance, antibiotic consumption surveillance systems, ICU leadership commitment, staff involvement and daily collaboration between ICU staff, pharmacists, infection control units and microbiologists.

To organize these activities, an antimicrobial stewardship programme should consist of

- Antimicrobial committee
- Antimicrobial formulary
- Antimicrobial team executing the day-to-day antimicrobial stewardship activities with key members including consultant microbiologist, consultant infectious diseases, antimicrobial pharmacist and senior representatives from clinical teams

Examples of Metrics to Assess and Evaluate Antimicrobial Stewardship Initiatives

- *Outcome measures*: 30-day mortality, surgical site infection rates, length of hospital stay, hospital readmission rates, *C. difficile* rates, infection recurrences
- *Prescribing related measures*: Duration of therapy, percentages of prescriptions in line with hospital guidelines, IV to oral switch

Surveillance of Antibiotic Prescription

- Surveillance is a first and essential step to measure antimicrobial consumption.
- Document physicians' incentives to prescribe antibiotics and to identify areas of potential overuse or misuse which could then be a target for antimicrobial stewardship interventions.
- Surveillance metrics are derived from antibiotic prescription data (pharmacy-based), microbiology results (laboratory-based) or diagnostic codes (administration-based) or a combination thereof.
- Monitor adherence to hospital guidelines/formularies, time to de-escalation of antibiotics, rate of *C. difficile* infections and drug toxicities, antimicrobial consumption and antimicrobial resistance.

Tackling Antimicrobial Resistance in the Hospital

- Raise awareness among staff and patients
- Improve sanitation and hygiene
- Prevent infections (and thus antibiotic use) by infection prevention and control strategies (including vaccinations)
- Surveillance
- Rapid diagnostics
- Rational use of antibiotics

Antimicrobial Stewardship Programmes Should be Adapted to Local Institutions and Culture

- Cultural background and habits for antibiotic prescription, MDRO prevalence, local organizational aspects and available resources.
- Identifying barriers and facilitators that impact the staff's compliance to guidelines in order to design and execute a structured plan for improvement is essential.

Antifungal Stewardship

Although it follows the same general principles as antibiotic stewardship, there some key differences:

- Therapeutic drug monitoring plays a bigger role in antifungal stewardship owing to azoles being the most used class of antifungals.
- Azoles are cytochrome P450 enzyme inhibitors and monitoring for drug-drug interactions is essential.
- Fungal culture has low sensitivity and the use of biomarkers and radiology is an important part of antifungal stewardship.
- Antifungal stewardship interventions depend on the patient population and fungus involved:
  - Candidaemia
  - Neutropenic fever
  - Pre-emptive treatment versus prophylaxis

Antifungal Stewardship for Patients with Candidaemia

- Restrict or avoid antifungal prophylaxis; in particular fluconazole
- Differentiate infection from colonization and do not treat colonization
- Use non-culture-based diagnostics for early detection of invasive candidiasis (IC) (1,3-β-D-glucan, Mannan Antigen and Anti-Mannan Antibodies)
- Limit the use of empirical therapy based only on risk factors
- Promote early pre-emptive antifungal treatment based on risk factors, (heavy) colonization and biomarkers
- Have adequate source control within 48 h (catheter removal, appropriate drainage, surgical control)
- Use an adequate dose; low dose is associated with resistance
- De-escalate whenever possible (if possible, within 5 days) from echinocandins to azoles
- Antifungal therapy (usually echinocandin or fluconazole) should be discontinued if there is a negative 1,3-β-D-glucan in serum combined with negative blood cultures and/or negative drain cultures.
- *Candida* scoring systems or a colonization index may be used to either withhold treatment for IC or to prompt the use of 1,3-β-D-glucan to enhance its positive predictive value.

Antifungal Stewardship in Patients with Profound Neutropaenia

Patients with profound neutropaenia (i.e. intensive chemotherapy for acute myeloid leukaemia or allogeneic haematopoietic stem cell recipients) are at risk of invasive mould infections, predominantly caused by *Aspergillus* spp. Close monitoring of clinical and radiological findings, complemented by detection of fungal biomarkers in serum and bronchoalveolar lavage, might substantially reduce the inappropriate use of empirical mould active therapy.

Effective management of invasive fungal infections (IFIs) depends on early individualized therapy that optimizes efficacy and safety (See Chapter 3.2 'Basic principles of antifungal treatment'). Considering the negative consequences of IFI, for some high-risk patients, the potential benefits of prophylactic therapy may outweigh the risks. When using a prophylactic, empiric or pre-emptive therapeutic approach, clinicians must take into account the local epidemiology, spectrum of activity, pharmacokinetic and pharmacodynamic parameters and safety profile of different antifungal agents, together with unique host-related factors that may affect antifungal efficacy or safety.

The Use of Biomarkers

The use of biomarkers plays a big role in antifungal stewardship owing to the low sensitivity of standard culture techniques.

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1.4 Infection Prevention and Control

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CLINICAL CONSIDERATIONS

The goal of infection control in a hospital setting is to prevent transmission of infectious agents which are difficult to treat or have the potential to cause severe illness. The type of isolation precautions is mainly determined by the mode of transmission and the severity of illness. Prevention and control of infections is an integral part of routine clinical care and should not be regarded as an additional set of practices and care. It is therefore worthwhile to consider the following.

Infectious Agent

An infectious agent is any bacterium, virus, fungus, parasite or prion causing disease. The type of precautions used to prevent transmission to others depends on the agent's treatability, mode of transmission and severity of illness.

CLINICAL PEARL

All body fluids are potentially infectious (except sweat): blood and blood-tinged fluids including open wounds, stools, urine, vomit, respiratory secretions, saliva, semen, vaginal secretions, breast milk and sterile fluids including blood, pericardial fluid, pleural fluid and synovial fluid.

Colonization versus Infection

Colonization is when an infectious agent is present without causing symptomatic disease. Infection is when the infectious agent is present and causes symptomatic disease. Colonization does not require treatment with antimicrobials but does require infection control precautions.

Hospital Sources of Transmission

- Infectious agents transmitted during healthcare come primarily from human sources, including patients, healthcare workers and visitors. Source individuals may be actively ill or may be temporary or chronic carriers of an infectious agent without symptoms.
- Infectious agents may arise from endogenous flora of patients (e.g. bacteria residing in the respiratory or gastrointestinal tract) or from environmental sources such as air, water, medications or medical equipment and devices that have become contaminated.

Modes of Transmission

- *Direct transmission*: Infectious agent transferred directly from one person to another person.
- *Indirect transmission*: Infectious agent transferred through a contaminated intermediate object (fomite) or person.

- *Large droplets (>5 microns)*: When a person coughs, sneezes or talks, and during certain procedures, large respiratory droplets are expelled which can enter other people through the nose, conjunctivae or oropharynx. Transmission via large droplets requires close contact as the droplets do not remain suspended in the air and generally only travel short distances (<2 metres). Droplets can also be transmitted by hands.
- *Airborne*: Small respiratory droplets, also called aerosols, which can travel over long distances and can remain suspended in the air for a prolonged time. Transmission similar to large droplets.
- Contaminated food, water, medications, devices or equipment.

Droplets versus Aerosols

Small aerosols are inhaled deep into the lung and cause infection in the alveolar tissues of the lower respiratory tract, whereas large droplets are trapped in the upper airways. Droplets travel over 1–2 metres and do not stay suspended in the air. Infection via aerosols may therefore lead to more severe disease and require more strict infection control precautions.

CLINICAL PEARL

Certain procedures, particularly those that induce coughing, can promote airborne transmission. These include diagnostic sputum induction, bronchoscopy, airway suctioning, endotracheal intubation, positive pressure ventilation via face mask and high-frequency oscillatory ventilation.

CLINICAL PEARL

The modes of transmission vary by type of organism. In some cases, the same organism may be transmitted by more than one route (e.g. influenza and respiratory syncytial virus [RSV] can be transmitted by contact and droplet routes).

Risk of Infection

Factors important to consider when risk assessing the need for specific infection control precautions or administration of post-exposure prophylaxis following infection exposure include:

- Age
- Immune status
- Comorbidities, i.e. diabetes mellitus, malignancy
- Virulence of infectious agent

CLINICAL APPROACH

Risk Assessment

For any given procedure, clinical situation or new admission/transfer, a risk assessment needs to be undertaken which involves going through the five pillars of infection prevention and control to ensure that besides clinical care, also appropriate infection control measures are in place.

- *Pillar 1*: Prevention of transmission
- *Pillar 2*: Source control

- *Pillar 3*: Environmental decontamination
- *Pillar 4*: Antimicrobial stewardship
- *Pillar 5*: Diagnostic stewardship

Pillar 1: Prevention of Transmission

The use of standard precautions is the primary strategy for preventing transmission of healthcare-associated infections. Transmission-based precautions are used in addition to standard precautions, where the suspected or confirmed presence of infectious agents represents an increased risk of transmission and/or severe illness.

Standard Precautions

The minimum standard of infection control precautions are to be used for all patients. Standard precautions are used by healthcare workers to prevent or reduce the likelihood of transmission of infectious agents from one person or place to another, and to render and maintain objects and areas as free as possible from infectious agents. Standard precautions include:

- Hand hygiene is the best evidence from the literature compared to other interventions in reducing transmission of infectious agents
- Use of personal protective equipment (PPE) during procedures that may result in exposure to bodily fluids
- Appropriate handling and disposal of sharps to protect healthcare workers against bloodborne diseases
- Appropriate handling of waste and linens
- Appropriate reprocessing of reusable equipment and instruments, including appropriate use of disinfectants
- Cleaning and spills management
- Hygiene and cough etiquette
- Implementation of intravascular and catheter care bundles

CLINICAL PEARL

The five WHO moments of hand hygiene:

- Before touching a patient
- Before clean/aseptic procedures
- After body fluid exposure/risk
- After touching a patient
- After touching patient surroundings

The process of hand washing using the correct technique takes 40–60 seconds. There can be as many as five opportunities per patient contact to wash the hands using the correct technique and duration. As a result, there is an overall low compliance with healthcare workers. Education is key in promoting good hand hygiene to prevent hospital-acquired infections.

Transmission-Based Precautions

Transmission-based precautions should be tailored to the particular infectious agent involved and its mode of transmission (see Chapter 6.5). For infectious agents that have multiple routes of transmission, more than one transmission-based precaution category is applied. Transmission-based precautions

should be used until the patient is not actively excreting the infectious agent anymore. This is usually when signs and symptoms of the infection have resolved. In immunocompromised individuals, the period of excretion may be prolonged until long after the patient has become asymptomatic.

Transmission-based precautions include continued implementation of standard precautions and, in addition:

- Intensified use of PPE (including gloves, apron or gowns, surgical masks or respirators [FFP2, FFP3 or N95] and protective eyewear) according to likelihood of exposure to bodily fluids and probable type and route of transmission
- Patient-dedicated equipment
- Allocation of single rooms or cohorting of patients when required
- Appropriate air-handling requirements
- Enhanced cleaning and disinfecting of the patient environment
- Restricted transfer of patients within and between facilities

The three categories of transmission-based precautions are:

- *Contact precautions*: When there is known or suspected risk of direct or indirect contact transmission of infectious agents that are not effectively contained by standard precautions alone.
- *Droplet precautions*: For patients known or suspected to be infected with agents transmitted over short distances by large respiratory droplets. Because of the short travel distance, special air handling and ventilation are not required.
- *Airborne precautions*: For patients known or suspected to be infected with agents transmitted person to person by the airborne route.

Hand hygiene must be performed before putting on PPE and after removing PPE. Don PPE before patient contact and generally before entering the patient room and remove before leaving patient area. Respirators should be taken off outside the patient room, once the door is closed. To ensure effective protectiveness of respirators, healthcare workers are required to face-fit testing.

Pillar 2: Source Control

The goal of source control is to further reduce the risk of transmission to patients and healthcare workers and to prevent environmental contamination. This includes:

- All beds should be spaced apart 1–2 metres
- Single-room isolation for high risk of transmission: droplet, airborne, infective diarrhoea or highly virulent organisms, i.e. carbapenemase-producing organisms (CPOs) and methicillin-resistant *Staphylococcus aureus* (MRSA)

Prioritization of Single Rooms

- Airborne > droplet > contact; *C. difficile* > CPO > MRSA > extended spectrum beta-lactamase (ESBL)-producing bacteria > vancomycin-resistant *Enterococcus* (VRE)
- Patients who are infected with the same pathogen may be cohorted in the same room or bay
- In the absence of diarrhoea, patients colonized with extended spectrum beta-lactamase (ESBL) producing bacteria and VRE can be nursed in an open bay using contact precautions

Types of Single Rooms

- *Positive pressure*: Protective isolation to keep organisms out of the room; to be used for severely immunocompromised individuals such as bone marrow transplant recipients

- *Negative pressure*: To prevent airborne transmission; 6–12 air cycles per hour; air exhausted directly to the outside or HEPA filtration on exhaust
- *Normal pressure*: Carbapenemase producing organisms, infectious diarrhoea, MRSA

Transportation of Colonized/Infected Patients

- Patients who are under respiratory precautions (droplet and airborne) and who need to be transported should wear a surgical mask
- Patients should follow respiratory hygiene and cough etiquette
- Skin lesions should be covered

Pillar 3: Environmental Decontamination

Preventing transmission of infectious agents from the environment to patients and healthcare workers:

- Frequently touched surfaces should be cleaned daily with detergent solution, as well as when visibly soiled and after every known contamination.
- For specific organisms, enhanced cleaning with chlorine, H_2O_2 fogging and ultraviolet light is indicated.

Pillar 4: Antimicrobial Stewardship

- Appropriate use of antibiotics ensures the best treatment outcome and minimizes risk of toxicity, emergence of resistance and aims to preserve the gut flora, which can act as a reservoir for multidrug-resistant organisms.
- Healthcare worker vaccination against influenza and hepatitis B, and in some countries, tuberculosis.
- Post-exposure prophylaxis, vaccines or immunoglobulins are indicated in pregnant women, neonates and immunocompromised individuals following exposure with influenza, measles and varicella zoster.
- Immunosuppressed individuals may require extra vaccinations, i.e. asplenia patients, bone marrow transplant recipients, individuals with severe liver or renal disease.
- MRSA decolonization treatment suppresses the bacterial load and reduces transmission. It is not 100% effective in eradicating MRSA and recolonization does occur.
- Monitoring of antimicrobial consumption is also part of antimicrobial stewardship.

Pillar 5: Diagnostic Stewardship

Rapid and accurate diagnosis of infections enables timely instigation of infection control precautions, as well as early de-isolation of patients. Besides rapid diagnosis, rapid and effective monitoring of infection rates (passive screening) and rates of patients colonized with drug-resistant organisms (active screening) can help to efficiently allocate resources and identify areas that are at high risk, as well as assess effectiveness of local infection control programmes.

- Screening can act as a tool to monitor the quality of infection control practices.
- Screening can also identify patients who need to be isolated in a single room.
- During outbreaks, screening for carriers helps identify those who need isolation as well as monitor the effectiveness of the implemented actions to stop the outbreak.
- Screening may also be indicated in hospitals where drug-resistant organisms are endemic or when a patient is transferred from a setting of high endemicity of specific organisms.
- Screening also has downsides: Depending on the laboratory method used, it can have a long turnaround time, increased costs, block patient flow and lead to increased use of single

rooms and PPE, especially when patients are prematurely isolated pending the result. Each facility needs to determine whether screening for specific organisms is cost-effective and which laboratory method to use (culture versus PCR).

Prioritizing Needs

In the case of infection control nurse capacity issues, it may be beneficial to initially focus efforts on wards with high antibiotic pressure, infection pressure and colonization pressure as patients on these wards are at particular risk of developing severe, difficult-to-treat infections. These wards are also important infection reservoirs with risk of transmission to other units.

CLINICAL PEARL

Educating and empowering patients and visitors ensures that patients are actively involved in decision-making about care, and able to participate in reducing the risk of transmission of infectious agents.

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Section II

Diagnosis of Infections

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