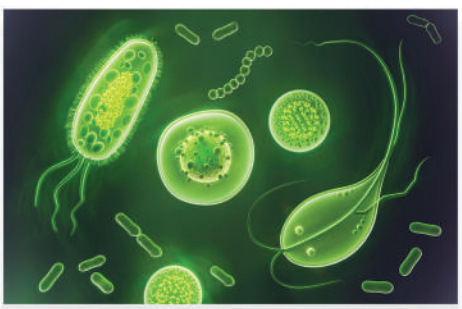
Principles of AMR and AMS

FOR UNDERGRADUATE STUDENTS



AMR DECLARATION TRUST

Principles of AMR and AMS

FOR UNDERGRADUATE STUDENTS

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Dedicated to all patients who lost their lives to drug-resistant infections.

Acknowledgement

We are indebted to the enthusiastic authors of this manuscript, advisors of our AMR Declaration Trust, and the student community eager to have a simple handbook on Antimicrobial resistance, Antimicrobial Stewardship and Infection Prevention and Control.

Introduction

"It is time to close the book on infectious diseases and declare the war against pestilence won." This is one of the most infamous quotes in medicine, although it is unclear who would have said this. Unfortunately, this statement has been proven wrong. From age-old infections like malaria and tuberculosis to newer infectious diseases like Nipah, Zika and COVID-19, infections remain the major cause of mortality and morbidity worldwide. Management of these infections becomes complicated as they acquire drug resistance, some of which arise because of the improper use of the agents we use to treat them. With pan-drug resistant organisms, which are now a reality, causing infections, we have very few therapeutic options left.

Antimicrobial resistance (AMR) is an emerging problem and can cause tens of millions of lost human lives in the coming future. AMR is regarded as a silent, slow, but steadily spreading pandemic that has not yet received its due importance. In 2019 alone, 4·95 million deaths were due to resistant bacterial infections. The primary driver of antibiotic resistance is antibiotic use (rather a misuse) in various settings. This is further fuelled by the high burden of infectious diseases in low-middle-income countries, which demands early initiation of antibiotic therapy in many clinical situations. Antibiotic use in humans accounts for only one-third of the total antibiotics consumed worldwide. Antibiotics are used as growth promoters in the cattle and animal husbandry industry. Besides this, the presence of antibiotics and other antimicrobial chemicals (disinfectants etc.) in municipal and industrial wastewater makes this a problem which has its roots deep in our system.

A multi-pronged approach is required to tackle the socio-economic challenge of AMR. Various steps have already been taken to handle this issue. A national policy for the containment of AMR was launched in 2011. Jaipur Declaration by Health Ministers of member states of the WHO South East Asia region was a significant step. Chennai Declaration, a position paper and initiative by medical societies and other stakeholders in India-launched in 2012, was one of civil society's first significant efforts. The initiative made a big impact at the national level. The Chennai Declaration

five-year plan, published in 2014, provided a time-bound strategy for implementing Chennai Declaration recommendations. ICMR and NCDC have AMR surveillance networks involving a few dozen centres across the country. The National AMR action plan prepared in 2017 was a significant step. NCDC released a National Treatment Guideline for Antimicrobial use in 2016. A significant political commitment came in 2016 when the Prime Minister of India announced the "red line" campaign. A red line on the antibiotic packaging is aimed to draw public attention to the dangers of its misuse of antibiotics. NCDC released National Guideline for Infection prevention in 2020. Recently, the national medical commission (NMC) also passed a regulation making it mandatory for training institutes should have practical education in AMS (Antimicrobial stewardship), AMR and IPC (Infection prevention and control). All these steps are welcoming and encouraging, but more is needed to understand and defeat the demon of AMR.

AMR Declaration Trust- a public charitable Trust founded on the principles of the Chennai Declaration, aims to coordinate constructive discussions to devise innovative solutions to the challenge of AMR. Education of future doctors (undergraduate medical students) and other healthcare professionals is one of the main aims of the trust. This module has been prepared by practising Infectious Diseases (ID) physicians, clinical microbiologists and clinical ID pharmacists; it covers all the fundamental aspects of AMR, AMS and IPC. This module will form a foundation and familiarise students with day-to-day activities in this field.

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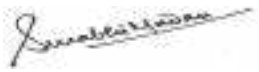

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Expert Reviews

Microbes invented antibiotics, and antibiotic resistance mechanisms, sometime around two billion years ago. Humans have only known of these miracle substances for eighty years. While bacteria use antimicrobial substances selectively and in ecosystem balance and thus have retained their ability to inhibit competitors' growth for all those two billion years, humans have not behaved so responsibly. Our lack of self-control and awareness has led to consistent overuse and abuse of antibiotics on a massive, global scale, which, in turn, has led to the emergence of bacteria resistant to all available antibiotics, converting previously curable diseases to incurable ones. In the past, we have counted on the pharmaceutical industry to bail us out of our irresponsibility as they kept developing newer, broader antimicrobials. But that no longer happens, as there is a market failure of these drugs. Antibiotic resistance is a One Health issue, and we need to learn to act sustainably to retain the miracle, life-saving power of these drugs. A comprehensive summary of the many clinical and policy aspects is needed to make this achievable.

Dr Brad Spellberg MD
Infectious Diseases physician, Chief Medical Officer at the Los Angeles County-University of Southern California (LAC+USC) Medical Center, USA

The global "call to action" to reverse the trend of the emergence and spread of antibiotic-resistant microorganisms must begin and be sustainable over the years. A key parameter that guides this action lies in education. Hospital infection prevention and control and the rational use of antimicrobials in patients presenting with infectious disease syndromes remain the cornerstone for combating the AMR nightmare. Supporting this notion and addressing these learning needs in a concise, easily readable and understandable manner via this booklet is a valuable addition to the new Competency-Based Medical Education (CBME) model and for the mainstream practitioners in clinical practice."

Dr Dilip Mathai MD PhD FRCP (London)
Distinguished Professor and Advisor, The Apollo University, Chittoor, AP

Antimicrobial resistance leads to treatment failure and therefore costs lives and economies. The development of AMR can be slowed by preventing infections in patients after they are admitted to healthcare facilities and by preventing over and underusing of anti-infective drugs through antibiotic stewardship. This book provides the blueprint for decreasing AMR by general practitioners and others in the healthcare profession.

David L Heymann, MD
Professor, Infectious Disease Epidemiology
London School of Hygiene and Tropical Medicine

The next biggest threat to the survival of humanity could very well be from the superbugs resulting from antimicrobial resistance (AMR). With the increasing indiscriminate use of antibiotics in humans and in the veterinary and agricultural domains, the mortal threat seems more proximate than ever. In this context, this book on antimicrobial resistance prepared by the AMR Declaration Trust for the benefit of students of medicine, general practitioners and health professionals is a timely, valuable resource. While congratulating all involved in producing this book, I recommend it to all health professionals and the public at large.

Dr PV Ramesh MBBS, (MS), IAS (R)
Former Health Secretary, Andhra Pradesh

It is a matter of grave concern that antibiotics are becoming increasingly ineffective due to Antimicrobial Resistance (AMR). This has happened over the years due to the rampant use of antibiotics. Antibiotics are erroneously perceived as; a universal cure for any ailment by the public. The publication by AMR Declaration Trust is a praiseworthy initiative which will help generate awareness among all stakeholders about AMR, including ways and means to have judicious use of antibiotics.

Dr Girdhar Gyani
Director General at ASSOCIATION of HEALTHCARE PROVIDERS (INDIA)
Former Secretary General, Quality Council of India

Antimicrobial resistance is considered (along with climate change-related infectious diseases and pandemic preparedness) as one of the emerging medical challenges faced by humanity in the 21st century. India will likely be severely affected by increasing antimicrobial resistance in the next few decades. Still, Indian medical professionals also have the potential to contribute the most in slowing or reversing this trend. This concise primer on Antimicrobial resistance, Infection control and Antibiotic stewardship is a most welcome first step in this direction and accurately summarizes the information in this area. I encourage all medical students, postgraduates and medical practitioners to use it as a ready reckoner and starting point for further education in all matters related to these areas.

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MODULE 1: Epidemiology

CHAPTER

1

Antimicrobial Resistance: Pathogenic Microbiology - Organisms of Interest

Dr Hari Prasad Sirigiri
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AIIMS Raipur

What is antimicrobial resistance?

Antimicrobial Resistance (AMR) is the mechanism which makes bacteria, viruses, fungi and parasites resistant to anti-infectives which makes them difficult to treat.

Why is antimicrobial resistance a global concern?

With the emergence and spread of drug-resistance in pathogens that have acquired new resistance mechanisms, our ability to treat common infections is threatened. Especially alarming is the rapid global spread of multi- and pan-resistant bacteria (also known as “superbugs”) that cause infections that are not treatable with existing antimicrobial medicines such as antibiotics.

The antibiotic pipeline of new antimicrobials has been dry for the past few decades. With the fast spread of multi-drug resistant bacteria, WHO and ICMR have identified a few bacteria and have prepared a list of priority pathogens as listed below. Furthermore, antibiotic shortages are affecting countries of all levels of development.

Antibiotics are becoming increasingly misutilised in various fields of agriculture, animal farming and research, which is also major contributing factors to the development of drug resistance. Free-hand availability of antibiotics over the counter without proper prescription is another leading factor to note. Newer antibiotics are urgently needed to meet this unending need–for example, to treat carbapenem-resistant gram-negative bacterial infections. However, if people do not change how antibiotics are used, these new antibiotics will suffer the same fate as the current ones and become ineffective.

Without effective antimicrobials, medical procedures such as surgeries, including caesarean sections or hip replacements, cancer chemotherapy, and organ transplantation, will become riskier.

The present situation in our country

The Indian Council of Medical Research (ICMR) has been monitoring antimicrobial resistance through the Antimicrobial Resistance Research & Surveillance Network (AMRSN) since 2013.

As per the latest report (2020), a total number of 65,561 culture-positive isolates were studied. Escherichia coli was most commonly isolated, followed by *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus aureus*. Imipenem susceptibility of *E. coli* has dropped steadily from 86% in 2016 to 63% in 2019 and showed a slight recovery to 72% in 2020, and that of *Klebsiella pneumoniae* dropped steadily from 65% in 2016 to 46% in 2019 and remained at 45% in 2020. *Staphylococcus aureus* has shown increasing trends of resistance to most antibiotics over the years; no such prominent trend could be observed with MSSA isolates. Susceptibility to erythromycin, clindamycin, ciprofloxacin, co-trimoxazole and high-level mupirocin was more evident in MSSA when compared to MRSA. The anti-MRSA antibiotics, such as vancomycin and tigecycline, showed excellent in vitro activity (100% against MRSA isolates). Teicoplanin and linezolid resistance was encountered in MRSA isolates, albeit at very low rates of 0.5 and 1 %, respectively. Fungal infections among hospitalized patients are significantly increasing. The majority of fungal infections are caused by a few common fungal agents. Nevertheless, rare species are also increasing, requiring newer treatment strategies. *Candida auris*, multidrug-resistant yeast known to cause hospital outbreaks, has been consistently isolated from regional centres across India. The majority of the *C. auris* isolates were resistant to fluconazole, and the incidence of echinocandin resistance is on the rise. In *A. baumannii*, reduced susceptibility of 10-20% was observed against cephalosporins, carbapenems, monobactams and β-lactam-β-lactamase inhibitors. In *Pseudomonas aeruginosa*, the least susceptibility of 40% was observed for fluoroquinolones; and 60-70% for cephalosporins, carbapenems, and aminoglycosides.

Drug resistance in Mycobacterium tuberculosis

Antibiotic-resistant *Mycobacterium tuberculosis* strains are threatening progress in containing the global tuberculosis epidemic. WHO estimates that, in 2018, there were about half a million new cases of rifampicin-resistant TB (RR-TB) identified globally, of which the vast majority have multi-drug resistant TB (MDR-TB), a form of tuberculosis that is resistant to the two most powerful anti-TB drugs (Isoniazid & Rifampicin). Only one-third of the approximately half a million people who developed MDR/RR-TB in 2018 were detected and reported. MDR-TB requires treatment courses that are longer, less effective and far more expensive than those for non-resistant TB. Less

than 60% of patients treated for MDR/RR-TB are cured. In 2018, an estimated 3.4% of new TB cases and 18% of previously treated cases had MDR-TB/ RR-TB and the emergence of resistance to new 'last resort' TB drugs to treat drug-resistant TB poses a major threat.

INDIAN PRIORITY PATHOGEN LIST

CRITICAL PRIORITY	
Enterobacteriaceae *(Klebsiella pneumoniae* and *Escherichia coli)*	Carbapenem–R Tigecycline–R Colistin–R
Non-fermenting bacteria *(Acinetobacter baumannii* and *Pseudomonas aeruginosa)*	Carbapenem–R Colistin–R
HIGH PRIORITY	
Staphylococcus aureus	MRSA, hVISA Daptomycin–NS Linezolid–R
Enterococcus species	Vancomycin–R Linezolid–R Daptomycin–NS
Salmonella species (Typhoidal and Non-typhoidal)	Azithromycin–NS Third-generation cephalosporins–NS Carbapenem–NS
MEDIUM PRIORITY	
Streptococcus pneumoniae	Cephalosporin–R Fluoroquinolones–R Linezolid–R
Staphylococcus, coagulase-negative	Vancomycin–R Linezolid–R
Shigella species	Third-generation cephalosporins–R Azithromycin–R
Haemophilus influenzae	Third-generation cephalosporin–NS Carbapenem–NS
Neisseria meningitidis	Fluoroquinolones–NS Third-generation cephalosporins–NS

R: resistant; NS: non-susceptible; MRSA: methicillin-resistant *Staph. aureus*; hVISA: heterogenous vancomycin-intermediate *Staph. aureus* Mycobacteria (including Mycobacterium tuberculosis) were not included in this prioritization exercise as it is a well-established global and national priority for which innovative new treatments are urgently needed and being developed.

Drug resistance in malaria parasites

The emergence of drug-resistant parasites poses one of the greatest threats to malaria control and results in increased malaria morbidity and mortality. Artemisinin-based combination therapies (ACTs) are the recommended first-line treatment for uncomplicated *P. falciparum* malaria and are used by most malaria-endemic countries. ACTs are a combination of an artemisinin component and a partner drug. In the WHO Western Pacific Region and in the WHO South-East Asia Region, partial resistance to artemisinin and resistance to a number of the ACT partner drugs has been confirmed in Cambodia, Lao People's Democratic Republic, Myanmar, Thailand, and Viet Nam through studies conducted between 2001 and 2019. This makes selecting the right treatment more challenging and requires close monitoring. So far, ACTs that have been tested remain highly efficacious. However, the further spread of resistance to artemisinin and ACT partner drugs could pose a major public health challenge and jeopardize important gains in malaria control.

CHAPTER

2

Super Bugs

Dr Divya Joshi,
Dr Naveen as–Apollo Hospitals, Chennai

1. What are superbugs?

Superbugs are strains of bacteria, viruses, parasites and fungi resistant to most antibiotics and other medications commonly used to treat the infections they cause.

2. What are the common SUPER-BUGS in India?

Group-1

- Carbapenem Resistant Enterobacterales
- Carbapenem Resistant *Acinetobacter baumannii*
- Drug-resistant *Salmonella typhi*
- *Candida auris*

Group-2

- ESBL producing Enterobacterales
- Multidrug resistant *P. aeruginosa*
- Vancomycin-resistant Enterococci
- Azole Resistant *Candida spp.*

Group-3

- Methicillin Resistant *Staphylococcus aureus*
- Azole resistant *Aspergillus fumigatus*
- Amphotericin B-resistant *Aspergillus flavus*
- Drug-resistant *Stenotrophomonas maltophilia*
- Colistin Resistant *Enterobacterales*
- Colistin resistant *Acinetobacter spp*

3. How does antibiotic resistance spread?

- Germs (bacteria and fungi) are everywhere. Some help us. Some make people, crops, or animals sick.
- Antibiotics kill germs that cause infections. But antibiotic-resistant germs find ways to survive.
- Antibiotic-resistant germs can multiply. Some resistant germs can also give their resistance directly to other germs.
- Antibiotics also kill helpful germs that protect us. Without the helpful germs, resistant germs have an even bigger advantage.
- Once antibiotic resistance emerges, it can spread into new settings and between countries.

4. What are the resistance mechanisms seen in bacteria and fungi?

- **Germs develop new cell processes** that avoid using the antibiotic's target.
- **Germs change or destroy** the antibiotics with enzymes and proteins that break down the drug (e.g., penicillinase, carbapenemases).
- **Germs restrict access** by changing the entryways or limiting the number of entryways (alteration of porin channels).
- **Germs change the antibiotic's target** so the drug can no longer fit and do its job(changing the antibiotic binding site, e.g., penicillin-binding protein sites).
- **Germs get rid of antibiotics** using pumps (Efflux pumps).

5. How resistance spreads among bacteria/fungi?

- Resistance traits can be inherited from generation to generation. They can also pass directly from germ to germ by mobile genetic elements.
- **Mobile genetic elements:**
  - **Plasmids:** Circles of DNA that can move between cells.
  - **Transposons:** Small pieces of DNA that can go into and change the overall DNA of a cell. These can move from chromosomes (which carry all the genes essential for germ survival) to plasmids and back.
  - **Phages:** Viruses that attack germs can carry DNA from germ to germ.
- Mechanisms involved:
  - **Transduction:** Resistance genes can be transferred from one germ to another via phages.
  - **Conjugation:** Resistance genes can be transferred between germs when they connect.
  - **Transformation:** Resistance genes released from nearby live or dead germs can be picked up directly by another germ.

6. Is there any difference in the superbug occurrence rate and differences in the concern in different parts of the world?

Yes, for example, the rate of ESBL-producing enterobacterales is around twenty to thirty per cent in the USA, whereas it is fifty to seventy per cent in India (ICMR Annual Report 2021), and

carbapenemase-producing organisms are on the rise in India due to excessive carbapenem use. Drug-resistant salmonella is an organism of concern all over the world but is an urgent threat in India since a large number of cases occur majorly in tropical countries.

7. What is the trend of superbugs in the USA?

According to CDC 2019 Antibiotic resistance threat reports, the trend from 2011 to 2017 with infection control measures is summarized as follows.

Organisms with the increasing trend: Drug-resistant *Candida auris* and other azole-resistant candida, ESBL and CR Enterobacteriaceae, Drug-resistant Neisseria gonorrhoea, Drug-resistant Campylobacter, Drug-resistant Salmonella and Shigella, Erythromycin resistant Group A Streptococcus.

Organisms with decreasing trend: CR Acinetobacter (but still an urgent threat), Clostridium difficile, Vancomycin-resistant Enterococci, MDR Pseudomonas, MRSA, Drug-resistant Tuberculosis.

An organism with almost similar occurrence: Clindamycin-resistant streptococcus.

8. What is the trend of superbugs in India?

According to the ICMR AMR report of 2020 trend of occurrence from 2017 to 2020

Organisms with the increasing trend: CR Enterobacterales (CRE), CR Acinetobacter baumanii (CRAB), Candida auris, ESBL-producing Enterobacterales, MDR Pseudomonas.

Organisms with the almost similar trend: Drug-resistant Salmonella typhi, Vancomycin Resistant Enterococci, MRSA.

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CHAPTER

3

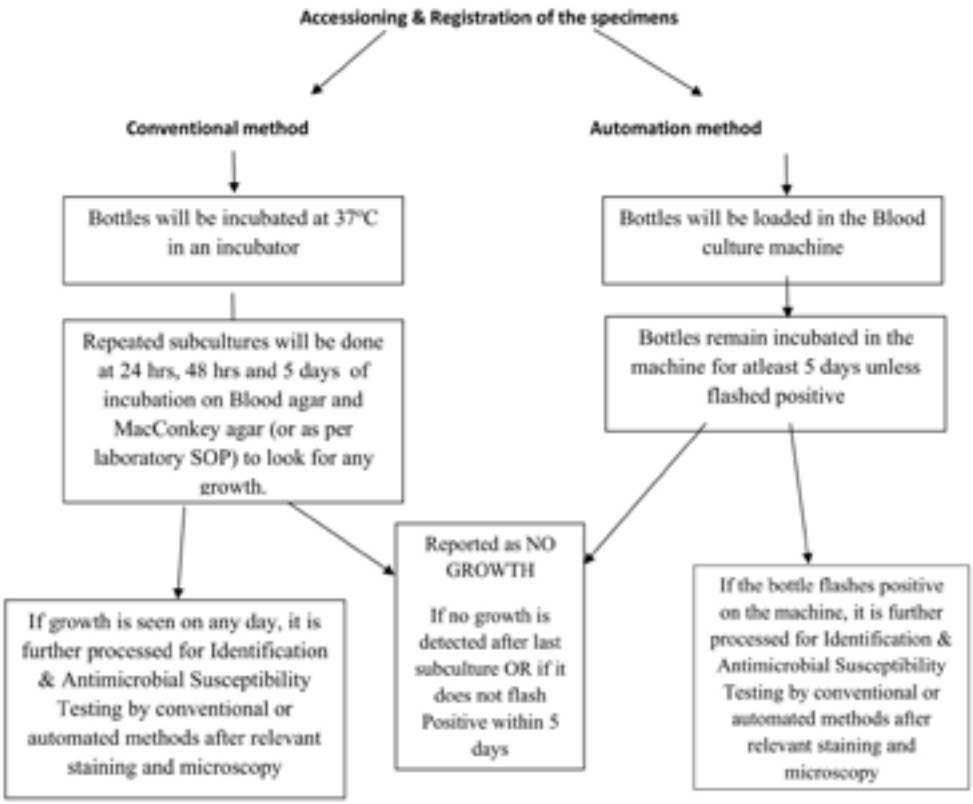
Talking to the Microbiology Lab: Understanding common microbiological tests and methodologies

Dr Ashima Jain Vidyarthi

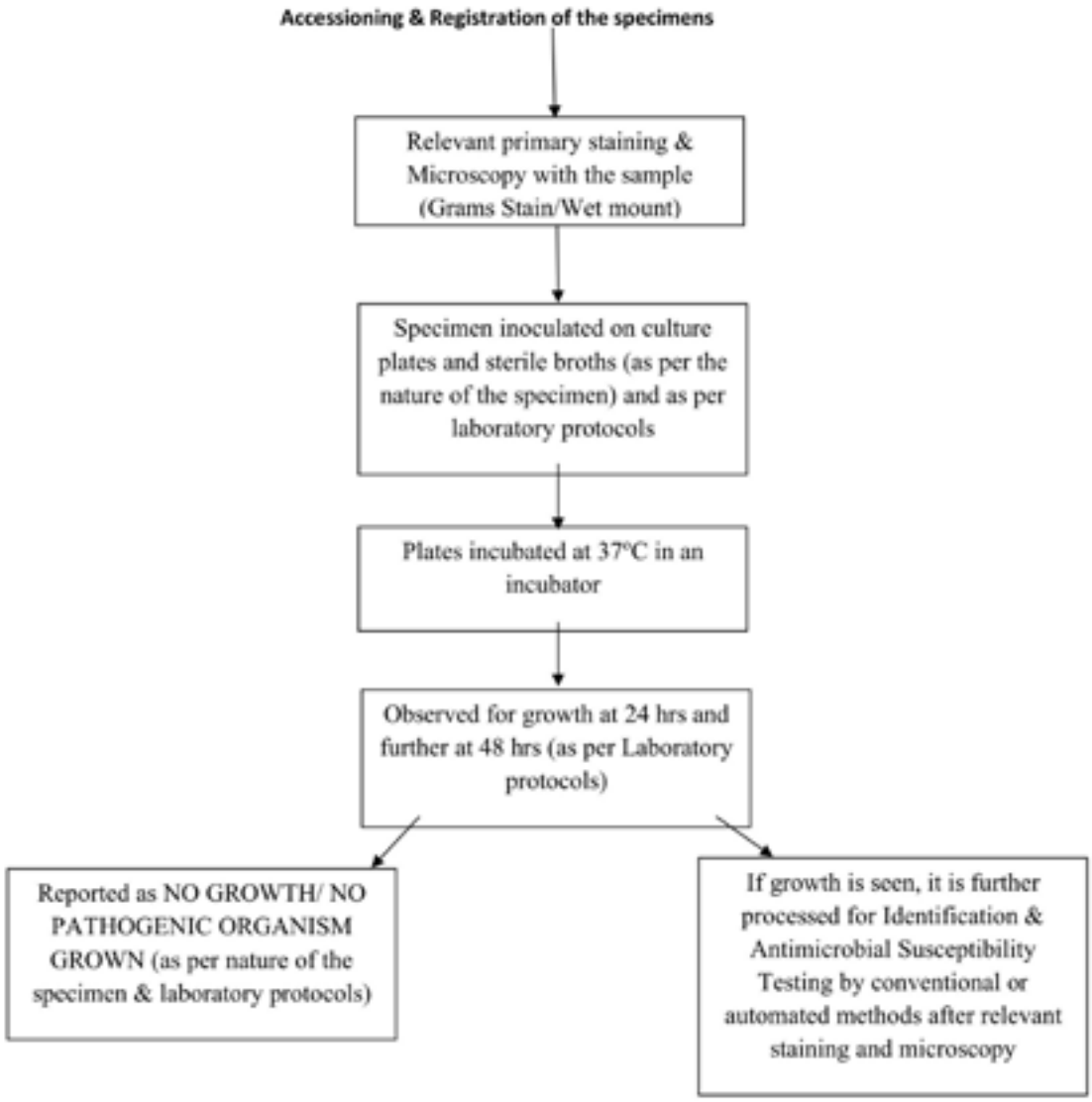
Question 1. What is the workflow for samples in a microbiology lab?

Answer 1. The workflow in a microbiology lab differs as per the specimen received. Following is the flow diagram depicting the workflow for different specimens:

a) Blood or any other body fluid (Pleural fluid/synovial fluid/peritoneal fluid, etc.) received for culture in blood culture bottles



b) Specimens are received in universal containers (Urine, stool, pus aspirates, body fluids etc.) or swabs.



Question 2. What are the routinely used culture media in a microbiology lab?

Answer 2. The standard practice is to use an enriched media with nutrients like blood, serum or eggs to facilitate growth, along with a differential media to differentiate between the growth of some bacteria from others based on colony characteristics. Hence, the most commonly used culture media for aerobic bacterial culture is Blood Agar and MacConkey Agar (Fig 1). However, other media may be utilized for specific specimens. For instance, Cysteine Lactose electrolyte deficient (CLED) agar may be used alone for a urine sample.

Further, the choice of media may also vary as per the suspected organism to be grown. For example, if anaerobic organisms are expected, Robertson's cooked meat medium and thioglycolate medium should be used. Thiosulphate citrate bile salt sucrose (TCBS) agar for *Vibrio spp*., and Lowenstein Jensen medium for *Mycobacterium spp*.

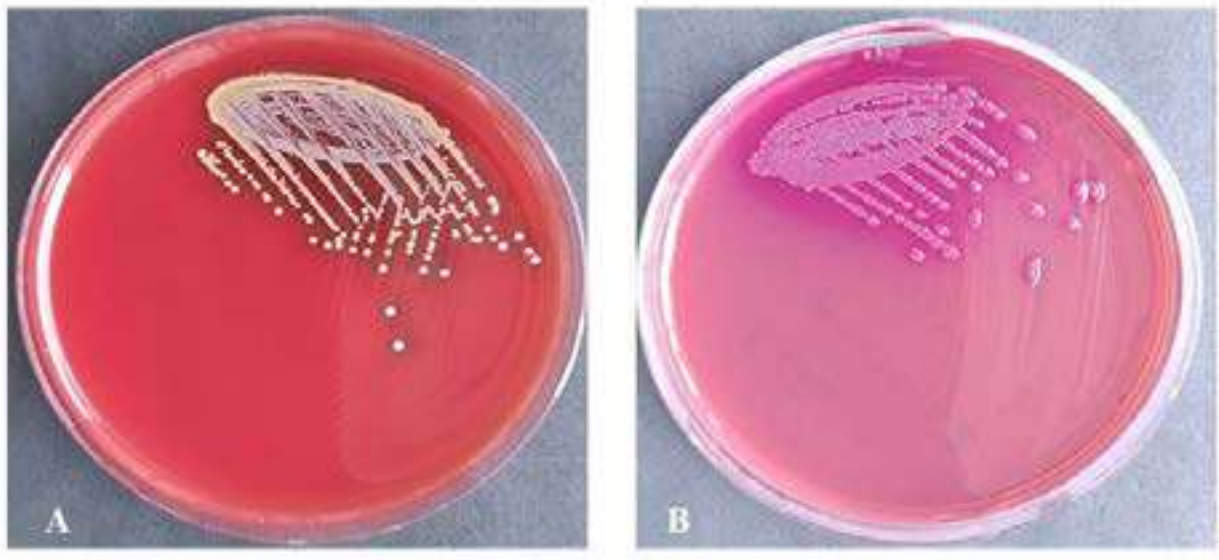


Fig 1: (A) Growth on blood agar (B) Lactose fermenting colonies on MacConkey agar

Question 3. What are the ways in which identification of the organisms may be made?

Answer 3. The identification of the organisms can be done depending on the colony characteristics and further by performing biochemical tests, either conventionally or on an automated platform. The preliminary biochemical tests usually used for Gram-positive organisms are catalase and coagulase tests. Further testing (conventional/automated) may be done based on the preliminary results.

For Gram-negative organisms, catalase and oxidase production tests are the usual preliminary tests. Further testing (conventional/automated) may be done based on the preliminary results.

Although various bio-chemicals (Fig.2) may be utilized to identify the organisms, automated instruments have been found to be far superior for this purpose due to their vast database, which is instrumental in detecting even rare pathogens.

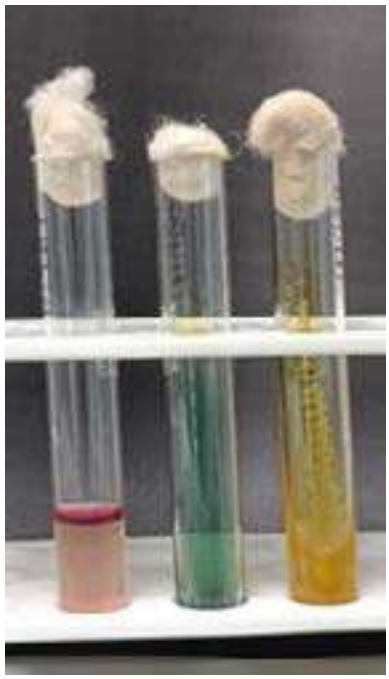


Fig 2: Biochemical tests (Indole production, Citrate utilization and Triple sugar iron test)

Question 4. What are the various methods of performing Antimicrobial Susceptibility Testing?

Answer 4. Antimicrobial Susceptibility Testing (AST) may be performed by the conventional method, i.e., the Modified Kirby-Baeur method or the disc-diffusion method, where the organism is inoculated on the culture media, and antibiotic discs are placed over it. The zones of inhibition formed due to radial diffusion of antibiotics leading to inhibition of growth (Fig.3) are measured, and the interpretation is performed depending on the relevant international guidelines being followed in the lab.

Manually, the Minimum Inhibitory Concentration (MICs) for antibiotics may be determined using Epsilometer test (E-test) strips, agar or broth dilution methods. However, most labs these days either use the Modified Kirby-Baeur test or automated platforms.

With the automated systems, the interpretation is automatically received based on the Minimum Inhibitory Concentration (MICs) of the organism for a particular antibiotic attained after processing. The automated systems have these interpretations saved in the database per the latest International guidelines.

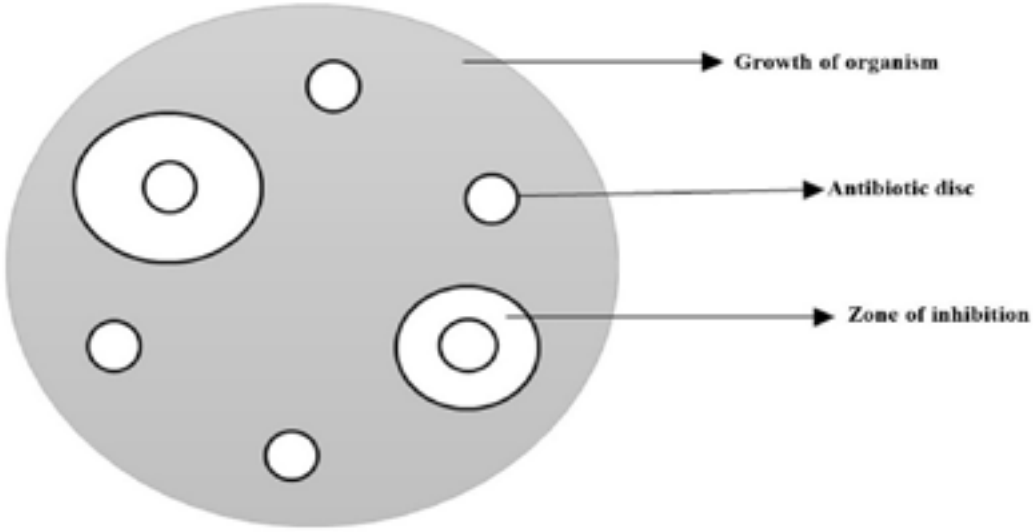


Fig.3: Disc- diffusion method (Modified Kirby Bauer)

Question 5. What are MIC and breakpoints? What is its significance in a Microbiology report?

Answer 5. Minimum Inhibitory Concentration (MIC) is the lowest concentration of an antibacterial agent, which can completely inhibit the visible growth of the test strain of an organism in a defined timeframe under strictly controlled laboratory conditions [1,2]. The values are expressed in mg/L (µg/mL). It is a measure of the potency of the antimicrobial agent.

The MIC or zone diameter value used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or non-susceptible is called **Breakpoint.** The MIC or zone diameter values are used to interpret the susceptibility test results based on accepted breakpoints per guidelines. The breakpoints are primarily established depending on extensive pharmacological and clinical research, generating rich *in vitro* and *in vivo* data. Thus, they are assumed to be good determinants of the likely clinical outcome [3].

Currently, clinical breakpoints are established and published primarily by two organizations: the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI), and partly by the FDA (Food and Drug Administration) [2].

Question 6. Can the MICs of two different anti-microbials be compared?

Answer 6. No. As recommended by International guidelines, each antimicrobial has a different breakpoint. Such a comparison should not be made just on the basis of MIC values. The difference

between the doubling dilutions for MIC of the test strain and the breakpoint can be compared between two anti-microbials to know the probable superiority of one of them. The farther the MIC value (but in the susceptible range) from the breakpoint, the more efficacious that agent may be clinically. Similarly, the closer the MIC value to the breakpoint, the more chance of acquiring resistance and, thus, clinical failure.

Question 7. Does the antibiotic selection vary with the type of organism grown? What are the other factors to be considered?

Answer 7. Yes, it depends on whether the organism grown is Gram-positive (e.g. *Staphylococcus spp., Streptococcus spp.*) or Gram-negative (*Klebsiella spp., Escherichia coli, Acinetobacter baumanii and Pseudomonas aeruginosa)*. The antibiotic selection for testing is a critical component of bacteriological reporting. The microbiological spectrum of the antimicrobial agent must be taken into consideration in addition to its possible routes of administration (oral agents to be preferred for OPD patients), site of infection, organ dysfunctions of the patient, expected allergies or toxicities etc.

Question 8. Does the antimicrobial testing differ from the site of infection?

Answer 8. Yes, the reporting of anti-microbials varies with the specimen. Depending on the pharmacokinetics/pharmacodynamics (PK/PD) of the agents, some might be more effective only at a particular site, and some others may be ineffective at that site. For example, nitrofurantoin may be used only in cases of urinary tract infection, while tigecycline would not be an effective agent at that site. Tigecycline is a wonderful drug for intra-abdominal infections; however, not very useful for bacteremia as it doesn't achieve adequate serum concentrations with regular doses. Thus, the reporting of antimicrobials should be done considering the specimen received.

Question 9. What is MRSA and its implications on the management of the patient?

Answer 9. Organisms tested to be resistant to the penicillinase-stable penicillins are called "methicillin resistance" or "oxacillin resistance." **Methicillin-Resistant *Staphylococcus aureus* (MRSA)** are strains of *S. aureus* expressing *mecA, mecC,* or another mechanism of methicillin (oxacillin) resistance, like changes in the affinity of penicillin-binding proteins (PBPs) for oxacillin. Cefoxitin or oxacillin testing is performed to diagnose these infections.

Implication: The organism should be resistant to other β-lactam agents, including penicillins, β-lactam combination agents, cephems (except for ceftaroline), and carbapenems [3].

Vancomycin or teicoplanin are the drugs of choice for these organisms.

Question 10. What are Vancomycin-resistant Enterococci (VRE) and their implications on the management of the patient?

Answer 10. Enterococci are notorious for developing various mechanisms of resistance to several antibiotics, including aminoglycosides, *β*-lactams, tetracyclines, quinolones, and vancomycin (glycopeptide). The presence of penicillin-binding proteins with low-affinity to beta-lactams, the ability to produce β-lactamases, and further decreased cellular permeability to several agents has contributed towards the growing isolation of multidrug-resistant strains. The main mechanism of glycopeptide resistance (*e.g.*, vancomycin) in enterococci involves the alteration of the cell wall peptidoglycan synthesis pathway, specifically with the substitution of D-Alanine-D-Alanine (D-Ala-D-Ala), to either D-Alanine-D-Lactate (D-Ala-D-Lac) or D- Alanine-D-Serine (D-Ala-D-Ser).

Implication: The treatment options for patients growing VRE are often limited. Usually, linezolid, daptomycin, quinupristin/dalfopristin (QD), and tigecycline have been found useful in treating serious infections caused by multidrug-resistant *Enterococci*, VRE and MRSA [4]. The organism also has the potential to spread in a hospital environment, and hence, contact precautions are recommended to be used for such patients.

Question 11. What are CRO and its implications on the management of the patient?

Answer 11. CRO stands for Carbapenem-Resistant Organisms. This entity is mostly encountered in Enterobacterales like *Klebsiella spp. and Escherichia coli* or non-fermenters like *Acinetobacter baumanii and Pseudomonas aeruginosa*.

Implication: The organism grown is resistant to the carbapenem group of antibiotics due to carbapenemase production or some other mechanism of resistance. Isolation of this MDR organism leaves the clinicians with only a few options of antibiotics like polymyxins, aminoglycosides, tigecycline or fosfomycin (if tested Susceptible) to treat the patients. The organism also has the potential to spread in a hospital environment, and hence, contact precautions are recommended to be used for such patients [5].

Question 12. What are the molecular platforms which help in the early detection of resistant genes in bacteria?

Answer 12. Various Polymerase Chain Reaction (PCR) based tests are available. Few fully automated systems like Biofire Filmarray (Biomerieux, France) and GeneXpert (Cepheid, USA) have introduced identification of the organisms as well as the resistant genes directly from the specimens. However, an important limitation of these tests is that in case of multiple organisms

are detected in the specimen, they are not able to associate the resistant genes with the appropriate organisms. Hence, correlation with a routine culture is indispensable.

Summary:

The right drug for the right bug, in the right dose and route of administration for the right site, is the target of our antimicrobial therapy.

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CHAPTER

4 Determination of Susceptibility and Antibiograms and Interpretation

Dr Subhashree Samantaray

Q. What is Anti-microbial susceptibility testing (AST)?

Antimicrobial susceptibility testing (AST) is a laboratory procedure performed by medical technologists (clinical laboratory scientists) to identify which antimicrobial regimen would be specifically effective for individual patients. On a larger scale, it aids in supporting the treatment services provided by hospitals, clinics, and national programs to control and prevent infectious diseases.

Q. Why is it important to conduct antimicrobial susceptibility testing (AST) while prescribing an antibiotic in a clinical condition?

To determine the in-vitro sensitivity of the pathogenic micro-organisms (especially bacteria and fungi) to various antimicrobial compounds so that a particular antibiotic will be effective in stopping the growth of the bacteria or fungi causing your infection.

Q. What sample is required to perform AST?

Blood, urine, cerebrospinal fluid, sputum, wound, stool, and other body fluids are collected from infected sites and cultured on specialized media to recover the bacteria or fungus causing the infection. AST is then performed on the isolated organisms as per laboratory protocols and guidelines.

Q. What are the different methods to determine AST?

There are conventional methods and rapid AST (RAST) methods.

1. Conventional methods:

- Dilution methods-broth dilution and agar dilution.

- Antimicrobial Gradient Method-for example, Etest, MIC Test Strip, Ezy MIC Strip.
- Disk Diffusion Test.
- Chromogenic Agar Media for Detection of Antimicrobial-Resistant Bacteria–For MRSA, VRE, and ESBL-and carbapenemases- producing or colistin-resistant Gram-negative bacteria.
- Colorimetric Tests for Detection of Antimicrobial-Resistant Bacteria- for example, Carba NP test.

2. Rapid AST

1. Automated and Semi-Automated Devices Based on Microdilution Susceptibility Testing. For example, VITEK 2 system and the Phoenix system.
2. Molecular-Based Techniques for Resistance Detection.
    - Polymerase Chain Reaction-multiplex assays for identifying numerous cephalosporins-and carbapenemase-encoding genes, such as *blaKPC*, *blaNDM*, *blaIMP*, *blaVIM*, *blaAmpC*, *blaTEM*, *blaSHV*, and *blaOXA*, or *mecA* gene-encoding methicillin resistance in MRSA.
    - DNA-Microarrays.
    - Whole-Genome Sequencing in Antimicrobial Susceptibility Testing.

Q. What are MIC and MBC?

MIC or minimum inhibitory concentration–It is the lowest concentration (in µg/mL) of an antibiotic that inhibits the visible growth of a given strain of bacteria.

MBC or minimum bactericidal concentration-It is the lowest concentration of an antimicrobial substance that can kill 99.9% of bacteria.

Q. Procedure for performing AST by classical or conventional method?

- Preparation of a standardized inoculum from a bacterial culture:
    - Choosing well-isolated colonies.
    - Creating a bacterial suspension (inoculum)
    - Standardizing the bacterial suspension using McFarland standards.
- Dilution of bacterial suspension (only for the MIC method)
- Inoculation of bacterial suspension to one of the following:
    - A particular growth medium (e.g., Mueller Hinton Agar for disk diffusion)
    - A MIC panel on automated platforms.
- Addition of antimicrobial disks (only for disk diffusion)
- Incubation of plates (disk diffusion) or panels (MIC)
- Measuring the zone of inhibition or reading the MIC panel.
- Interpretation of AST results.

Q. Procedure for commercial systems?

- Commercial systems have their own sets of laboratory procedures that should be followed according to the manufacturer's guidelines.
- The "Direct colony suspension method" is used for preparing inoculum from colonies grown within eighteen to twenty-four hours, while the "growth method" can be used by incubating the inoculated broth (with fast-growing bacteria) within two to six hours.
- The usual McFarland standard for the turbidity of the inoculum is 0.5.

Q. Indications for performing AST?

- No two patients can be managed with the same anti-infective agent, even if they have the same signs and symptoms (disease manifestation), because the same causative organism can have different resistance patterns. For example, two patients may present with an ordinary strain of *Staphylococcus aureus* vs methicillin-resistant *Staphylococcus aureus* (MRSA); and another example would be patients with drug-susceptible (DS-TB) and drug-resistant tuberculosis (DR-TB).
- The choice of the best therapeutic option for the treatment of bacterial infections relies on the results of AST.
- Surveillance of antimicrobial resistance is based on routine clinical antimicrobial susceptibility data from microbiological laboratories.
- Policymakers and health administrators revise the recommendations for empirical treatment for community or hospital-acquired infections according to the local, national, and international AMR data.
- Infection Prevention and Control (IPC) measures are implemented based on the antibiogram data as a part of AMS programs.

Q. Differentiation between colonizer and pathogen?

- Cultures may be obtained from sites that are either colonized with bacteria or sterile.
- Those colonized with bacteria increase the risk of contamination from normal flora and may lead to false results. Sites that are typically thought of as sterile include cerebral spinal fluid, blood, and pericardial fluid. Sites that are well-known for colonisation include the upper and lower respiratory tract, gastrointestinal tract and urinary tract. So, culture growth from a sample collected from these sites may represent colonisation rather than true infection. Hence, an inspection of these sites (local examination), the presence of pus cells on microscopy and the clinical condition of the patient help in deciding whether the organism isolated is a coloniser or a true infection.
- The poor culture-collection technique may also increase the risk of contamination.

Q. Selection of Antimicrobial Drugs for Susceptibility Testing, Interpretation, and Reporting?

- Interpretation of AST results and reporting of bacterial susceptibility is based on the breakpoints published by the two most commonly used systems worldwide: CLSI and EUCAST.
- Accurate identification of bacteria is crucial in the choice of antibiotics.
- It is well known that resistance mechanisms have not been observed in some bacterial species so far, e.g., the continued penicillin susceptibility of *Streptococcus pyogenes.*
- It is also known that some bacterial species are intrinsically resistant to particular antibiotics or antibiotic classes.

Q. Interpretation of AST?

- For disk diffusion, measuring the zone of inhibition is done by using a dedicated calliper. Correctly measure the diameter by the edges of the inhibition zone.
- For MIC panels, we need to look for a well that doesn't have any growth. The well without growth will be clear and not turbid.
- The results of the inhibition zones and MIC breakpoints are reported using either the terms "susceptible" or "resistant" based on the set cut-off range for zone diameter.
- The Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) developed expert-approved guidelines on breakpoints for reporting the results of these methods.

Q. How are AST interpretation criteria derived?

Derived from:
- Microbiology characteristics.
- MIC distribution of a large no. of isolates.
- PK-PD parameters.
- Clinical outcome data.

Q. Definition of the breakpoint?

Breakpoint–Minimal inhibitory concentration (MIC) or zone diameter value used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or non-susceptible.

Q. Define susceptible, intermediate and resistant breakpoints?

Susceptible: Isolate is inhibited *in-vivo* when the drug is given at standard dosage and has a high likelihood of therapeutic success with the drug.

Intermediate:

- Uncertain therapeutic effect (in-vivo response rates may be lower than for susceptible isolates when given at standard dose).
- It may be active at sites where the drug is physiologically concentrated.
- It may be active when a high dose/frequency of the drug is used.

Susceptible dose-dependent (SDD)- Isolate is inhibited when the drug is given at an increased dosage

- ↑Dose/frequency or both
- Literature (clinical trial) supported. Safe to use.

Resistant–Isolate is not in-vivo inhibited when the drug is given at standard/increased dosage and has a high likelihood of therapeutic failure.

Non-susceptible–Isolate with zone diameter/MIC falls outside susceptible breakpoint and for which no resistant breakpoint is designated.

Q. Clinical significance of antimicrobial susceptibility testing?

Once antimicrobial susceptibility results become available, treatment regimens for each patient can be developed by healthcare providers.

Q. Limitations of conventional AST methods?

- The main limitation is that the results are obtained for most clinically important bacteria after at least eighteen to twenty-four hours or forty-eight hours, including prior bacterial isolation and identification.
- The turnaround time is prolonged for anaerobes or some slow-growing fastidious bacteria such as the HACEK group (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species), *Brucella* spp., etc.

Q. What are the global networks available for AMR surveillance?

Numerous AMR surveillance systems exist, including the WHOs Global Antimicrobial Resistance and Use Surveillance System (GLASS), the European Antimicrobial Resistance Surveillance Network (EARS-Net), and the ICMR AMR network and NCDC network in India.

Q. What is an antibiogram?

- The cumulative antibiogram is a periodic profile of antimicrobial susceptibilities of various organisms isolated from patients within an institution or can be developed to track patterns of resistance in broader geographic areas using data from multiple institutions.

- It is commonly utilized to monitor recent antimicrobial susceptibility patterns in order to guide empirical antimicrobial therapy selection.

Q. Why do we need an antibiogram?

- Although resistance surveillance at the national and international levels is of great benefit to public health, knowledge of the local resistance rates is of even greater practical importance to physicians. An antibiogram represents a convenient and widely available measurement of an institution's pathogens and susceptibilities.
- Therefore, it is increasingly suggested that there is a necessity to create local (hospital or institutional) antibiograms specific for each hospital and even ward periodically (annually or every six months). This principle applies to hospital departments with high resistance rates, such as intensive care units.
- Additionally, this is particularly relevant for secondary and tertiary hospitals that treat chronically ill patients who have already received multiple antibiotic courses and thus increase antimicrobial selective pressure.
- A combination antibiogram is used to determine in vitro rates of susceptibility to potential antibacterial combination regimens consisting of a first-choice antibiotic plus alternatives.
- A syndromic antibiogram displays the likelihood of adequate coverage for a specific infection syndrome, considering the weighted incidence of pathogens causing that syndrome.
- While combination antibiograms are useful in determining combined empiric antibiotic regimens for multidrug-resistant pathogens, syndromic antibiograms provide effective antibiotic therapy for a specific infectious syndrome, such as hospital-and ventilator-associated pneumonia.
- The Clinical and Laboratory Standards Institute (CLSI) has developed guidelines to provide a standardised template for the preparation of institutional antibiograms.

Q. What is the CLSI M-39 guidance to develop an antibiogram?

- CLSI identified modalities of antibiogram presentation to enhance its usefulness, including stratification of susceptibility data by body site (e.g. urine and non- urine isolates), hospital unit (e.g. ICU, emergency department [ED]) and/or specific patient populations. Other components added to the antibiogram have been described, such as drug cost, dosing guides and drug-use policies. Thus, the preparation, reporting and utilization of the antibiogram can be customized to meet the needs of each institution.

Q. Uses of antibiogram?

1. Guides antimicrobial stewardship programs to optimize antimicrobial use.
2. Guides Clinicians to select empirical therapy.
3. Helps to design the Antibiotic Policy of a facility/nation.
4. Guides pharmacy for formulary decisions.

5. Educating clinicians for Antimicrobial Selection.
6. To monitor the effect of AMSP interventions and AMR containment strategies.
7. Guides Epidemiologists to monitor trends in AMR within the facilities.
8. Guides Epidemiologists to compare trends in AMR across facilities.
9. Can contribute to the national AMR surveillance database.
10. Helps to detect the emergence of a new resistance.

Q. Limitations of antibiogram applicability?

- A traditional cumulative antibiogram has potential limitations that may hinder its general applicability. For example, it does not reveal the timing of isolate collection relative to a patient's hospital admission. Hence, it cannot reliably distinguish between a community-acquired versus hospital-acquired infection.
- Another intrinsic limitation is that a traditional antibiogram does not differentiate between true infection and coloniser.

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CHAPTER

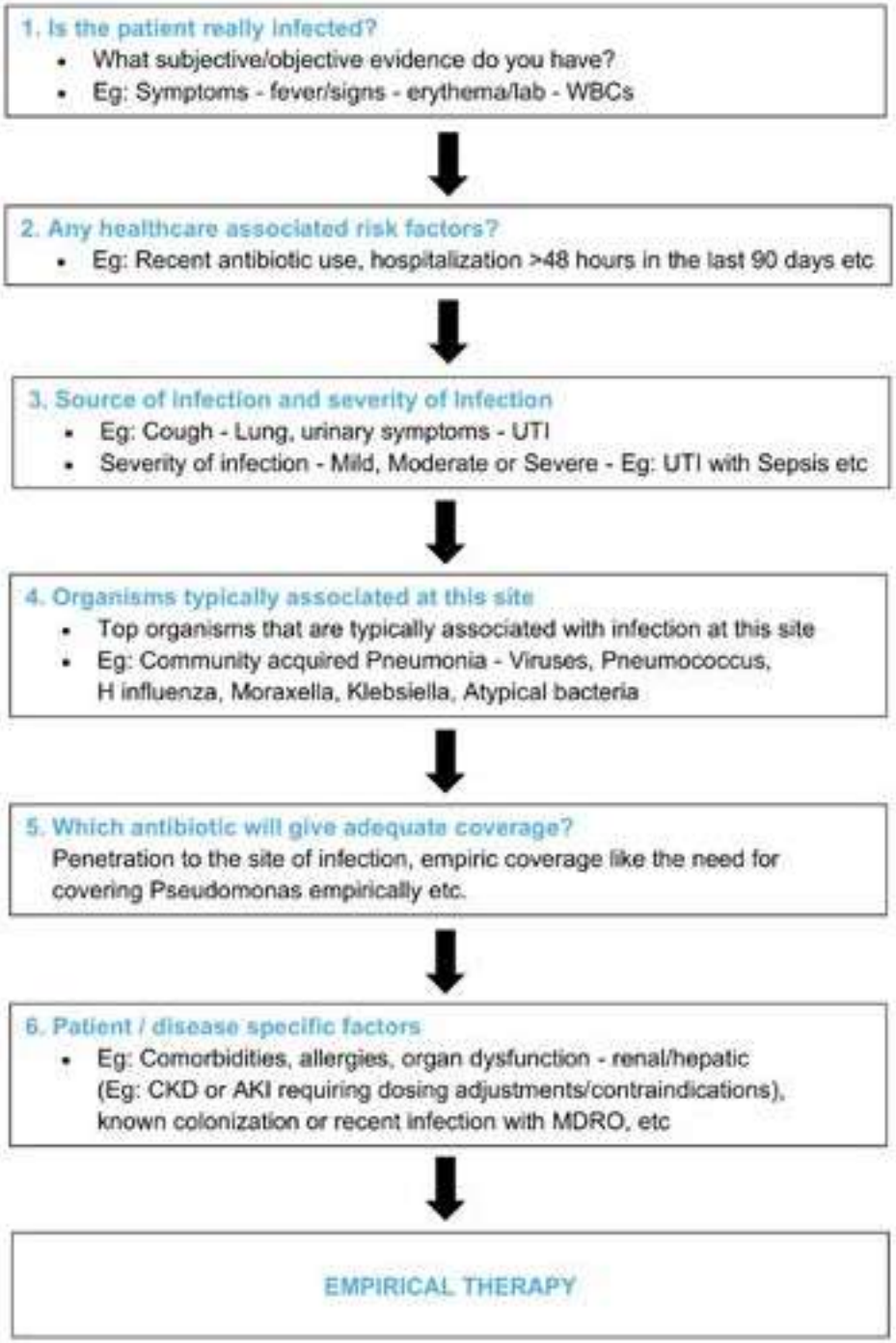
5

PK-PD principles

Dr Grace Mary John

CASE STUDY-1
Mrs SJ, an 80-year-old female, presented to the ER with complaints of altered mental status. She was experiencing shortness of breath, cough and expectoration for two days, progressing over time. She was recently admitted to the hospital, had undergone hip replacement surgery twenty days ago and was currently doing rehabilitation post-surgery. **Past Medical History:** K/C/O DM, HTN, Osteoarthritis **O/E: Vitals:** T: 101.3°F, BP: 80/50mmHg, HR: 105/min, RR: 26/min, SpO2: 90–92% on room air CVS- S1S2 +, RS – crepts +, PA – Normal, CNS- NFND, Surgical site- clean and looks healthy Height: 165 cm Weight: 74 kg **Labs**: WBC: 17200/mm^3 Hb: 13mg/dL Platelets: 2.59lac/mm^3 / Na:139meq/L K : 4meq/L Creatinine: 0.8mg/dL / Gluc 135mg/dL / CRP 154 IU/mL CXR: + left lower lobe infiltrate // UA: negative //Blood and Sputum culture: pending Rapid influenza: negative
Question 1: What are the choices for empirical therapy for this patient?

In order to select the right antibiotic for treating any infection of any severity, there is a basic evaluation framework that can direct you to choose the best empirical regimen for your patient.


1. Is the patient really infected?
What subjective/objective evidence do you have?
Eg: Symptoms - fever/signs - erythema/lab - WBCs
2. Any healthcare associated risk factors?
Eg: Recent antibiotic use, hospitalization >48 hours in the last 90 days etc
3. Source of infection and severity of infection
Eg: Cough - Lung, urinary symptoms - UTI
Severity of infection - Mild, Moderate or Severe - Eg: UTI with Sepsis etc
4. Organisms typically associated at this site
Top organisms that are typically associated with infection at this site
Eg: Community acquired Pneumonia - Viruses, Pneumococcus, H influenza, Moraxella, Klebsiella, Atypical bacteria
5. Which antibiotic will give adequate coverage?
Penetration to the site of infection, empiric coverage like the need for covering Pseudomonas empirically etc.
6. Patient / disease specific factors
Eg: Comorbidities, allergies, organ dysfunction - renal/hepatic (Eg: CKD or AKI requiring dosing adjustments/contraindications), known colonization or recent infection with MDRO, etc
EMPIRICAL THERAPY

Case Study 1: Answer 1

Step 1: Is the patient really infected? List all subjective and objective data to support or dismiss the possibility of infection.
Yes, the patient is infected.

Subjective – Fever, shortness of breath, and cough. Altered mental status
Objective – T: 101.3°F, BP: 80/50, HR: 105, RR: 26, SpO2: 90–92% WBC 17200, CRP 154, + infiltrate on CXR

Step 2: Does the patient have any healthcare-associated risk factors? If so, consider how many risk factors, types of risk, etc.
Recent hospitalization - Risk for Multi-Drug resistant Organism

Step 3: What is the suspected site/source of infection? What is the severity?
Sepsis with Source: Lung—cough, shortness of breath, infiltrate

Step 4: What organisms are typically associated with infection at this site?
Gram negatives: Escherichia coli, Klebsiella pneumoniae, Enterobacter spp. Proteus spp., Serratia marcescens, Pseudomonas aeruginosa, Acinetobacter spp. Gram +: Pneumococcus +/− MRSA

Step 5: What anti-infectives will provide adequate coverage and will reach the site of infection?
Gram – coverage: antipseudomonal b-lactam (e.g., piperacillin/tazobactam, cefepime, ceftazidime, meropenem, imipenem/cilastatin, or doripenem), monobactam (e.g., aztreonam), +/− fluoroquinolone (e.g., ciprofloxacin or levofloxacin) or aminoglycoside (e.g., gentamicin, tobramycin, or amikacin) Gram + coverage: vancomycin or linezolid

To combat the rising global concern of antimicrobial resistance, it is of utmost importance to optimize the antimicrobial resources at hand. So as to ensure the optimal prescribing of antimicrobials to maximize the likelihood of clinical cure, it is essential to understand the relationship between antimicrobial exposure in the body (Pharmacokinetics - PK) and the corresponding clinical response (Pharmacodynamics - PD).

Pharmacokinetic - Pharmacodynamic (PK-PD) Principles

Pharmacokinetics and pharmacodynamics are crucial in determining how much and how often the drug should be prescribed.

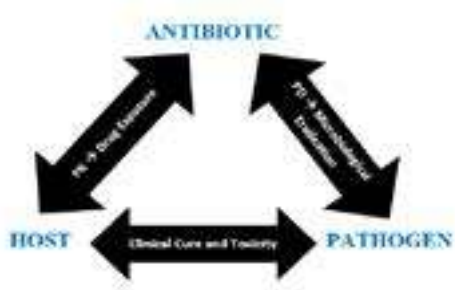
Dose response following the administration of a single dose

Pharmacokinetics, in short, describes "*what the body does to the drug*". It deals with the movement of a drug from its administration site to the place of its pharmacologic activity and its elimination from the body. The major steps involved in PK are Absorption, Distribution, Metabolism, and Elimination of a drug, usually abbreviated as ADME.

Pharmacodynamics refers to "*what the drug does to the body*", and in this context, it means the action of the drug on both *pathogen and host*. Antimicrobial pharmacodynamics deals with the relationship between measures of drug exposure and the efficacy (the ability of the drug to kill or inhibit the growth of microorganisms) & toxicity of antimicrobial agents.

PK is essential in establishing the best clinical outcome. If a very potent antibiotic known for its killing effect in a specific bug does not reach the site of infection in adequate concentration, it will result in clinical failure. Hence a combination of PK PD indices is best suited to optimizing antimicrobial therapy.

E.g., Nitrofurantoin for E.coli pyelonephritis-Even though Nitrofurantoin is only indicated in treating UTI, it doesn't reach an adequate concentration in the renal parenchyma, thereby rendering it ineffective for any upper UTIs.



PK PD relationship between antibiotic, host and pathogen.

The parameter used to measure the microbiological activity of an antimicrobial is the minimum inhibitory concentration (MIC). It's the minimum concentration an antibiotic has to reach the site of the infection, to inhibit bacterial growth.

Case Study 1: Question 2
Based on PK PD principles, what is the best empirical regimen for this patient?

Antimicrobial PK/PD indices

Through various in vitro and animal model studies, characterization of the pathogen–antimicrobial exposure relationship - the PK/PD index, has been done. There are three PK/PD indices used to categorize current antimicrobials. (Figure 1)

1. Time-dependent antimicrobials (fT> MIC)

Antibiotics coming under this category exert their best killing effect when you **maximize the time the** free/ unbound drug concentration(fT) is maintained **above the MIC**. With time-dependent

antibiotics, your goal is to keep the drug concentration above the MIC for as long as possible - The X-axis matters.

- Beta lactams- Penicillins, Cephalosporins, Carbapenems and Aztreonam
- In order to exploit this PKPD, the strategies are to 1) Reduce the dosing interval and dose the drug more frequently, 2) give the antibiotic as a continuous infusion or 3) increase the antibiotic dose.
  - The most practical and followed practice is to dose the antimicrobial as frequently as possible without causing toxicity.
- E.g.:
  - 1. Meropenem, given as extended infusions over three hours, preferred to thirty-minute intermittent infusion
  - 2. For A patient requiring renal dosing for PiperacillinTazobactam, it is preferred to give it as 2.25g IV Q6H rather than 4.5g Q12H, even though the total dose/ day is the same for both.

Case Study 1: Answer 2

Step 6: What patient- or disease-state-specific factors affect your decision (e.g., patient weight, renal and hepatic function, comorbidities, allergies, etc.)?

- The patient has Sepsis, probably with the lung as a source-hence based on the recent clinical evidence, a carbapenem should be used
- As per PK PD considerations, the patient should receive an extended infusion of carbapenem

Therefore the final empirical recommendation would be:

Inj Meropenem IV 1g Q8H as a three-hour extended infusion

2. Concentration-dependent antimicrobials (Cmax/MIC)

For these antibiotics, the best predictor of efficacy is the ratio of the maximum antibiotic concentration (Cmax) to the MIC. Here, the peak or the concentration matters (Y axis).

- E.g., Aminoglycosides, fluoroquinolones, metronidazole, and Polymyxins.
- The best strategy to get that peak as high as possible - increase the dose and decrease the frequency of administration.
- E.g.,
  - 1. Once daily dosing of Aminoglycosides is preferred over conventional three times a day.
  - 2. Renal dosing of Levofloxacin: 500 mg Q48H preferred over 250 mg Q24H

3. Concentration-dependent antimicrobials with time dependence (AUC0–24/MIC).

Activity is best described according to the ratio of the area under the curve(AUC) or total concentration of the drug during a twenty-four-hour period (AUC0–24) to the MIC.

- E.g., Vancomycin, Macrolides, Tetracyclines, Linezolid

- For Vancomycin, the best predictor of the clinical response is to achieve an AUC/MIC ratio of >400 for *S. aureus.* Therefore for *S.aureus* isolates with MIC > 1, it becomes difficult to eradicate the pathogen at lower doses.

Post Antibiotic Effect (PAE)

Some antibiotics continue to exert their killing effect on bacteria even after their concentration falls below the MIC - this is called the post-antibiotic effect. This effect lasts for a few hours. Mostly seen in concentration-dependent antibiotics or antibiotics that target protein/ DNA synthesis as their mechanism of action.

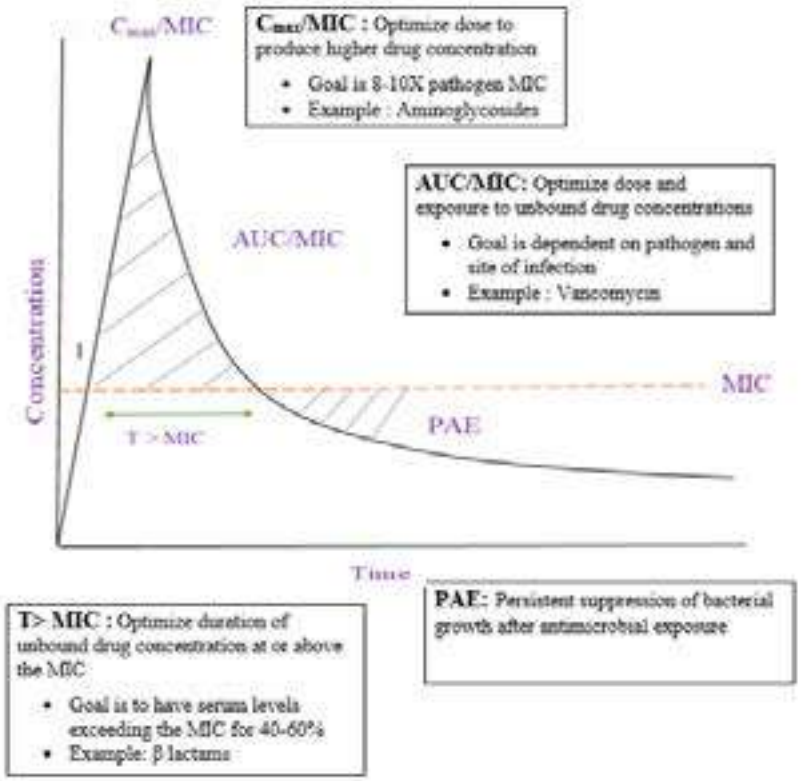


Figure: 1PKPD analysis of a drug with respect to time

Important pharmacokinetic considerations

The two most important PK parameters that can be very helpful in dosing antimicrobials are **Volume of Distribution(Vd) and Clearance (Cl)**.

- Vd refers to the theoretical volume necessary to contain the total amount of an administered drug at the same concentration observed in blood plasma.
- Clearance refers to the volume of the blood cleared of the drug in a unit of time

These two parameters fluctuate to great extents along with physiological changes associated with various disease conditions and can greatly affect the effectiveness of antimicrobials.

Below is a table depicting the Pk of drugs during various disease states.

Conditions	Vd (L)	Cl (mL/ hr)	Comments
Normal Physiology	10	20	
Renal Failure	10	5	For drugs primarily excreted via the renal route, dose adjustments are required.
Burns	10	40	Increased elimination due to augmented renal clearance. Hyperdynamic physiology. Higher doses are required.
Sepsis	60	20	Increased capillary leakage/ tissue hypoperfusion, low albumin levels, altered fluid balance and hepatic/ renal function fluctuations. Loading the dose is important. Prefer antibiotics with higher Vd and not highly protein bound.
Obesity	For drugs with high Vd or lipophilic in nature, they get distributed to the fat tissue as well. Hence the dosing weight ideally should be the total body weight to prevent clinical failure. E.g., Vancomycin Hydrophilic drugs, or those with lower Vd, tend to concentrate in the serum and can cause toxicity. Hence Ideal Body weight or adjusted body weight should be used. E.g., Aminoglycosides		

The values of Vd & Cl provided are theoretical to aid in easy comprehension

CASE STUDY-2

A 38-year-old woman with a history of hypertension presents to the emergency department (ED) with a severe headache and photophobia. She states that she was fine until yesterday, when she developed a fever and severe neck pain. She has no known drug allergies. Vital signs include a temperature of 101.8 °F (38.8 °C), blood pressure of 142/90 mm Hg, and heart rate of 100 beats/ minute. Physical examination reveals nuchal rigidity, positive Kernig sign, and no rashes.

Laboratory results are remarkable only for an increased white blood cell count (WBC) of 15 × 10□3 cells/ mm3; all other laboratory values are within normal limits. A lumbar puncture (LP) reveals WBC 1700 cells/mm3 with 80% neutrophils and 20% lymphocytes, protein 180 mg/dL, and cerebrospinal fluid (CSF)/ serum glucose ratio 0.3. Blood, urine, and CSF are sent for culture and Gram stain. Head computed tomography (CT) is negative.

Question: In addition to dexamethasone therapy, which is the best treatment option for this patient?

A. *Vancomycin and ceftriaxone*
B. *Vancomycin, ceftriaxone, and acyclovir*
C. *Teicoplanin and ceftriaxone*
D. *Teicoplanin, ceftriaxone, and acyclovir*

Another important pharmacokinetic parameter for choosing an antibiotic is the **Distribution** and **Penetration** of the antibiotic to the suspected source of infection. This is especially valuable when the source of infection is a difficult one to penetrate, like the brain, bone tissue, etc. A thorough knowledge of this is essential to mastering the art of infectious diseases.

Some examples are as follows:

- ➔ Urinary concentration of Polymyxins
  - ◆ Colistin is really excreted and therefore is seen in high concentrations in the urine, whereas Polymyxin B undergoes biliary excretion and, therefore, does not reach adequate urinary concentrations. Hence Polymyxin B should never be used as an agent to treat multidrug-resistant gram-negative infections arising from the urinary source.
- ➔ Ceftriaxone versus Cefotaxime for treating Spontaneous Bacterial Peritonitis
  - ◆ The ascitic fluid concentration of Cefotaxime is much higher than Ceftriaxone, and therefore in various GI guidelines, Cefotaxime is preferred as the drug of choice.
- ➔ Fluoroquinolones have very good bone penetration and hence are indicated for the treatment of established, susceptible organisms for the indication of osteomyelitis

Case Study 2: Answer

- *Step 1: This patient has Bacterial meningitis, and therefore early, and appropriate antibiotic therapy is indicated*
  - *Therefore the choices with Acyclovir are not correct*
- *Step 2: No evidence of risk factors for resistant organisms*
- *Step 3: Source - Brian; Meningitis - Emergency treatment warranted*
- *Step 4: Usual pathogens associated: For this age group - S. pneumoniae, N. meningitidis*
- *Step 5: antibiotics providing adequate coverage: 3rd generation IV cephalosporin + glycopeptide*

Even though teicoplanin and vancomycin are used interchangeably for various infections in clinical practice, the penetration of Teicoplanin is negligible in the CNS compared to Vancomycin.

Hence, ***the best empirical therapy for this patient is Vancomycin + Ceftriaxone (Answer A)***

CHAPTER

6

Biomarkers in sepsis

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1 What is CRP, and when should I get it?

A: CRP stands for C reactive protein; this is a marker of inflammation. It increases due to many reasons, and infection is one of them. Just the increase in CRP doesn't necessarily mean there is an infection. It is not a specific test for infection and hence should not lead to starting of empiric antibiotics unless clinically indicated. It is used in monitoring infections and inflammatory diseases.

2 Two patients come with community-acquired pneumonia, one has a WBC count of 13000/mm3, and the other has a WBC count of 25000/mm3. Will the choice of antibiotic change based on the WBC count?

A: No. The difference in WBC count only means that the individual's body response to infection differs and has nothing to do with the organism causing the infection. Hence a patient infected with *Streptococcus pneumoniae* leading to pneumonia may have a different WBC count, but the choice of antibiotics will be guided based on clinical and epidemiological history and not alone on the WBC count.

3 What is procalcitonin, and when should I send this test?

A: Procalcitonin is the intracellular precursor of calcitonin, and it is produced in the thyroid C-cells. It increases, especially in bacterial infection. It has a high negative predictive value, meaning if the procalcitonin is low, there is a low likelihood of an infection. So this test can be used when a clinical scenario can be confused with infection, and we need to rule out infection. But we have to keep in mind that there are many conditions in which it can be falsely elevated, like trauma, burns, carcinomas (medullary C-cell, small cell lung, & bronchial carcinoid), immunomodulator therapy that increases proinflammatory cytokines, cardiogenic shock, during peritoneal dialysis, cirrhotic patients and chronic kidney disease.

4 A patient comes with confirmed malaria/dengue; should I send procalcitonin?

A: The test should only be sent if the patient's clinical picture does not follow the natural history of malaria and dengue, for instance, if the patient continues to be febrile even after 48-72 hours of antimalarial and in dengue febrile period crosses more then 7-10 days.

5 If my malaria patient has high Procalcitonin, should I start antibiotics?

A: There are many studies where malaria patients have elevated procalcitonin even without secondary bacterial infection. It can also be increased due to kidney injury. Hence clinical judgment should be used to decide on the further course and not just based on a lab test.

6 My patient has high procalcitonin. Should I start antibiotics?

A: Clinical context is very important in deciding the initiation of antibiotics. There have been conflicting results regarding the use of procalcitonin to initiate antibiotics. Hence clinical judgement along with lab results should be used for this.

7 I started antibiotics for a patient, and now his procalcitonin is normal. Can I stop antibiotics?

A: Studies have shown more favourable results regarding the use of procalcitonin to stop antibiotics. Clinical improvement of the patient and normalization of procalcitonin can be used to guide the stopping of antibiotic therapy.

8 My patient has a normal WBC count but has clinical suspicion of sepsis; what should I do?

A: The change in WBC count is due to bodies' response to inflammation, which can be normal or even decreased in some cases of sepsis. WBC count has poor specificity for infection, and hence its value should be supported by clinical scenarios and microbiology evidence of infection.

9 My patient with infection is clinically improving. Should I do CRP, WBC Count, and Procalcitonin daily?

A: Monitoring of labs should only be done when the patient has any unexpected change in clinical parameters. It can also be done if the test results will change your management. For example, in neutropenic patients, empiric antibiotics can be stopped once the patient is afebrile and the neutrophil count has improved. A daily lab test to prove that the patient is clinically improving is unnecessary and painful for the patient (taking blood samples daily)

10 My patient has come for a regular check-up and was found to have a total count of 12000/mm3. Should I start him on antibiotics?

A: Antibiotic use should be guided by clinical diagnosis. Appropriate history needs to be taken to rule out infection syndromes like respiratory tract infection, UTI, skin and soft tissue infection etc. if you do not get any clinical or microbiological evidence of infection, you should not start antibiotics.

11 The patient presents a high WBC count, CRP and Procalcitonin with a clinical diagnosis of community-acquired pneumonia. Should I start him on meropenem, or can I still give him ceftriaxone as per guidelines?

A: Antibiotics act on the possible bacteria causing the infection, which in this case is strep pneumonia. It does not directly act on the WBC/CRP/Procalcitonin. Hence the choice of antibiotics should not be based on these tests but rather on the clinical context; for, e.g. does the patient have a risk factor for Multi-drug resistant organisms/has s structural lung disease which predisposes him to Pseudomonas infection. If these are not present, use ceftriaxone no matter what the lab results are

Summary

A. Antibiotics treat bacteria, not the WBC/CRP/Procalcitonin of the patient.
B. Treat the patients, not their investigations.
C. Clinical context and judgment are important when deciding to use antibiotics.
D. Investigations are like bullets in a gun; use them wisely, or you may cause collateral damage with unnecessary antibiotics.

Module 2:
Syndromic Approach

CHAPTER

1

Urinary Tract Infections

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1) How do you clinically differentiate between acute cystitis and pyelonephritis?

- Urinary tract infections (UTIs) include cystitis and pyelonephritis. Cystitis refers to an infection which is limited to the urinary bladder. On the other hand, pyelonephritis refers to an infection involving the renal parenchyma.
- The usual symptoms of cystitis are dysuria, urinary frequency, and urgency.
- The presence of fever and/or flank pain suggests that the upper urinary tract is involved, i.e., pyelonephritis.

2) What are the common bacteria that cause community-acquired urinary tract infections?

- *E. coli* accounts for more than 75% of urinary tract infections.
- Other common bacteria that cause urinary tract infection includes *Klebsiella, Proteus, Enterococcus, Citrobacter* and *Staphylococcus saprophyticus.*

3) What instructions should be given to a patient to collect a urine sample for culture and antibiotic susceptibility testing?

A clean catch mid-stream sample is required for urine bacterial culture. The following instructions should be given to the patient for collecting urine:

- Wash and dry your hands thoroughly.
- Remove the container lid and set it aside. Do not touch the inner surfaces of the container.
- Wash your urogenital area:
  Women: wipe from front to back between the folds of the skin.

Men: retract the foreskin (if un-circumcised), and clean the glans penis.

- Pass a small amount of urine into the toilet (women: hold skin folds apart), and then midway through urination, urinate into the container.
- The container should only be 1/2 to 2/3 full.
- Replace the lid and tighten it firmly.
- Wash and dry your hands thoroughly.

4) How do you store and transport urine for culture and sensitivity testing?

- Because it is an excellent supportive medium for the growth of most bacteria, urine must be immediately sent to the laboratory and plated within one hour.
- In case of any delay, urine should be refrigerated at 4°C. Bacterial counts in refrigerated (4°C) urine remain constant for as long as twenty-four hours.

5) What investigations should be for a patient with a suspected urinary tract infection?

The following investigations can be done in a patient with a suspected UTI:

- Urine microscopy: the presence of 10 leukocytes/mm^3 of uncentrifuged urine or
- 10 leukocytes/hpf of the centrifuged sample indicates pyuria. However, Pyuria also can be associated with other clinical diseases and therefore is not specific to UTI.
- Urine dipstick tests: These are rapid screening tests for UTIs. Commonly used dipstick tests detect the presence of leukocyte esterase (an enzyme released by leukocytes, indicating pyuria) and nitrite (indicating the presence of Enterobacteriaceae, which convert urinary nitrate to nitrite). Negative results for both these tests do not reliably rule out UTI.
- Urine culture: Considering the increasing prevalence of antimicrobial resistance among uropathogens, a urine culture should be obtained prior to the initiation of antibiotics in patients with cystitis and pyelonephritis.
- In patients with suspected pyelonephritis blood culture also should be obtained before initiating antibiotics.

6) What is asymptomatic bacteriuria? What are the indications for antibiotic therapy in asymptomatic bacteriuria?

- Asymptomatic bacteriuria is defined as the isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen from a person without symptoms of urinary tract infection.
- The threshold for asymptomatic bacteriuria from a clean-catch voided urine specimen is the isolation of a single organism in quantitative counts $\geq 10^5$ colony-forming units (CFU)/mL.

- In most individuals, asymptomatic bacteriuria does not require antibiotic treatment. Indications for the treatment of asymptomatic bacteriuria are the following:
  1) Pregnancy
  2) Patients undergoing urologic interventions in which mucosal bleeding is anticipated
  3) Renal transplant recipients
- Antibiotic regimens are the same as that for acute cystitis.

7) What are the antibiotic regimens recommended for patients with acute cystitis?

The first-line treatment options for patients with acute uncomplicated cystitis are the following:

Drug	Dose and duration
Nitrofurantoin	100 mg BD x 7 days
TMP-SMX (Cotrimoxazole)	1 DS tablet BD x 3 days
Fosfomycin	3g single dose sachet

8) What are the empiric treatment options for patients with acute pyelonephritis?

The following treatment options can be considered for empirical treatment of acute pyelonephritis pending culture and susceptibility reports:

Drug	**Dose**
Cefoperazone-Sulbactam	3g IV BD
Piperacillin – tazobactam	4.5 g IV q6h
Ertapenem	1g IV OD
Meropenem	1g IV TDS
Imipenem	500 mg IV q6h

- Results of urine culture and susceptibility testing should be used to tailor the regimen, if appropriate. Whenever possible, the broad-spectrum empiric antibiotic should be replaced by a more narrow-spectrum agent.
- When treating pyelonephritis with bacteremia due to Enterobactarales (e.g., *E. coli, K. pneumoniae*) that are resistant to ceftriaxone, a carbapenem is a preferred agent
- Patients initially treated with an intravenous antibiotic can be switched to an oral antibiotic once symptoms have improved if suitable oral options are available as per culture and susceptibility reports.
- Nitrofurantoin and oral fosfomycin should be avoided in the setting of acute pyelonephritis because they do not achieve adequate tissue levels outside the bladder.
- The duration of antibiotic therapy is 7-10 days.

CHAPTER

2

Approach to Pneumonia

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1. What is pneumonia?

Pneumonia is defined as the presence of microorganisms in the pulmonary parenchyma leading to the development of an inflammatory response by the host, which may be localized in the lung or may extend systemically.

2. What are common pathogens causing pneumonia?

Community-acquired Pneumonia

Bacteria	Virus	Atypical Pathogen
1. *Streptococcus pneumoniae* 2. *Klebsiella pneumoniae* 3. *Haemophilus influenzae* 4. *Staphylococcus aureus* 5. Group A *Streptococcus* 6. *Burkholderia pseudomallei*	1. Influenza 2. SARS COV2 3. Parainfluenza 4. Respiratory syncytial virus 5. Adenovirus 6. Rhinovirus 7. Human metapneumovirus	1. *Chlamydia pneumoniae* 2. *Legionella pneumophila,* 3. *Mycoplasma pneumoniae*

It is important to note that *Mycobacterium Tuberculosis* is an important pathogen which can present as community-acquired pneumonia in TB-endemic countries like India.

Common pathogens causing Nosocomial pneumonia

1. *Klebsiella pneumoniae*
2. *Pseudomonas aeruginosa*

3. *Acinetobacter baumanii*
4. Methicillin resistant *Staphylococcus aureus*

Fungal pathogens (more common in immunocompromised patients)

1. *Aspergillus spp*
2. *Pneumocystis jiroveci*
3. *Histoplasma capsulatum*
4. *Cryptococcus neoformans*

3. What is the anatomical classification of pneumonia?

1. **Bronchopneumonia**: A descending infection starts around the bronchi and bronchioles, which then spreads locally into the lungs. Lower lobes are usually involved. Patchy areas of consolidation represent neutrophil collection in the alveoli and bronchi, and involvement of both lobes may be seen.
2. **Lobar pneumonia:** Acute exudative inflammation of the entire lobe, classically single lobe involvement.
3. **Interstitial pneumonia**: Interstitial pneumonia is characterized by an inflammatory process within the interstitial walls rather than the alveolar spaces.

4. How do you classify pneumonia?

Pneumonia can be classified into two types based on how the infection is acquired:

1. **Community-acquired pneumonia (CAP):** Most common type of infection of the lower respiratory tract occurring in ambulatory patients in the community.

Further divided into typical pneumonia or atypical pneumonia

Atypical pneumonia: pneumonia differs from typical/classical pneumonia. There is a paucity of signs/symptoms, and silent hypoxia may be present. Causative pathogens include *Chlamydia pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae,* and respiratory viral pathogens. It presents radiologically as interstitial pneumonia.

2. **Nosocomial pneumonia: acquired after forty-eight hours of hospital admission**
   a. Healthcare-associated pneumonia (HCAP)–a patient develops pneumonia during or following a stay in a healthcare setting. Healthcare settings include hospitals, long-term care facilities, and dialysis centres

b. Hospital-acquired pneumonia (HAP)
c. Ventilator-associated pneumonia (VAP): is seen in patients who are mechanically ventilated for more than forty-eight hours.

5. What are the symptoms of pneumonia?

1. Fever.
2. Cough.
3. Sputum production (may or may not be present). The colour and quality of sputum may provide a clue to microbiological aetiology.
4. Blood-tinged sputum or haemoptysis.
5. Pleuritic chest pain due to localized inflammation of the pleura can be seen with any kind of pneumonia but is more common with lobar pneumonia.
6. Constitutional symptoms such as fatigue, headache, myalgia, and arthralgia can also be seen.
7. Shortness of breath.
8. Confusion in severe cases.

6. What are the signs in patients with pneumonia?

- Inspection: Increased respiratory rate (tachypnoea), use of accessary respiratory muscles. The respiratory rate closely correlates with the degree of oxygenation and, therefore essential in determining the severity. Hypoxia is seen in severe pneumonia, which leads to hyperventilation.
- Palpation: Increased vocal fremitus
- Percussion: Dullness to percussion
- Auscultation: Chest auscultation reveals crackles, rales, and bronchial breath sounds.

7. What are the complications of pneumonia?

Most people with pneumonia respond well to treatment, but pneumonia can be very serious and even deadly. The complications are commonly seen in patients with a weakened immune system, extremes of the ages-an older adult, a very young child or immunocompromised patients with diabetes, cirrhosis, malignancy, etc. Complications may include:

1. Acute respiratory distress syndrome (ARDS)- This is a severe form of respiratory failure.
2. Lung abscesses- These are pockets of pus that form inside or around the lung. They may need to be drained with surgery
3. Respiratory failure- This requires the use of a breathing machine or ventilator.
4. Sepsis- This is when the infection gets into the blood. It may lead to organ failure.
5. Multi-organ failure.
6. Empyema.

8. What are the common scoring systems used to assess patients with pneumonia?

CURB-65: The CURB-65 is a severity score for community-acquired pneumonia, helps in the initial triage of patients and determines severity and mortality Each parameter is assigned one point

- Confusion
- Urea >7 mmol/L
- Respiratory rate ≥30/minute,
- Systolic blood pressure <90 mmHg and/or diastolic blood pressure ≤60 mmHg
- Age ≥65 years

CURB-65 of more than two indicates hospitalization, while a score of more than four indicates the need for ICU admission.

9. How will you investigate pneumonia?

The choice of investigation depends on the clinical condition of the patient, following tests are generally recommended.

1. Chest x-ray–not mandatory to diagnose pneumonia.
2. Blood investigation: Complete blood count, procalcitonin (may help in differentiating viral vs bacterial pneumonia), Blood culture, and Blood gas analysis (if the patient is hypoxic or shows signs of respiratory failure).
3. Sputum examination–Direct stains: Gram stain, Fungal stain, AFB stains, Stains for PCP (if dealing with immunocompromised patients), Cultures–Bacterial /fungal cultures. It is important to asses the quality of sputum, as poor quality sputum may indicate colonisation of the respiratory tract rather than a true pathogen. The quality of sputum is best judged by the Bartlett scoring system (the presence of > 25 neutrophils per low power field and < 10 epithelial cells per low power field is considered good quality specimen).
4. Nasal and throat swabs for viral PCR–depending on the local epidemiology (for example, PCR for H1N1 or COVID can be done if there is an ongoing outbreak)
5. CT scans: not recommended as the initial investigation, but can be done if the patient is not improving on standard therapy.
6. Bronchoscopy: not recommended as the initial investigation, but it can be done if the patient is not improving on standard therapy.

10. How will you treat community-acquired pneumonia (CAP)?

A tabulated version of the management of CAP is given below (adapted from ICMR guidelines on common infectious syndrome-2019).

Type of CAP	Preferred drug	Alternative	Comments
Outpatients without co-morbidities	Co amoxiclav	Macrolides** Cefuroxime Cefpodoxime	Beta-lactam is preferred over macrolides due to the high prevalence of macrolide resistance in *S. pneumoniae* in India. Doxycycline monotherapy is not recommended
Outpatients with co-morbidities* or use of antimicrobial in 3 months	Co-amoxiclav and macrolide/ doxycycline	Cefuroxime/ cefpodoxime and macrolide/doxycycline	
Inpatient, non-ICU	Ceftriaxone with macrolide/ doxycycline	Cefotaxime/ amox clav with macrolide/ doxycycline	If there is hypersensitivity to beta-lactams: respiratory fluoroquinolones (exclude TB first)
Inpatient ICU	Ceftriaxone with macrolide/ doxycycline	Cefotaxime, piperacillin-tazobactam with macrolide	
Inpatient ICU with risk factors for *Pseudomonas aeruginosa*/ other enteric gram-negative bacteria#	Piperacillin tazobactam/ macrolide/ doxycycline	Cefepime/imipenem with macrolide/doxycycline	The use of carbapenems is preferred over beta-lactam beta-lactamase inhibitor combinations in patients with septic shock
The empiric addition of oseltamivir in patients with CAP should be considered in the setting of an influenza outbreak			
If CA MRSA## is suspected, then vancomycin or teicoplanin may be added			

Chronic heart, liver, renal or lung disease, diabetes mellitus, malignancies, alcoholism or use of immunosuppressive drugs.

*** Azithromycin/ Clarithromycin.*

 # Chronic respiratory disease (COPD, bronchiectasis, asthma, chronic bronchitis), neurologic disorders, enteral tube feeding and immunocompromised states.

Preceding influenza, cavitary infiltrates with no underlying aspiration, shock, or empyemas.

- The role of fluoroquinolones is well established in CAP in western guidelines. However, in India, where there is a high burden of TB and where TB may present as CAP, the use of empiric fluoroquinolone therapy may lead to masking and delayed diagnosis of TB and promotion of drug resistance. **Therefore, fluoroquinolones are best avoided for the management of CAP unless TB has been ruled out**.

The duration of therapy for outpatients is five days and for uncomplicated pneumonia in inpatients is 7 days.

CHAPTER

3

Management of Skin and Soft tissue infections

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Q.1 What are the different types of skin infections based on aetiology?

Answer-

There are different types of skin infection based on aetiology [1]:-

- Bacterial skin infection-like folliculitis, cellulitis, abscess, pustules, furuncles, carbuncles
- Viral skin infection-like shingles (herpes zoster), chickenpox, Molluscum contagiosum, warts, measles, hand, foot, and mouth disease
- Parasitic skin infection-Scabies
- Fungal skin infection-Tinea infection, Disseminated systemic mycoses like histoplasmosis, cryptococcosis, penicilliosis, blastomycosis, chromoblastomycosis, zygomycosis

Q.2. Discuss Ecthyma, impetigo, and erysipelas-their causative organism and management

Answer-

Ecthyma: -

It is an infection caused by gram-positive bacteria- *Staphylococcus aureus* or *Streptococcus pyogenes.* It is characterized by crusted sores under which the ulcers are formed. There are deeper erosions of the skin into the dermis. [2]

Treatment – Antibiotics commonly covering gram-positive bacteria like beta-lactam antibiotics-amoxicillin clavulanic acid, cephalosporins, linezolid, clindamycin, etc

Impetigo: -
Impetigo is a superficial skin infection caused by a bacterial infection. It presents as yellowish crusts on the face, arms and legs. It is highly contagious and commonly seen in young children. [3]

Treatment – by oral antibiotics covering gram-positive organisms.

Erysipelas: -
Erysipelas is a superficial form of cellulitis caused due to bacterial infection of the skin. It affects the upper part of the dermis and can involve superficial cutaneous lymphatics.

Treatment- by oral antibiotics covering gram-positive organisms.

Q.3. Management of cellulitis/Bacterial skin and soft tissue infection

Answer-

Definition
Cellulitis is an infection of the skin and soft tissue caused by bacterial infection. Patients suffering from cellulitis have a fever, swelling in the affected area, warmth, pain and redness over the affected skin. [4]

Management of cellulitis

Diagnostic work up- Complete blood count – shows leucocytosis, usually neutrophilic

Liver function test, Kidney function test, C-reactive protein, ESR, Procalcitonin, Blood culture (before starting antibiotics)

Intravenous antibiotics are preferred.

Preferred first-line treatment-Amoxycillin -clavulanate plus clindamycin or linezolid

If vancomycin /teicoplanin is added, clindamycin is to be added

Duration of antibiotics- Ten to fourteen days

Q.4. Discuss the management of Necrotizing Fascitis?

Introduction

Necrotizing fasciitis is a skin and soft tissue infection that spreads rapidly and can involve underlying muscles as well as subcutaneous tissue. It is a severe life-threatening condition

Group A streptococci is a common pathogen involved, but mostly it's a mixed infection with the involvement of anaerobes also. There is significant toxin generation in tissues, also leading to inflammation and necrosis.

Management

Send routine investigation, pus culture, and blood culture

Start broad-spectrum antibiotics–including a combination of beta-lactam and beta-lactam inhibitor plus clindamycin (covering anaerobes and significant antitoxin activity), plus Glycopeptides like vancomycin/teicoplanin

Alternatively, it can give a combination of beta-lactam (covering anaerobes like piperacillin) and beta-lactam inhibitor plus Linezolid (also have MRSA activity/ And antitoxin activity)

Q.5 Discuss the management of fungal skin infection

Answer

Types of Fungal Skin infection [5]

- Superficial skin infection-Dermatophytes
- Systemic mycoses-causing skin involvement like disseminated histoplasmosis

Cryptococcosis, conidiobolomycosis, zygomycosis, etc.

Management

Laboratory diagnosis

Histopathology-Using fungal stains like PAS, GMS etc.- the fungal elements can be identified in tissue

KOH mount- A type of hyphal elements/fungal cells that can be appreciated in microscopy using KOH mount

Fungal culture- The fungal culture helps in the identifying type of fungus

Different serology methods like- galactomannan, Histoplasma antigen detection, Histoplasma antibodies

Molecular methods- Not commonly available and used.

Treatment

Based on the type of infection- Different antifungals are available that have different coverage

Antifungals major classes are

- polyenes
- azoles
- allylamines
- echinocandins

Based on the type of infection- different antifungals are used for treatment

Q.6. Briefly discuss -Scabies, their cause and management?

Answer

Scabies is caused by an itch mite called **Sarcoptes scabiei that burrows under the skin.**

There is a significant itch over the affected area. Careful examination can help to identify the burrows under the skin.

The patient's itch increases on coming in contact with water.

Treatment

Permethrin lotion-local application below the neck and affected area

Ivermectin is given orally

Disinfecting the surroundings and change of bed linens and clothing is always required.

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CHAPTER

4

The highlight of Bundle Care in Sepsis Management

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What do you mean by bundle care?

The care bundle implies grouping together certain key elements of care which, when performed together, have an improved outcome. Prompt completion of any individual component of the bundle is not associated with a better outcome. In other words, care bundles are targeted to ensure that all patients receive the best care or treatment consistently, all the time.

What is the importance of Bundle care in sepsis management?

This bundle care approach has been successfully implemented in managing several conditions, more so in the critical care setting. Protocols that combine multiple interventions for early sepsis care or sepsis bundles are recommended for all patients with sepsis, including those with community-onset and hospital-onset sepsis.

What is the Survival Sepsis Campaign?

The Surviving Sepsis Campaign (SSC) was formed in collaboration between the Society of Critical Care Medicine and the European Society of Intensive Care Medicine in 2002. The aim of SSC is to reduce mortality from sepsis globally. Their first evidence-based clinical practice guidelines were published in 2004, with updates every four years after that. The latest update was published in 2021.

What components of Bundle care are included in the Survival Sepsis Campaign in sepsis management?

It begins with “time zero” or “time of presentation”, defined as the time of triage in the emergency department. The 3-hour and 6-hour bundles given earlier by the SSC are now combined into an hour-1 bundle; all of these bundles need to be initiated within one hour of emergency department triage or sepsis diagnosis.

The components of the 1-hour bundle include:

1) Measure lactate level and re-measure if initial lactate is > 2 mmol/L
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad-spectrum antibiotics
4) Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L
5) Apply vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure≥ 65mm Hg

What are the newer Recommendations for the Survival Sepsis Campaign Update in 2021?

- The newer recommendations include the following:

1) For patients with sepsis- induced hypoperfusion or septic shock, use of at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 hours of resuscitation.
2) For adults with sepsis or septic shock, using balanced crystalloid instead of normal saline for resuscitation is preferred.
3) For adults with septic shock, starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until central venous access is secured.
4) For adults with sepsis or septic shock, evidence is against using IV vitamin C.
5) For adult survivors of sepsis or septic shock, assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge is advised.
6) For adults with septic shock and an ongoing requirement for vasopressor therapy, using IV corticosteroids is suggested.

What are the limitations of bundle care in sepsis management?

Care bundles differ from standard care pathways in the way that compliance is measured and accordingly rated, i.e., only if all elements of the bundle are applied will the healthcare team receive a “pass”. The team fails even though they achieve all the targets except even one (all or none).

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CHAPTER

5

CNS Infections

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Questions and Answers:

1. What are the common CNS infections?

Meningitis, Encephalitis, Brain abscess

2. What is meningitis? When do you suspect?

Meningitis means inflammation of the meninges.

When to suspect meningitis- Patients with acute meningitis present with acute onset of one or more of the following features: fever, headache, nuchal rigidity and change in mental status. Patients with fever, headache and neck stiffness for > 1 month are classified under Chronic Meningitis.

3. What are the investigations for the evaluation of Meningitis?

Blood investigations- CBC, Blood sugar levels, LFT, CRP, Chest X-ray (to look for old or new tuberculosis features), and Renal function tests.

Two blood cultures should be taken under aseptic precautions to look for bacteraemia within an hour of admission to the casualty before administration of antibiotics (10ml each in aerobic and anaerobic bottles)

Lumbar puncture: It is mandatory to perform LP within an hour of admission to casualty in a suspected case of meningitis.

4. What are the samples to be sent for CSF analysis in case of acute Meningitis/ Chronic meningitis?

6ml of CSF with minimum of 1ml for viriology, 0.4ml for protein, sugar,0.5ml to microbiology for gram staining, AFB and culture, 0.1ml for glucose, 2ml for Xpert MTB Ultra(If indicated based on clinical scenario). CSF opening pressure has to be checked. Always check Concomitant blood sugar levels before the tap.

CSF analysis has to be repeated/stored if there is suspicion of autoimmune meningoencephalitis.

5. What is the brain imaging of Choice in cases of Meningitis/CNS infections?

Though lumbar puncture (LP) is the most essential test for the diagnosis and management of acute CNS infections, it is nowadays accepted practice to perform brain imaging before this invasive test, where available. CT imaging is often sufficient in assessing the risk of performing a lumbar puncture in an acutely ill patient, although this cannot exclude raised intracranial pressure.

The presence of focal lesions with the mass effect would indicate an increased risk of brain herniation from performing the test. Established brain abscesses can be identified in CT imaging. Complications of meningitis, such as infarcts, may be seen in CT as well. Meningeal enhancement in a contrast-enhanced CT scan suggests the presence of exudates which suggests more in favour of tubercular aetiology.

Magnetic resonance imaging, though not often practical in the acute setting, provides additional information about the diagnosis. The presence of signal changes in the medial temporal and orbitofrontal regions would suggest herpes simplex encephalitis.

6. Indications for Brain Imaging before LP?

Age greater than 60 years
Immunocompromised state
History of CNS lesion
History of seizures within one week before the presentation
Altered level of consciousness
Gaze palsy

Abnormal visual fields
Facial palsy
Arm drift
Leg drift
Bradycardia

Table 1: Clinical features that would suggest the need for imaging before performing a lumbar puncture

7. What are the CSF differentiating features between Bacterial, Viral, Tubercular and Fungal etiologies of Meningitis?

CSF FINDINGS

Investigation	Normal (>1 month)	Bacterial	Viral	Tuberculosis	Fungal
Opening pressure	10-20cm	High	Normal/High	High	High/ very high
Colour	Clear	Cloudy	Clear	Cloudy yellow	Clear/ cloudy
Cells	< 5	↑↑↑	↑	↑↑	↑
Differential	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
CSF glucose	50-65%	↓↓	Normal or ↓	↓	↓
Protein (g/L)	< 0.45	↑↑↑	Normal or ↑	↑↑↑	↑↑

TABLE 2: Depicting CSF Findings

8. What is Encephalitis? What are the types based on aetiology?

Encephalitis is inflammation of the brain parenchyma. It is technically a pathologic diagnosis, but the term is commonly used to describe a clinical syndrome of brain inflammation. The differential diagnosis for encephalitis is broad, with infectious (viral, bacterial, or parasitic), post-infectious, and non-infectious (metabolic, toxic, autoimmune, paraneoplastic) causes possible.

Viral infections are associated with two distinct forms of encephalitis. The first is a direct infection of the brain parenchyma due to viremia (*e.g.*, West Nile virus) or viral reactivation in neuronal tissue (*e.g.*, HSV, VZV). The second is a post- infectious encephalomyelitis [also known as acute disseminated encephalomyelitis (ADEM)], likely an autoimmune phenomenon more often seen in children and young adults following a disseminated viral illness or vaccination.

9. When do you suspect Encephalitis?

Encephalitis should be suspected in all patients with fever and altered sensorium. Other supportive findings include new-onset seizures, focal neurological signs and radiological abnormalities.

Investigations should be obtained in all patients suspected of encephalitis, including complete blood counts, blood cultures, and appropriate tests for diagnosing HIV, malaria, dengue, scrub typhus and leptospirosis based on clinical presentation.

Lumbar puncture is mandatory if there are no contraindications with PCR for HSV and other viruses based on suspicion and exposure. MRI is mandatory for viral encephalitis; if not available, CT can be done.

Causes: HSV, malaria, scrub typhus, dengue, leptospirosis. CSF lactate will be elevated in cerebral malaria(the rest of the CSF findings can be normal).

10. Any score other than GCS Studied in CNS infections?

A full outline of unresponsiveness(FOUR) score can be used as a tool to predict outcomes in patients with suspected meningitis at ED. It uses eye response, motor response, brain stem reflexes and type of respiration. Scores more than twelve are safe and have a good outcome. However, a score less than six requires intensive monitoring. Studies have shown that the Four scores are better than GCS in cases of suspected meningitis.

11. What are the empiric antimicrobials after LP in acute meningitis?

Community-associated: Ceftriaxone 2gm IV BD+ vancomycin 1-2gm IV BD

Healthcare-associated: Replace ceftriaxone with meropenem 2gm TDS.

Ampicillin 2gm IV six times a day + Gentamicin 80mg TDS in pregnant women, elderly, malignancy patients and transplant patients to cover listeriosis.

Dexamethasone: 0.15mg/kg q6h for four days, with the first dose administered ten to twenty minutes before or at least along with antimicrobial therapy.

12. What are the indications for steroids in Meningitis?

Purulent CSF, CSF cell count> 1000, CSF protein> 1000, bacteria on gram staining.

13. What are the empiric antimicrobials in acute encephalitis?

INJ. Ceftraixone 2gm iv BD+ Vancomycin 1gm IV bd+ INJ Acyclovir 10mg/kg TDS+ Doxycycline 100mg BD. This can be changed based on preliminary CSF findings.

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CHAPTER

6

Acute Febrile Illness and Pyrexia of Unknown Origin in India: A Diagnostic Approach

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a. What are the types of fever, and what is the short duration of fever (acute-sub acute febrile illness), and to classify it?

Fever (temp > 38.3 degrees F) of duration less than seven and fourteen days at presentation to any healthcare setting is called acute and sub-acute or short-duration fever. Based on the diagnostic approach, it can be divided into localized (differentiated) and non-localization (undifferentiated). A fever of a duration of more than two weeks is considered as chronic (persistent) fever and can stretch up to months in untreated cases.

1. **The localized (differentiated)** form includes the causes that can be localised to an organ system like **central nervous system**- meningitis/meningo-encepahlitis (with cerebral abscess); **respiratory tract and cardiac**- upper respiratory tract (URT) infection -sinusitis, thyroiditis, pyogenic or viral lymphadenitis, lobar pneumonia, empyema, endocarditis; **gastrointestinal tract**-liver and splenic abscess, cholangitis, colitis, diarrheal disease; **urinary and reproductive tract**- urethritis-funiculitis, prostatitis, pyelonephritis, cervicitis; **bone and joint**- osteomyelitis, arthritis and tenosynovitis.
2. **Non-localization (undifferentiated)** forms are those where the cause cannot be localised to one organ system and considered after excluding the localized form. Examples include- **tropical infections** like malaria, rickettsia, typhoid, leptospirosis, and brucellosis; **non-infectious** causes include-

3. **Why do we need to correctly identify the causes of AFI and treat them accordingly?**
   Each infection is caused by an agent who belongs to any one of these categories- bacteria, viruses, parasites or rickettsia. Each organism has a specific treatment as well as a prognosis. All of these infections do not require reserved antibiotics, and therefore correct diagnosis will prevent unnecessary use. Recently, the rising antimicrobial resistance at the community level is making correct diagnosis even more important, and hence the conventional treatment might be ineffective in such cases, and the expected outcome will not be achieved. Among uncomplicated cases, every case should be subjected to a diagnostic microbiological test and only after confirming the diagnosis should treatment be started.

b. Can we systematically diagnose these infections based on available investigations in our country? How?

Any patient presenting with fever should be subjected to meticulous history taking and clinical examination in order to arrive at a provisional diagnosis. Mostly, differentiated fevers are easily diagnosed by clinical findings, and radio-laboratory tests and causative organisms should be suspected based on local or national epidemiological data. Diagnosing undifferentiated fever poses a challenge because of non-specific and overlapping clinical and laboratory features. Therefore, specific diagnosis requires a systematic approach and appropriate diagnostic tests. Most of the AUFI causes share common features as well as complications. Therefore, the syndromic approach is helpful in narrowing down the differentials. (An algorithm depicts this)

c. When empiric treatment for these infections can be given?

In the presence of life-threatening complications at a presentation, a differential diagnosis should be considered, and investigations like blood culture, serology or PCR should be immediately sent, followed by starting appropriate antimicrobials. Inappropriate epidemiological background and laboratory tests findings, a positive microbiological report will help in establishing the diagnosis and guided therapy. Never empirically treat a persistent (chronic) fever with antimicrobials as the causes could be malignancies, connective tissue disorders, infections which do not cause short-duration fever but tuberculosis, fungal and atypical bacteria like Nocardia. Salvaging common antimicrobials like azithromycin, doxycycline, antimalarial, and cephalosporin so these infections can be easily treated.

d. What is PUO?

The difficult-to-diagnose cases of febrile illness that require extensive workup are often classified as fever or pyrexia of unknown origin (PUO/FUO). It is further divided into- classical, nosocomial, neutropenia and HIV associated. The classical & HIV-associated PUO is associated with persistent fever with the inability to diagnose with the meticulous investigation with three days of in-hospital

stay. The most common causes include- infection (>40%), malignancies (<20%), immunological/ connective tissue disorders (<20%) & undiagnosed (<20%). In Indian settings, empiric anti-tubercular treatment has resulted in multidrug resistance bugs and thus should be on the diagnosis of illness rather than empiric therapy.

Acute undifferentiated febrile illness (AUFI) [without localisation]

AFI with possible diagnostic clues: #Complications aiding the diagnosis

1. **Encephalopathy/ Encephalitis/**- Malaria, Leptospirosis, Scrub typhus> typhoid, chikunguniya
2. **Dry cough/ sore throat-** COVID19/influenza> Malaria,Dengue
3. **Jaundice with AKI-** Malaria, Leptospirosis>> Scrub typhus
4. **Coagulopathy/DIC-** Scrub typhus, Malaria, Leptospirosis, COVID
5. **ARDS-** COVID19/influenza> Malaria, Leptospirosis, Scrub typhus
6. **Myocarditis**- Scrub typhus>> Malaria, Dengue
7. **Hepato-splenomegaly**- Malaria, Leptospirosis, Scrub typhus, Dengue fever, typhoid, visceral leishmaniasis (HLH as complication)
8. **Maculo-papular rash**- Leptospirosis, Scrub typhus, Dengue (Meningococcal disease)
9. **Restiform purpura**- Indian tick typhus, Scrub typhus
10. **Shock**- Malaria, Leptospirosis, Scrub typhus, Dengue
11. **Vasculitis-** Scrub typhus, COVID19,Infective endocarditis (IE)
12. **Arthritis-** Chikunguniya, Brucellosis, Adult onset stills disease (AOSD)
13. **Thrombocytopenia with leucocytosis-** Scrub typhus, leptospirosis

#- more than 1 complication can be found at presentation

AFI with potential diagnostic clues (Classical features- most specific)

Fever with multisystem involvement

1st line: Most common causes

1. Eschar with regional lymphadenopathy**- Scrub typhus [IgM ELISA/PCR scrub]**
2. Rash, leukopenia with evidence of plasma leakage ± minor bleeding= **Dengue fever [IgM ELISA/PCR]**
3. Pneumonitis with URTI= **COVID/ Influenza (H1N1) [RT-PCR throat swab]**
4. Rose spots, step ladder fever, progressive neutropenia= **Typhoid [Blood culture, IgM]**
5. Conjunctival suffusion, jaundice, meningism, myalgia, rash= **Leptospirosis [PCR, MAT, IgM]**
6. Haemolytic anaemia, thrombocytopenia= **Malaria [Microscopy, lateral flow-antigen]**

2nd line: Uncommon- Acute Brucellosis, Infectious Mononucleosis, Visceral Leishmaniasis & Meliodosis (endemic state), IE

1st line: Most common

1. Fever with Chills with Eosinophilia, lymphedema ± lymphangitis ± funiculitis = **Filariasis [Microfilare antigen, blood microscopy]**
2. Large joint arthritis ± rash around joints ± hyperpigmentation on body= **Chikunguniya [PCR/IgM ELISA]**

2nd line: Uncommon

1. Acute olio- polyarthritis, rash, splenomegaly= **Brucellosis**

Supplementary table 1:

A comparative profile of common causes of AUFI in India and similar tropical country

Features	COVID-19/ Influenza	Dengue	Malaria	Leptospirosis	Rickettsial fever	Enteric fever
Epidemiology	Urban > rural	Urban>>rural	Rural>urban	Rural>>Urban	Rural>>urban	Rural and urban
Situation/ exposure	Close contact, laboratory person	Outbreak	Outbreak-sporadic	Outbreak-sporadic	Outbreak-sporadic	Sporadic
Dyspnoea	+/+++	+	++	++	++	+
Myalgia	++	+++	++	+++	++	+
Rash	Rare	+++	Absent	+/Rare	++/+++	+
URTI (cough)	+++/++++	+	++	++	+	+
CNS involvement	Rare	Rare	++	++/+++	++/+++	+
Jaundice	Rare	+	++/+++	++/+++	++	+
Conjunctiva suffusion	Absent	+++	Rare	+++	++	Rare
Hepato-splenomegaly	Rare	+/ +++	+++	+	++	++/+++
Bleeding	Rare	+++	Rare	++	+	Rare
AKI	+/++	+	++/+++	+++	++	Rare
Leukocytosis	+	Rare	+	+/++	+++	+
Leukopenia	++	++++	+	+	+	++
Plasma leakage	+	+++	Absent	++	Absent	Absent
Pneumonitis	+++/++++	+	++	+/++	++/+++	+
Diagnostic tests/ criteria used commonly in a clinical setting	RT-PCR/ NAAT/ Antigen-nasopharyngeal swab	NS1 antigen and IgM antibody by ELISA	Thick and thin blood smear microscopy, RDT	Modified Faine's criteria, Thai-lepto score, IgM ELISA	IgM Elisa, PCR	Blood culture, IgM typhidot test by ELISA
Feature(s) increasing the probability of diagnosis over other differential diagnoses	Anosmia, Agusia, and pneumonitis early in the illness	*Fever with rash, evidence of plasma leakage, AST>60 IU/mL, ANC<3000/ mm^3, TLC< 5000/mm^3 PC< 100,000/ mm^3	Absence of viral infection features, haemolysis, oliguric AKI	Meningismus, Muscle pain, Non-oliguric AKI with hypokalemia, conjunctival suffusion, Pulmonary haemorrhage	Eschar, neutrophilic leukocytosis	Rose spots, step ladder fever, progressive neutropenia, initial gastrointestinal symptoms

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Module 3: Antimicrobial Stewardship

CHAPTER

1 Rapid Review of Antibiotics and Antifungal Agents

Dr Grace Mary John

RAPID REVIEW OF ANTIBIOTICS

Antimicrobial agent: Defined as a natural or synthetic substance that kills or inhibits the growth of microorganisms such as bacteria, fungi and viruses

Antibiotics: Broad chemical class of therapeutic agents originally derived from natural sources (molds, bacteria, etc.)

- Discovery: 1928–Dr Alexander Fleming–penicillin

Dr Fleming presciently warned about the dangers of antibiotic resistance:

"The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and exposing his microbes to non-lethal quantities of the drug make them resistant."

CLASSIFICATION OF ANTIBIOTICS

Antibiotics can be classified in many different ways - based on the spectrum, based on the class, based on the mechanism of action, based on PK PD parameters etc.

BETA LACTAMS

- Largest class among antibiotics
- Since beta-lactam antibiotics are highly efficacious and are generally well-tolerated, as a general rule, if the pathogen is susceptible and the patient is non-allergic, beta-lactams are the preferred drug for most situations.

Oral beta-lactams are **not** generally preferred to treat serious or deep-seated infections due to their poor bioavailability, resulting in low serum concentrations.

Mechanism of action

All beta-lactams exert their action by binding to the Penicillin Binding Proteins (PBP).

- This results in the inhibition of the synthesis of the peptidoglycan layer of bacterial cell walls, which is an essential component of the bacteria's cell wall. This binding, therefore, inhibits cross-linking of peptidoglycan in the cell wall, leading to autolysis and cell death.
- Works best when there is rapid bacterial growth/ active cell wall synthesis

Common toxicities:

Allergic reaction (may be rash, hives, and anaphylaxis)

- Penicillins: 1 -10%, cephalosporins/ carbapenems: 1-3%

Drug fever, Seizures (very high doses in patients with renal insufficiency), Interstitial nephritis, GI effects (nausea, diarrhoea, and *C.diff*)

Beta Lactamase enzymes

Some bacteria can produce Beta-lactamase enzymes which can break down beta-lactam antibiotics and thereby cause drug resistance.

The most common bacteria having beta-lactamases are *Staphylococci* (Penicillinase) and many gram-negative bacteria - including *Escherichia coli (E. coli), Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas, Neisseria gonorrhoeae, H. influenzae,* etc. Also, *Bacteroides spp*. (anaerobe)

PENICILLINS

Natural penicillins:
Penicillin G (IV) and penicillin V (PO).

- Penicillin V is similar to penicillin G, but it has a longer half-life in the body and is generally taken orally. These agents are active against gram-positive bacteria.
- Long-acting depot formulations (procaine, benzathine) are available for intramuscular administration.
- Nowadays most commonly used for Syphilis, particularly neurosyphilis.

Antistaphylococcal Penicillins

Nafcillin, oxacillin, dicloxacillin, methicillin, cloxacillin

- Also called "Penicillinase-resistant," penicillins-Developed to overcome penicillinase production in *S.aureus*
- Based on their sensitivity - *S.aureus* classified as *MSSA* (Methicillin-sensitive *S. aureus*) vs *MRSA* (Methicillin-resistant *S. aureus*)
- No added coverage for gram-negative bacteria.
- Generally only used to treat drug-sensitive staphylococcal infections
- Best suited for *MSSA* (drug of choice) - Endocarditis/SSTI
- Oxacillin is more likely to cause hepatotoxicity; reversible with discontinuation
- Methicillin is not used due to its nephrotoxicity

Aminopenicillins

Ampicillin (IV), amoxicillin (PO)

- Developed to increase activity against gram-negative aerobes
- Aminopenicillins are susceptible to beta-lactamases just like penicillin G and, therefore, rarely active against *Staphylococci* because *Staphylococci* almost always produce penicillinases. Gram Positive coverage, as with natural penicillins
- Amino side chain- more hydrophilic-better penetration for some Gram-negative organisms
- Preferred: *Listeria* meningitis & *Enterococcal* infections (if sensitive)
- Bacterial meningitis and Endocarditis (ampicillin), AOM(Acute Otitis Media), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, Lyme disease, RTI, UTI
- Aminopenicillins have a high incidence of diarrhoea when given orally.
- The bioavailability of amoxicillin is better than ampicillin

Anti-Pseudomonal penicillins

Piperacillin / ticarcillin

- Active against *P. aeruginosa* and other more drug-resistant GNRs
- They are just as susceptible to beta-lactamases as penicillin, so they are not antistaphylococcal
- Rarely ever used clinically by themselves

β-Lactam - β-Lactamase Inhibitor (BL-BLI) Combinations

Ampicillin sulbactam/ amoxicillin clavulanate

- Developed to gain or enhance activity against β- lactamase producing organisms lactamase producing organisms
- the β-lactamase inhibitor binds irreversibly to β-lactamase by mimicking the structure of beta-lactams, preventing it from breaking down penicillin

- Have little antimicrobial activity on their own.
- Gram Positive: *S. aureus* (similar activity to penicillinase-resistant penicillins).
- Added coverage to *Klebsiella* / Anaerobes like *Bacteroides* - as they usually produce Beta lactamases enzyme
- High-dose ampicillin/sulbactam has a role in the treatment of MDR *Acinetobacter baumannii.*

Piperacillin tazobactam/ticarcillin clavulanate

- Developed to further increase activity against often resistant gram-negative aerobes. Very broad spectrum.
- The good empirical choice for nosocomial infections.
- Use higher doses for pneumonia, nosocomial infections and *Pseudomonas.*
- Watch for sodium overload; piperacillin/ tazobactam 1 g = 2.79 mEq Na.

CEPHALOSPORINS

- Origin from the Fungus - Cephalosporium acremonium
- Divided into four major groups called “Generations.”
- Are divided into Generations based on
- Antimicrobial activity
- Resistance to β-lactamase
- Resistant to Penicillinase, but vulnerable to other β-lactamases
- Considered to be intrinsically resistant to *Enterococcus sp*
- Poor anaerobic coverage (except for cephamycins - cefoxitin/cefotetan)
- ~2% cross-reactivity with penicillins

First Generation Cephalosporins

cefadroxil (PO) cefazolin (IV) cephalexin (PO)

- Activity attributed to the large R1 side chains protect them from β-lactamases produced by aerobic gram-positive cocci (staphylococci & streptococci)
- Do not protect them from β-lactamases produced by most gram-negative bacteria.
- No anaerobic activity
- Most commonly used as surgical prophylaxis
- Overall good distribution to tissues and doesn’t cross the Blood-brain barrier

Second Generation cephalosporins

Cefuroxime and cefoxitin

- Slightly less active against gram-positive aerobes
- But more potent against *E. coli, K. Pneumoniae* & *P. mirabilis* than 1st generation cephalosporins.
- Particularly active against *Haemophilus influenzae* and *Neisseria gonorrhoeae*
- Several second-generation agents have activity against anaerobes.

Third Generation cephalosporins

ceftriaxone, cefotaxime, ceftazidime, cefixime (PO)

- Good streptococcal activity but generally lesser staphylococcal activity than previous generations of cephalosporins
- More gram-negative activity: *Citrobacter, Enterobacter, Acinetobacter, Serratia*
- Ceftazidime: Even though antipseudomonal, it lacks clinically useful activity against Gram-positive organisms.
- Notorious for inducing resistance among GNRs
- Better penetration into body tissues
- Crosses the BBB and is useful for treating meningitis.

Fourth Generation cephalosporins

cefepime

- Stability against β-lactamases
- Good activity against Gram-negatives, including *Pseudomonas* and Gram-positive organisms
- The good empiric choice for many nosocomial infections
- Weak inducer of extended-spectrum β-lactamases (ESBL)

Fifth Generation cephalosporin

ceftaroline

- "Anti-MRSA cephalosporin"
- Has modest activity against *E. faecalis* - unlike other cephalosporins
- Indicated for treating *MRSA*, skin & soft tissue infections & community-acquired bacterial pneumonia

Cephalosporin/beta-lactamase Inhibitor Combinations

ceftazidime - avibactam, ceftolozane -tazobactam

- Developed against carbapenem resistance

ceftazidime - avibactam

- Restores the activity of ceftazidime
- Works against many beta-lactamases (including a few carbapenemases) produced by *K. pneumoniae*, *E. coli* and *P. aeruginosa*

ceftolozane-tazobactam

- Ceftolozane - 3rd Gen cephalosporin
- Active against *P. aeruginosa*
- Not best suited for CRE (Carbapenem-Resistant Enterobacteriaceae)

- Neither of the agents has good activity against *Acinetobacter*
- Unlike other BL BLI agents, they lack anaerobic activity

CARBAPENEMS

Imipenem/cilastatin, meropenem, ertapenem, and doripenem

- Broadest spectrum of β-lactams, effective against most gram-negative bacteria, narrower spectrum against gram-positives, good activity against B. fragilis
- No cover: *MRSA, Methicillin-resistant coagulase-negative Staph, C. difficile, S.maltophilia*
- Ertapenem does not cover *Pseudomonas, Acinetobacter*
- Primarily reserved for treating bacteria with multi-drug resistance (MDR) and for typically hospitalized patients - e.g. abdominal infections, complicated UTIs, Pneumonia, Sepsis,
- Pharmacokinetics:
  - Renal
  - Generally well tolerated
  - Cross-reactivity with penicillin allergy <1%
  - Seizure risk
    - At high plasma concentrations
    - Renal failure

MONOBACTAM

Aztreonam

- Binds only to the Penicillin Binding Protein 3 (PBP3)
- Spectrum:
  - Selective effect against gram-negative bacteria, including *P. aeruginosa* (that express PBP3)
  - Not useful against gram-positives or anaerobes (different PBPs)
  - Activity similar to aminoglycosides
- Resistant to some β-lactamases, but it is inactivated by ESBLs
- No immunologic cross-reactivity with penicillins due to their different ring structure, hence often used as an alternative in penicillin allergy.

GLYCOPEPTIDE

Vancomycin/teicoplanin
telavancin /dalbavancin/oritavancin

- Bactericidal (except for *Enterococcus*)
- Inhibits bacterial cell wall synthesis - Binds firmly to the D-alanine-D-alanine portion of the cell, preventing further elongation of peptidoglycan chains
- Resistance - Modification of D-alanine-D-alanine binding site of peptidoglycan
- Spectrum: aerobic and anaerobic Gram-positive bacteria only
  - Vancomycin resistance in *Enterococcus* is rising

- Inferior to Beta lactams in treating *MSSA* bacteremia
- Adverse reactions
  - Red-Man Syndrome
  - Nephrotoxicity and Ototoxicity
  - Hematologic - neutropenia and thrombocytopenia with prolonged therapy
  - Thrombophlebitis
- Pharmacokinetics
  - Negligible GI absorption - used against *C. difficile*
  - Widely distributed into body tissues and fluids, including adipose tissue -hence should be dosed using total body weight.
  - Renal elimination - half-life greatly dependent on renal function - dosing frequency usually based on renal function
  - An AUC/MIC ratio of 400 has been advocated as a target to achieve clinical effectiveness with vancomycin.

NEWER GLYCOPEPTIDES

Telavancin	Dalbavancin	Oritavancin
Semisynthetic lipoglycopeptide Approved for cSSTI and HAP/ VAP Once daily administration Adverse Effects - Metallic taste - Foamy urine - QTc prolongation Black box warning - Pregnancy Cat C	Long-acting parenteral lipoglycopeptide Approved for ABSSSI Once weekly dosing Adverse Effects - Hypersensitivity - Infusion Related Reactions - Hepatic - ALT elevation	Long-acting parenteral lipoglycopeptide Half-life - 245 hours Approved for ABSSSI Not for treating osteomyelitis Single dose treatment Adverse Effects - The artificial prolongation of INR and aPTT - Unfractioned Heparin is contraindicated for five days following Oritavancin - Infusion Related Reactions

cSSI: complicated skin-soft tissue infection; HAP: Hospital Acquired Pneumonia, VAP: Ventilator-Associated Pneumonia, ABSSI: Acute Bacterial skin and skin-structure infections

LIPOPEPTIDE

Daptomycin

- Binds to bacterial membrane causing rapid depolarization of membrane potential- resulting in inhibition of protein, DNA and RNA synthesis - rapid cell death
- Spectrum: aerobic and anaerobic Gram-positive bacteria only
- Indications: cSSTI, endocarditis, osteomyelitis, bacteremia, UTIs

    - Do not use for primary pneumonia- inactivated by pulmonary surfactant
- Adverse reactions
    - Myopathy - monitor weekly CPK
    - Eosinophilic pneumonia
- Drug Interaction: Consider stopping statins while on Daptomycin therapy

OXAZOLIDINONE

Linezolid/ tedizolid

- Inhibits protein synthesis by binding to a site on the ribosomal RNA 50S subunit
- Spectrum: Gram-positive organisms
- AUC/MIC and t>MIC, bacteriostatic, short PAE (post-antibiotic effect)
- Excellent oral bioavailability and excellent tissue penetration (including CNS)
- Adverse effects
    - Bone marrow suppression (thrombocytopenia)
    - Monitor CBC with differential weekly
    - Peripheral neuropathy - long-term therapy
- Drug interaction with SSRI (selective serotonin reuptake inhibitors) - Uncommon but serious - monitor for serotonin syndrome

LINCOSAMIDE

Clindamycin

- Binds to the 50S subunit preventing the peptide-bond formation and inhibiting protein synthesis
- Spectrum
    - Gram-positive: *MSSA, MRSA, Streptococcus spp.*
    - Anaerobes, protozoa (*Plasmodium, Toxoplasma)*
- Adjunct therapy in infections with toxin production (ex. Necrotizing fasciitis), skin and soft tissue infections
- Alternative for gram-positive infections when the patient is penicillin allergic
- Good tissue penetration, including bone, but minimal CSF penetration
- Adverse effects
    - GI: diarrhoea and abdominal pain, Pseudomembranous colitis due to *C.difficile*
        - Monitor for diarrhoea

POLYMYXINS

Polymyxin E (colistin) & polymyxin B

- A cationic agent that binds to the anionic bacterial outer membrane - Has a detergent effect, disrupting the membrane integrity.

- Spectrum: Gram negatives only - esp used for MDRO - CRE, CRAB (Carbapenem-resistant *Acinetobacter baumannii*, CRPA (Carbapenem-resistant *Pseudomonas aeroginosa)*
  - No activity against - Anaerobes /*Proteus/Providencia/Serratia/Morganella/B. cepacia*
- Concentration-dependent killing: AUC/MIC
- Polymyxin B is preferred over colistin for all indications except UTI - due to the PK-PD advantage. Both are nephrotoxic.
  - DO NOT use Polymyxin B for UTI
- Colistin is available as colistimethate Sodium - prodrug. Polymyxin B is the active agent.
  - Dosing and unit conversions can be very confusing. Colistin dosing calculators are available.
    - Polymyxin B: 1 mg = 10,000 units
    - Colistin: usually based on Colistin base activity (CBA): 1mg CBA = 30,000 IU CMS
- Adverse reactions
  - Nephrotoxicity - due to ATN
  - Neurotoxicity; Exacerbate Myasthenia gravis
  - Inhalation - Bronchospasm

AMINOGLYCOSIDES

Gentamicin/amikacin/tobramycin

- Irreversibly bind to 30S ribosome and inhibits protein synthesis
- Spectrum of Activity
  - Excellent activity against all gram-negatives, including *Pseudomonas*
  - No gram-positive or anaerobic activity
- Common Indications
  - Rarely used as monotherapy
  - Often combined with beta-lactams for moderate-severe gram-negative infections in critically ill patients
  - Synergy with beta-lactams for gram-positive organisms
- Pharmacokinetics:
  - Concentration-dependent killing: Cmax/MIC, bactericidal, PAE
  - Dosing frequency based on renal function: Extended vs Conventional dosing strategy
  - Hydrophilic - Distribute poorly into adipose tissue
    - Use ideal/ adjusted body weight for dosing
- Adverse effects:
  - Nephrotoxicity & ototoxicity
  - Avoid concomitant use of Other oto/nephrotoxic medications like loop diuretics
  - Neuromuscular junction blockage
- Monitoring:
  - Auditory testing at baseline and follow-up esp in those receiving therapy for a prolonged duration (i.e., infective endocarditis)
  - Renal function
  - Therapeutic Drug Monitoring advised

FLUOROQUINOLONES

Ciprofloxacin(2nd)/ levofloxacin(3rd)/ moxifloxacin(4th)

- Inhibit DNA-gyrase in bacteria, promote breakage of double-stranded DNA
- Spectrum: Gram-negatives: *Enterobacteriaceae, Pseudomonas*/Gram-positive: *MSSA*, some *Streptococcus*/Atypicals
  - Anti-pseudomonal: ciprofloxacin, levofloxacin
  - Respiratory FQs: moxifloxacin, levofloxacin (*H. influenzae, Moraxella, Neisseria, Strep. pneumoniae*)
  - Anaerobes: moxifloxacin (Modest activity against *Bacteroides)*
- Pharmacokinetics
  - Concentration-dependent killing: AUC/MIC
  - Fluorinated quinolones - Improved PK properties
  - Excellent bioavailability
  - Tissue penetration
  - Prolonged half-lives
- Adverse effects
  - GI: nausea, diarrhoea, abdominal pain
  - Neurological: insomnia, headache, dizziness
  - QT prolongation
  - Dysglycemias
  - Tendinitis: Steroids, older age at higher risk
- Avoid in Pregnancy (Cat C) and Paediatrics (cartilage toxicity)
- Drug interactions with divalent and trivalent cations

TETRACYCLINES

Doxycycline/ minocycline

- Inhibit bacterial protein synthesis by reversibly binding to the 30S ribosomal subunit
- A very broad spectrum of activity: Gram-negative/Gram-positive/Atypical/ Anaerobes
  - Drug of choice for a variety of uncommon infections - *Spirochetes/ NTM/ Rickettsiae* / Parasites
- Considered bacteriostatic
- Adverse effects
  - Contraindicated in children - permanent tooth discolouration
  - Esophageal ulceration and/or esophagitis
  - Increased LFTs
  - Phototoxicity
  - Vestibular toxicity (minocycline)
- Drug interactions with divalent and trivalent cations

GLYCYLCYCLINE

Tigecycline

- Bind to the bacterial ribosome at the 30S subunit
- Evade most tetracycline resistance mechanisms and have a broad spectrum of activity
- Sensitive against *MRSA/ VRE/CRE/ CRAB/ Stenotrophomonas*
  - No pseudomonal coverage
- FDA approved for CAP/ cIAI (complicated intra-abdominal infections)/ cSSTIs
- Pharmacokinetics
  - AUC/MIC, bacteriostatic
  - Extensive tissue penetration, high protein binding and high Vd - not good for bacteremia
- Adverse effects
  - Elevated LFTs
  - GI (high incidence of nausea and vomiting)
  - Hyperbilirubinemia
  - Pancreatitis

MACROLIDES

Azithromycin, clarithromycin

- Bind to the 50S subunit of bacterial ribosomes
- Excellent for respiratory infections esp CAP
- Good GP coverage and excellent atypical coverage
  - Limited Gram-negative coverage (*H influenza, Moraxella, Bordetella, Pasteurella, Bartonella, Campylobacter, H. pylori, Neisseria*); Poor enteric GNB coverage
- Concern regarding increasing resistance to *Streptococcus pneumoniae*
- Pharmacokinetics
  - Long half-life
  - Increased stability in acid media - the higher bioavailability
- Adverse effects
  - Diarrhoea and other GI symptoms are prominent. Rare hepatotoxicity. QT prolongation
- Pregnancy - first trimester - increased risk of malformation

FOLATE ANTAGONISTS

Trimethoprim–Sulfamethoxazole (TMP/SMX)

- Mechanism
  - Sulfamethoxazole: interferes with bacterial folic acid synthesis and growth via inhibition of dihydrofolate formation from PABA

    - Trimethoprim: inhibits dihydrofolate reduction to tetrahydrofolate, resulting in sequential inhibition of the folic acid pathway
    - TMP/SMX comes in a fixed 1:5 ratio
- Active against both bacterial and parasitic infections
    - High incidence of resistance, thereby reducing its use
    - If susceptible can be used in uncomplicated cystitis, bacterial prostatitis, enteric fever
- Pharmacokinetics
    - PKPD: T>MIC
    - Excellent oral bioavailability
    - Obese patients- use actual body weight for severe infections
    - Metabolized in the liver via N-acetylation and glucuronidation, eliminated renally.
- Adverse reactions
    - Bone marrow suppression
    - GI (especially with higher doses)
    - Hepatitis, LFT elevations, Pancreatitis
    - Nephrotoxicity, Hyperkalemia (reversible)
    - Kernicterus in newborns
    - Photosensitivity, rash and pruritus
- Monitoring
    - CBC with differential, Renal function, Potassium (esp those on ARB/ ACEi)
- Significant drug interaction with Warfarin - avoid concurrent use

Fosfomycin - PO

- MOA:
    - Interferes with bacterial cell wall synthesis by inhibiting the enzyme enolpyruvyl transferase, thereby preventing the production of the building blocks of peptidoglycan.
- Approved for the treatment of Uncomplicated UTI
- PO formulation: Fosfomycin trometamol -3 g sachet; Only for Uncomplicated UTI
- Drug interaction: Antacids—reduce the absorption of Fosfomycin
- Adverse reactions: Diarrhea ~10%, HA

Fosfomycin - IV

IV form: fosfomycin disodium

- Off label uses
    - Rx of complicated UTI w/o bacteremia
    - Rx of *VRE*, *P. aeruginosa*, ESBL (Extended Spectrum beta-lactamase) & CRE pathogens
- Clinical trials on a wide variety of indications
    - Pyelonephritis/ Nosocomial pneumonia/cSSTI/ Osteomyelitis
- High doses: 12-24g/day
- Prefer to use the combination to lessen the chances of resistance

- Caution:
  - Hypokalemia
  - Large sodium load
    - 14.4 mEq Na per gram
    - 10g of IV Fosfomycin ~ 1L of NS

ANTIFUNGALS-RAPID REVIEW

Fungi exist in two basic forms

- Yeasts - unicellular form
- Molds - multicellular form with hyphae. Spore producing
  - Some fungi can exist in two forms and are called **dimorphic fungi** (usually mold form at room temperature and a yeast form at body temperature)

The choice of medication and length of treatment will depend on the type of infection and the overall health of the patient.

Clinically relevant fungi that can cause deep mycosis

Yeast	Mold	Dimorphic
Candida *Cryptococcus*	*Aspergillus* *Mucorales* *Fusarium* *Scedosporium*	*Histoplasmosis* *Blastomyces* *Coccidioides* *Paracoccidioides*

Antifungal agents are usually classified based on their mechanism of action. Here is a short review of agents used in systemic therapy for serious fungal infections.

Azoles:

Triazoles - Fluconazole, Itraconazole, Voriconazole, Posaconazole
Imidazoles - Ketoconazole, Clotrimazole, Miconazole

Imidazoles are usually used to treat superficial mycosis

- Inhibit the synthesis of ergosterol, a component of the fungal cell membrane, resulting in increased permeability of the fungal cell membrane.
- Triazoles: Mainstay of antifungal therapy for susceptible pathogens
- Adverse effects
- Nausea; diarrhea; abdominal pain; rash; photophobia; deranged LFTs
- Significant drug interactions: Itra > Vori> Fluc > Posa

Fluconazole:
- Fluconazole is effective against Esophageal, oropharyngeal, vulvovaginal, cutaneous and invasive candidiasis
- Usually given as a prophylactic agent in severely immunocompromised patients and to treat Candida infections
  Excellent oral bioavailability - hence can be given as oral therapy when the patient can tolerate feeds.
- Contraindicated during pregnancy

Itraconazole:
- Better absorbed in an acidic environment - hence advised to be taken on an empty stomach or mixed with soda/ lime juice. Not to co-administer proton pump inhibitor while on itraconazole
- Itraconazole is the drug of choice for histoplasmosis, blastomycosis and sporotrichosis.

Voriconazole
- Preferred to treat invasive aspergillosis
- Adverse effects: With IV formulation, the vehicle used - cyclodextrin can accumulate in renal dysfunction and can be nephrotoxic; visual effects, hallucinations, photosensitivity
- Voriconazole is eliminated via the liver and is therefore not much useful in the treatment of candiduria.

Posaconazole:
- Spectrum: *Candida, Aspergillus, Fusarium, Mucorales*
- Absorption increases with food, especially fatty food
- Serum monitoring required
- Relevant drug interactions with immunosuppressants

Isavuconazole
- Newest azole
- Approved for the treatment of invasive aspergillosis and invasive mucormycosis
- IV and oral formulation available, excellent oral bioavailability
- Has a very long half-life

Polyenes

Amphotericin B

- Binds directly to ergosterol in the fungal cell membrane and creates holes in the membrane, leading to the death of the cell
- Different formulations:

- Amphotericin B deoxycholate (ABD) or Conventional Amphotericin B (C- AMB)
- Amphotericin B colloidal dispersion (ABCD)
- Amphotericin B lipid complex (ABLC)
- Liposomal amphotericin B (LAmB).

- Amphotericin B deoxycholate is generally dosed between 0.5 and 1.5 mg/kg/day, whereas lipid formulations are dosed at 3–6 mg/kg/day. **Beware of the dosing of various formulations - common medication error…!!!!**
- Amphotericin is effective for almost all systemic mycosis, but due to the toxicity, azoles are preferred in many fungal diseases
- Adverse effects
  - Infusion-related reactions: Fever, chills, phlebitis, anaphylaxis: Premedication with acetaminophen and phenylephrine prior to infusion
    - Liposomal amphotericin B has the lowest incidence of infusion-related reactions
  - Renal toxicity: Increased creatinine: Prevention by giving saline load
    - Nephrotoxicity also leads to the wasting of magnesium and potassium, such that patients frequently need supplementation. Hypokalemia: Prevention: IV K+ replacement or amiloride 5-10mg/day
  - Renal tubular acidosis
  - Anaemia - less frequent with lipid formulations

Echinocandins:

Caspofungin, Micafungin, Anidulafungin

- Inhibit the synthesis of 1,3 β glucan synthase involved in fungal cell wall biosynthesis, leading to the death of the cell.
- Poor bioavailability; IV only
- Adverse effects
  - Headache, limited LFT abnormalities
- Spectrum
  - *Candida* (cidal) *Aspergillus* (static)
  - No activity against *Cryptococcus, Fusarium, Zygomycetes, Trichosporon spp*

Flucytosine:

- This is an antimetabolite that interferes with DNA synthesis
- Pharmacokinetics
  - Adequate penetration into - aqueous humour, joints, bronchial secretions, peritoneal fluid, brain, bile, and bone.
- Intrinsic resistance to C. krusei
- Induction of resistance during monotherapy is sufficiently frequent and rapid that flucytosine is essentially always used as part of combination therapy.

- Not the drug of choice for any infection
- Indication: **C**urrent recommendation is that flucytosine be added during the first two weeks of IV amphotericin B therapy for patients with AIDS and cryptococcal meningitis
- Adverse effects:
  - Most common-Diarrhea
    - Look for flucytosine toxicity - developing loose stools or dull abdominal pain suddenly - check levels (should be less than 100 to 125 μg/mL)
  - Bone marrow depression - leukopenia, Thrombocytopenia
  - Monitoring-weekly creatinine, leukocyte count, platelet count, alkaline phosphatase, and aminotransferase
- Teratogenic-contraindicated in pregnancy

CHAPTER

2

Terminologies in Antimicrobial Stewardship

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1. What are the common terms used in Antimicrobial Stewardship?

- Multidrug-resistant bacteria
- Health-care-associated infection (also referred to as "nosocomial" or "hospital-acquired infection")
- Empirical antibiotic therapy
- Definitive antibiotic therapy
- 5 "D" of antimicrobial therapy
- Dose optimization
- De-escalation
- Redundant therapy
- Days of therapy (DOT)
- Defined daily dose (DDD)
- IV-to-oral switch
- Antibiotic timeout
- Therapeutic drug monitoring
- Antibiotic cycling
- Bug-drug mismatch

2. Multidrug resistant bacteria:

- Bacteria resistant to at least one agent in three or more antibiotic categories are multidrug-resistant (MDR).
- Extensively drug-resistant (XDR) is non-susceptibility to at least one agent in all except two or fewer antibiotic categories (i.e. bacterial isolates remain susceptible to only one or two categories).

- Pan drug-resistant (PDR) is non-susceptibility to all agents in all antibiotic categories.

3. Health-care-associated infection:

- Infection occurring in a patient during care in the hospital or other health-care facility, which was not present or incubating at the time of admission. Health-care-associated infections can also appear after discharge.
- Infections occurring ≥ forty-eight hours after admission to a health care facility.

4. Empirical antibiotic therapy:

- Initial broad-spectrum antibiotic treatment targeted the most probable causative microorganism. The recommendations should be based on local susceptibility data, available scientific evidence or expert opinion when evidence is lacking.

5. Definitive antibiotic therapy

- Targeted narrow-spectrum antibiotic treatment for the causative microorganism as per the report of culture & susceptibility or genotyping testing by polymerase chain reaction/next-generation sequencing analysis or serological testing

6. 5 "D" of antimicrobial therapy

Antimicrobial stewardship focuses on the five 'D's:

- Diagnosis: Correct diagnosis and source of infection
- Drug: Correct choice of antimicrobial agent
- Dose: Correct dose with respect to the glomerular filtration rate, site of infection, body weight etc.
- De-escalation of therapy: From broad spectrum to narrow spectrum therapy as per the available culture or genotypic reports
- Discontinuation of therapy: Stopping antimicrobials after completing the duration of therapy as per evidence-based guidelines or when the infection is not confirmed, or an alternative non-infectious condition is diagnosed.

7. Dose optimization:

Optimization of antimicrobial dosing based on:

- Patient characteristics (e.g., weight, renal/liver function),
- Causative organism
- Site of infection (e.g., central nervous system, blood)
- Pharmacokinetic and pharmacodynamic characteristics of the drug (e.g., concentration or time-dependent activity)

- For example, Modifying Meropenem to 500 mg q24h when the patient is on hemodialysis.

8. De-escalation:

- Antimicrobial de-escalation (ADE) is defined as the discontinuation of one or more components of combination empirical therapy and/or the change from a broad-spectrum to a narrower-spectrum antimicrobial.
- It is most commonly recommended in the intensive care unit (ICU) patient who is treated with broad-spectrum antibiotics as a strategy to reduce the antimicrobial pressure of broad-spectrum empirical therapy and prevent antimicrobial resistance.
- For example, a patient with a suspected urinary tract infection on empirical meropenem grows extended-spectrum beta-lactamase-producing E. coli. Meropenem is changed to Ertapenem and is considered de-escalation as ertapenem has no coverage for *Pseudomonas spp*.

9. Redundant therapy

- Patients receiving treatment with overlapping antibiotic spectra for two or more consecutive days constitute redundant therapy. Redundant antibiotic combinations are a potentially remediable source of antibiotic overuse. Excessive antimicrobial use is an important contributor to drug resistance, treatment costs, and adverse effects.
- For covering anaerobic organisms, if metronidazole is administered along with piperacillin-tazobactam, then this is considered redundant therapy as both of them have adequate anaerobic coverage.

10. Days of therapy (DOT)

- The number of days a patient receives an antibiotic is independent of the dose.
- It is also independent of the frequency of dosing required per day for any antibiotic.
- For example, if piperacillin-tazobactam is used at a dose of 4.5 g q6h for five days and if ertapenem is used at 1g q24h for 5 days, then their DOT will be 5 days each irrespective of the difference in dosing and frequency.

11. Defined daily dose (DDD)

- It is the assumed average maintenance dose per day for an antimicrobial used for its main indication in adults, as established by the WHO Collaborating Centre for Drug Statistics and Methodology.
- The DDD is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose. Therapeutic doses for individual patients and patient groups will often differ from the DDD as they will be based on individual characteristics (such as age, weight, ethnic differences, type and severity of disease) and pharmacokinetic considerations.

- The DDD enables the comparison of drug usage between different drugs in the same group or between different healthcare environments or to look at trends in drug utilisation over time.
- The DDD is not to be confused with the therapeutic dose or prescribed daily dose (PDD), or recorded daily dose (RDD), and will often be different to the dose actually prescribed by a physician for an individual person.
- For example, a patient has been prescribed oral Amoxicillin 500 mg q8h for five days. A daily dose of amoxicillin taken by the patient is 1.5 g. DDD of Amoxicillin (WHO) is 1 g. So, the patient is taking 1.5/1 DDD = 1.5 DDD of amoxicillin daily. When he/she takes it for five days, the calculation stands at 1.5 DDD x 5 = 7.5 DDD of amoxicillin. This can be compared with other antibiotics.
- A major limitation of DDD is when a modified dose of the antimicrobial is used in view of renal or hepatic impairment, and the higher dose is administered targeting a specific site of infection.

12. IV-to-oral switch

- Most patients admitted to a hospital with severe infections are initially started with intravenous medications. The short intravenous course of therapy for 2–3 days, followed by oral medications for the remainder of the course, is found to be beneficial to many patients. The advent of newer, more potent or broad-spectrum oral agents that achieve higher and more consistent serum and tissue concentration has paved the way for the popularity of intravenous to oral medication conversion.
- Early switch over from IV to oral therapy has the following major advantages:
  - Reduced risk of cannula-related infections.
  - No Risk of thrombophlebitis.
  - Reduction in the hidden costs: Hidden costs mainly refer to the cost of diluents, equipment for administration, needles, syringes, and nursing time.
  - Earlier discharge from the hospital.
- There are mainly three types of IV to PO conversions:
  - *Sequential therapy*: Refers to the act of replacing a parenteral version of a medication with its oral counterpart of the same compound. For instance, conversion of inj. linezolid 600 mg q12h to tab linezolid 600 mg q12h
  - *Switch therapy*: Describes the conversion of an IV medication to a PO equivalent; within the same class and has the same level of potency but of a different compound. For example, switch over from inj. ceftriaxone 1 g q12h to tab cefixime 200 mg q12h.
  - *Step-down therapy* refers to the conversion from an injectable medication to an oral agent in another class or to a different medication within the same class where the frequency, dose, and spectrum of activity may not be exactly the same. For example, conversion of inj. Cefotaxime 1 g to tab ciprofloxacin 500 mg.
- Patient selection criteria for IV to oral switch over therapy
  - The patient is able to eat orally and tolerates oral feeds.

- Signs of resolving an infection.
- The absorption and bioavailability of oral formulation are almost comparable to that of the parenteral form.

13. Antibiotic timeout

- An antibiotic time-out (ATO) at 48–72 hours is a critical component of antimicrobial stewardship programs to improve judicious antibiotic use. It is a strategy to prompt clinicians to re-evaluate antibiotic appropriateness, including the need for de-escalation and discontinuation.

14. Therapeutic drug monitoring

- Therapeutic drug monitoring (TDM) is the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individual dosage regimens.
- It is used mainly for monitoring drugs with narrow therapeutic ranges, drugs with marked pharmacokinetic variability, medications for which target concentrations are difficult to monitor, and drugs that are known to cause therapeutic and adverse effects.
- TDM helps in the individualization of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range or window. By combining knowledge of pharmaceutics, pharmacokinetics, and pharmacodynamics, TDM enables the assessment of the efficacy and safety of a particular medication in various clinical settings.
- Example: TDM needs to be done for voriconazole, posaconazole, vancomycin etc.

15. Antibiotic cycling

- Antibiotic cycling refers to the scheduled rotation of antibiotics with similar spectrums of activity, with a return to the original antibiotic after a defined period and re-initiation of the rotation.
- The basic premise of this intervention is that during periods when an antibiotic is out of rotation, resistance to that agent declines because of reduced selective pressure on that antibiotic class

16. Bug-drug mismatch:

- "Bug-drug mismatch" refers to a situation in which the antimicrobial(s) a patient is receiving do(es) not provide adequate therapy (e.g., is resistant) for the microbiologically identified organism presumed to be causing the clinical infection.
- For example, culture and susceptibility results of drainage from an intra-abdominal abscess may isolate Klebsiella sp. resistant to piperacillin/tazobactam in a patient empirically started on piperacillin/tazobactam for intraabdominal infection. Or a patient may be receiving intravenous levofloxacin for pyelonephritis, with Escherichia coli resistant to levofloxacin cultured from the blood and urine.

CHAPTER

3

Availability of diagnostic tests for common infectious diseases syndromes in India

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Q1. What is a syndromic approach in infectious diseases, and why is it important?

Infectious diseases are caused by micro-organisms, namely- bacteria, fungi, viruses and parasites. Different organ systems' involvement leads to different clinical presentations and variable organisms causing it. Therefore, in order to identify a particular causative organism, it is practical to use the syndromic approach as it saves money and resources along with providing rapid, relevant results and thus promoting appropriate prescription of antimicrobials.

Q2. What are the different syndromes in infectious diseases?

The common syndromes (based on the organ system involved) includes-1. Meningitis/ Meningo-encephalitis;2. Pneumonia (lower respiratory tract infection); 3. Diarrhoea; 4. Urinary tract infection (UTI); 5. Sexually transmitted infections (STIs); 6. Acute Undifferentiated acute febrile illness (AFI) & 7. Bloodstream-related infections (BSI).

Q3. What conventional (routine) investigations are available in our country based on the syndromic approach?

There are conventional tests which are important in daily practice and are economical as well as sensitive. The syndromic approach includes-

1. **Meningitis/Encephalitis syndrome**
   A. CSF
   - Direct staining: Gram, AFB, KOH & India ink stain.
   - Antigen detection: By ICT (especially capsulated organisms, ex.- Cryptococcus neoformans)
   - Serology by ELISA, especially Japanese encephalitis and measles.
   - Culture & antimicrobial sensitivity testing (AST)

   B. Serum: Automated methods such as ELFA and CLIA(especially useful for dengue IgM/ IgG etc.)
   C. Blood: Culture and antimicrobial sensitivity testing (AST)
   D. Urinary antigen detection for Streptococcus pneumonia
   E. Viral isolation by culture.

2. **Pneumonia**
   a. Sputum/ BAL/TA/Pleural fluid:
   - Microscopy- Gram, ZN, GMS &KOH
   - Culture & antimicrobial sensitivity testing (AST)

   b. Blood- Serology for antibody & Antigen detection(by ICT & ELISA, ELFA, CLIA)
   c. Viral isolation

3. **Diarrhoea: for a stool sample**
   a. Naked eye examination(Colour- ex. Green in Giardia infection, consistency- rice watery in Vibrio cholerae, Mucus- in Entamoeba histolytica etc.)
   b. Microscopy
   - Wet mounts preparation (especially for detection of parasitic ova and cysts)
   - Hanging drop preparation (to demonstrate darting motility of Vibrio cholerae)
   - Gram-stained smear (typically in the case of Vibrio cholerae, candida species)
   - Modified acid-fast staining (Oocyst of cryptosporidium, isospora and cystoisospora)

   c. Culture & antimicrobial sensitivity testing (AST) (to look for Salmonella, Shigella and Vibrio species)
   d. Antigen detection (esp. *Clostridium. difficle*)

4. **UTI**
   a. Urine microscopy, leukocyte esterase & nitrite reductase test
   b. Gram stain(to rule out contamination by comparing pus and epithelial cells per HPF), AFB stain
   c. Culture & antimicrobial sensitivity testing (AST)

5. **STI**
   A. Pus/discharge sample-

a. Microscopy
   - Wet mount examination- carried out from vaginal discharge in case of Trichomoniasis and candidiasis
   - Gram-stained smear- useful for bacterial vaginosis (Clue cells), gonorrhoea (intracellular Gram-negative cocci) and candidiasis(Budding yeast-like cells)
   - Giemsa stain- done for Klebsiella granulomatis and chlamydia trachomatis
   - Dark field microscopy and silver impregnation methods- in syphilis

b. Culture & antimicrobial sensitivity testing (AST)

B. Serum sample- Serology for syphilis as VDRL/ FTA-ABS, Chlamydia IgM/IgG by ELISA, ELFA, CLIA (useful for HSV antibody detection)

6. **Bloodstream-related infections (BSI)**

A. Culture & antimicrobial sensitivity testing (AST) (Three sets of blood samples from two different sites to confirm pathogen and rule out contamination)

a. Automated blood culture: BactAlert 3d (for rapid detection of the pathogen in blood culture bottle), MALDI-TOF, VITEK

b. Automated serological methods: ELFA, CLIA (for antigen, antibody detection)

c. Molecular test: RT-PCR, BioFire FilmArray

Supportive tests: - serum Procalcitonin
   - Serum Galactomanon

B. Viral markers- HIV, Hepatitis B, Hepatitis C (ICT, ELISA)

7. **Acute undifferentiated febrile illness (AFI)**

Blood
   - microscopy- detection of malarial parasites, microfilariae, Leishmania donavani (HIV infected).
   - Culture & AST: for typhoid fever & brucellosis

A. Serological tests
   - Antibody detection by ELISA and rapid test- for scrub typhus, typhoid, dengue, leptospirosis, viral diseases such as hepatitis, HIV, CMV, EBV infections etc
   - Standard agglutination test- for brucellosis
   - Microscopic agglutination test- for leptospirosis
   - Cold agglutination test- for mycoplasma
   - Weil Felix test- for rickettsial diseases
   - Paul-Bunnell test- for infectious mononucleosis
   - Widal test- for enteric fever
   - Complement fixation test- for chlamydial infections

Q4. What are the recent advancements in the diagnosis of infectious diseases, especially with regard to the syndromic approach?

Over the last two decades, infectious disease diagnostics has seen a major reform. It has focused on increasing the sensitivity and specificity for detection, lower turn around time and a wider array of organisms with their antimicrobial sensitivity. This has enabled us to make a fast diagnosis and appropriate treatment without or minimally exposing the patients to unrequired antimicrobials. A few of such tests being increasingly used include- RT-PCR, multiplex PCR, MALDI-TOF (matrix-assisted laser desorption ionization-time of flight mass spectrometry) and NAAT (Nucleic acid amplification test) detection, e.g. TruNAAT being used in tuberculosis and COVID-19. Multiplex PCR or molecular assay currently being utilised as syndromic approach testing have combined multiple pathogens and resistance genes into a single test, thereby decreasing the turnover time as well as providing a pin-point organism and its resistance pattern. Whereas RT-PCR, MADI-TOF and NAAT provide information about 1 organism at a time. Multiplex PCR is commonly involved in diagnosing CNS, gastrointestinal, respiratory and bloodstream infection syndrome.

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CHAPTER

4 Introduction to different guidelines in the management of infectious diseases

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1. What is the spectrum of infectious disease guidelines?

Ans: Infectious diseases centre around the agent, host, and environment triad. The exposure of the susceptible host to the agent in a favourable environment causes the disease. Like any other disease, human intervention can prevent infectious diseases by breaking the triad at any level or can alter the normal course of the disease by treating the disease. The appropriate treatment of an infectious disease needs appropriate diagnostic tools.
Thus the spectrum can be classified broadly as preventive, diagnostic, and therapeutic guidelines. The guidelines are dynamic and change as per the availability of new evidence.

2. What are the aims of the guidelines:

Ans: The aims of the guidelines are:

1. To improve the quality and appropriateness of care.
2. To improve the cost-effectiveness of interventions.
3. To serve as educational guidance tools.
4. To identify pertinent research directions.

The preventive guidelines aim to mitigate the exposure to the agent, reduce the susceptibility of the host or modify the environment depending on the nature of the disease. Preventive guidelines for community-acquired infections, as well as hospital-acquired infections, are available. These

guidelines prevent the acquisition of the disease in an individual or in a mass on exposure to the agent, like pre and post-exposure prophylaxis and vaccination, respectively.

The diagnostic guidelines help to choose the most appropriate tools as per their sensitivity, specificity, availability, and cost-effectiveness, depending on whether the tool is being used for screening or confirmation of diagnosis.

The therapeutic guidelines are based on best-quality evidence that helps to choose the most appropriate therapy available, maintain uniformity of therapy and improve the quality of care provided to patients. This reduces the irrational use of antimicrobial agents, thereby decreasing antimicrobial resistance and collateral damage.

3. Who makes the guideline?

Ans: There are different national and international societies, organisations, and councils to formulate the guidelines as per available evidence. E.g., the National Centre for Disease Control (NCDC), the Indian Council of Medical Research (ICMR), the Infectious diseases society of America (IDSA), World Health Organisation (WHO).

State Health Ministry can have guidelines per the logistics and disease burden commensurate with the national and global guidelines.

4. How are the guidelines formed?

Ans: The guidelines are based on available best-quality evidence. The cornerstone of evidence-based medicine (EBM) is the classification of the evidence as per hierarchy. Multiple well-designed, blinded, randomised controlled trials (RCT) and systematic reviews (e.g., Cochrane review) provide high-quality evidence.

The scheme of formulation of the guideline is as follows:

Figure 1:The scheme of formulation of guideline

PICO= Patient, Intervention, Comparison, and Outcome.

The majority of the guidelines are in recommendation format as per the strength of the available evidence. The GRADE working group grades the evidence, and thereby guidelines are made by the expert panellists.

5. What is the GRADE recommendation?

Ans: The Grades of Recommendation, Assessment, Development, and Evaluation Working Group (GRADE Working Group) has developed a system for grading the quality of evidence. The GRADE approach specifies four levels of quality of evidence as per the methodology used (table 1). Many guideline working groups have accepted GRADE recommendations.

Table 1. Categories of quality of a body of evidence in the GRADE approach.

Underlying methodology	Quality rating
Randomized trials; or double-upgraded observational studies.	High (++++)
Downgraded randomized trials; or upgraded observational studies.	Moderate (+++)
Double-downgraded randomized trials; or observational studies.	Low(++)
Triple-downgraded randomized trials downgraded observational studies; or case series/case reports.	Very low(+)

6. What are the levels of evidence and classes of recommendations:

Ans:

Level of evidence	
Level A	Data derived from multiple randomized clinical trials
Level B	Data derived from a single randomized trial or nonrandomized studies.
Level C	The consensus opinion of experts.
Classes of recommendations	
Class I	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. IIa. The weight of evidence/opinion is in favour of usefulness/efficacy. IIb. Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/ effective and, in some cases, may be harmful.

7. What are the major international and national guidelines for infectious diseases available?

Ans:

Preventive guidelines	National	International
Community-acquired infection	• Indian Council of Medical Research(ICMR) Guideline • National vector-borne diseases control programme (NVBDCP) guideline	• World Health Organisation (WHO) guidelines. • Infectious diseases society of America (IDSA) guideline
Hospital-acquired infection	• ICMR guideline • NCDC guideline(National Treatment Guideline for Antimicrobial use in Infectious Diseases)	• Centre for Diseases Prevention and Control (CDC) /IDSA guideline • Society for Hospital Epidemiology of America (SHEA) guideline
Vertical transmission prevention	• Prevention of parent-to-child transmission (PPTCT) of HIV guideline by the National AIDS control programme (NACO)	• WHO guideline of PPTCT in HIV • CDC guideline
Diagnostic/ Therapeutic guidelines	• ICMR guideline • Standard Operating Procedures for Fungal Identification and Detection of Antifungal Resistance (ICMR)	• WHO guideline • IDSA clinical practice guidelines for infectious diseases
Specific antimicrobial	• Nil	• International consensus guidelines for the optimal use of polymyxins (Endorsed by ACCP, ESCMID, IDSA, ISAP, SCCM, SIDP • Vancomycin guideline IDSA
Major clinical syndrome based	• NCDC guideline(National Treatment Guideline for Antimicrobial use in Infectious Diseases) • ICMR guideline	• WHO guideline • IDSA guideline • British infection association (BIA) guideline
Sepsis	• ICMR guideline • NCDC guideline(National Treatment Guideline for Antimicrobial use in Infectious Diseases)	• IDSA guideline • Surviving Sepsis Campaign Guidelines
Diseases/microorganism based	• ICMR guideline	• IDSA guideline

Bacteria		
Tuberculosis	• Guideline by the central TB division under National Tuberculosis Elimination Programme (NTEP) • Index TB guideline for extrapulmonary TB	• WHO guideline • IDSA guideline
Non-tuberculous mycobacterial diseases (NTM)	• Nil	• IDSA • British Thoracic Society(BTS) • American Thoracic Society (ATS) clinical practice guideline. • ATS/ERS/ESCMID/IDSA guideline (Pu • ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases
Multidrug-resistant organisms (MDRO)	• ICMR guideline	• IDSA guideline • European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli
Virus		
HIV	• NACO guideline	• WHO • IDSA/HIV Medicine Association • The Department of Health and Human Services (DHHS) guideline • BHIVA (British HIV Association) guideline
Hepatitis B and Hepatitis C	• National Viral Hepatitis Control Program (NVHCP) guideline	• The European Association of Study of the Liver (EASL) guideline. • American Association for the Study of Liver Diseases (AASLD) • IDSA guideline • WHO guideline
Fungus		
Candidiasis	• ICMR guidelines for candida auris infection treatment and management	• IDSA guideline • European Organization for Research and Treatment of Cancer (EORTC) and Mycoses Study Group (MSG) guidelines

Invasive fungal infections	• Nil	• IDSA guideline • European Organization for Research and Treatment of Cancer (EORTC) and Mycoses Study Group (MSG) guidelines.
Specific fungal infection	• Nil	• European Conference on Infections in Leukemia (ECIL) guideline • Global guideline for the diagnosis and management of mucormycosis: an initiative of the ECMM in cooperation with MSG and Research Consortium. • ESCMID-ECMM-ERS guideline for the management of aspergillus diseases.
Parasite	• National vector-borne diseases control and prevention (NVBDCP) guidelines for malaria, filaria • ICMR guideline	• CDC guideline • Prevention and control of parasitic intestinal infections: WHO
Vector-borne diseases	• NVBDCP	• CDC guideline
Sexually transmitted diseases	• National RTI/STI prevention and management guideline by NACO	• WHO guideline • CDC guideline
Infections in hematopoietic stem cell transplant recipients	• Nil	• ECIL guideline • CDC
Infections in solid organ transplant recipients	• Nil	• American Society of Transplantation Infectious Diseases Community of a Practice guideline.
Vaccination guidelines	• ICMR guideline	• CDC: Advisory Committee on Immunization Practices (ACIP) guideline • WHO guideline

American College of Clinical Pharmacy (ACCP), European Confederation of Medical Mycology in cooperation (ECMM); European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA); International Society for Antiinfective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), Society of Infectious Diseases Pharmacists (SIDP)

8. What are the principles of rational antibiotic use?

Ans:

Step 1: Making a clinical diagnosis
Step 2: Limiting empiric antibiotic therapy
Step 3: Know your bugs
Step 4: Choose the appropriate antibiotic
Step 5: De-escalation/modification
Step 6: Stop antibiotics in the appropriate clinical situations
Step 7: Reduce the duration of therapy
Step 8: Optimize pharmacokinetic and pharmacodynamics (PK-PD) parameters

9. What are the clinical situations where antibiotics should be stopped?

Ans:

I. Respiratory tract syndromes
- Viral pharyngitis
- Viral rhinosinusitis
- Viral bronchitis
- Non-infectious cardio-pulmonary syndromes misdiagnosed as pneumonia

II. Skin and Soft Tissue Infections
- Subcutaneous abscesses
- Lower extremity stasis dermatitis

III. Asymptomatic bacteriuria and pyuria, including in catheterized patients
IV. Microbial colonization and culture contamination
V. Low-grade fever

10. What are the recommended durations of antibiotics for specific clinical syndromes?

Ans:

Clinical Syndromes	Duration of antibiotics
Community-acquired pneumonia	5 days
Hospital-acquired pneumonia	8 days
Skin and Soft tissue infections	5 days
Urinary tract infections	

Cystitis Pyelonephritis Catheter-associated	3-5 days 5-14 days 7 days
Staphylococcal aureus bacteremia	
Low risk of complications High risk of complications	2 weeks 4-6 weeks
Intra-abdominal infection	4-7 days
Surgical antibiotic prophylaxis	1 dose

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CHAPTER

5

Outcome Measures of the Antimicrobial Stewardship Programme (AMSP)

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Implementation of a stewardship programme in any healthcare setting should be followed by monitoring some parameters at specific intervals, collectively known as outcome measures of an antimicrobial stewardship programme. These measures help authorities or stakeholders to determine whether the existing protocol is working in a pre-defined direction or if any amendments need to be made for the successful outcome of the programme.

1. What are the program measures which are commonly used?

Ans: Broadly divided into four groups:

a) Structural measures
b) Process measures
c) Outcome measures
d) Balancing measures

2. What are the structural measures of AMSP?

Ans:

i) Availability of a multi-disciplinary antimicrobial stewardship team
A decade ago, only a very few hospitals in the country had multidisciplinary AMS teams. The situation has changed now. The NABH has made it mandatory for all hospitals to have

an AMS team to be eligible for accreditation. Hence most tertiary care centres in the country have AMS teams. However, the quality of the functioning of these teams is not yet uniform.

ii) Availability of guidelines for empiric treatment and surgical prophylaxis
Ministry of Health and Family Welfare, as well as ICMR and several medical societies, have published guidelines on empirical antibiotic choice in common ailments as well as surgical prophylaxis, which is being updated from time to time.

1	Treatment Guidelines for Antimicrobial Use in Common Syndromes	ICMR, 2019
2	National Treatment Guidelines for Antimicrobial Use in Infectious Diseases(NCDC)	Version 1.0 (2016), MoH&FW, GOI
3	Guidance on Diagnosis & Management of Carbapenem-Resistant Gram-negative Infections	ICMR, March 2022
4	Hospital infection control guideline	ICMR
5	National Guideline for Infection Prevention and Control in Healthcare Facilities	NCDC, MoH&FW Jan 2020

iii) Provision of education
Educating practising physicians about the ill effects of the irrational and rampant use of antibiotics should be an ongoing process.

3. What are the process measures?

Ans:

i) Amount of antibiotic in *Defined daily doses(DDD)*/100 bed days.
Example: If the total number of Meropenem used in 1 month is 500 and the total inpatients days is 1000 in the last month, then DDD = (500/1000 X 100) days.

This can be used to compare the consumption of any antibiotic pre and post-AMSP implementation.

ii) Compliance with an empiric guidance document.
iii) Percentage of appropriate de-escalation.
iv) Percentage of the appropriate switch from IV to oral.
v) Compliance with surgical prophylaxis.
vi) Compliance with care bundles.

4. What are outcome measures?

Ans:

i) C. difficile rates: Clostridioides difficile infection (CDI) is transmitted via the faecal-oral route and is implicated in antibiotic-associated colitis. It is an important indicator of antibiotic usage, most importantly the high-end ones. It is calculated as:

CDI rate= Total number of CDI over a duration/Total inpatients days over that duration x 1000

ii) Surgical site infection: A surgical site infection (SSI) is an infection that occurs after surgery in the part of the body where the surgery took place. Surgical site infections can sometimes be superficial infections involving the skin only. Other surgical site infections are more serious and can involve tissues under the skin, organs, or implanted material.

Symptoms include:

- Redness and pain around the area where you had surgery
- Drainage of cloudy fluid from your surgical wound
- Fever

Criteria for defining a surgical site infection

	Degree of involvement	Onset	Criteria
Superficial incisional SSI	Skin and subcutaneous tissue	Within thirty days of the procedure	One or more ➢ Purulent drainage ➢ Positive aseptically obtained culture of fluid or tissue ➢ Pain, tenderness, swelling, erythema ➢ Diagnosis by a surgeon or physician
Deep incisional SSI	Deep soft tissue	30-90 days of the procedure	One criterion ➢ Purulent drainage from the deep incision but not organ space ➢ Spontaneous dehiscence with a positive culture or culture negative but has fever or pain at the site ➢ Deep incision abscess ➢ Diagnosis by a surgeon or physician
Organ/ space SSI	Any part opened during the operative procedure except skin/ fascia/muscle	30-90 days	One criterion ➢ Purulent drainage from a drain into organ space ➢ Positive culture ➢ Evidence of infection by direct examination

iii) Surveillance of resistance

ICMR conducts nationwide surveys from time to time in order to update the information regarding antimicrobial resistance patterns in the country. The most recent document was the Annual Report: Antimicrobial Resistance Surveillance and Research Network, January 2021 to December 2021.

Similar surveillance is to be done at individual hospital levels from time to time in order to improve stewardship practices.

iv) Mortality: The total number of deaths due to infection is a very crucial indicator after the implementation of stewardship practices. The striking reduction in infection-related mortality suggests a successful AMSP program.

5. What are balancing measures?

i) Mortality
ii) SSI rates
iii) Re-admission within thirty days of discharge: It is a measure of healthcare-associated infection. The chances of infection with a multidrug-resistant (MDR) pathogen are very high in such cases and directly lead to poorer patient outcomes
iv) Admission to ICU
v) Rate of complications
vi) Treatment-related toxicity: Stewardship practices helps in identifying adverse drug reaction (ADR) to certain antibiotics which are otherwise ignored or underreported. Rare ADRs can also be identified, especially the newer antimicrobials.

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CHAPTER

6

Pediatric AMSP

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What are the important drivers of antibiotic prescribing in children in the community?

The majority of paediatric antibiotic prescriptions happen in the community, and the reasons include the following.

1. The belief is that children of all age groups are equally vulnerable and susceptible to serious infections if not treated with antibiotics promptly.

Newborns and children under three months of age are particularly vulnerable to serious bacterial infections and should be managed as such. The aetiology in most early childhood infections is viral, and young children rarely develop suppurative complications like quinsy or mastoiditis.

2. Improper understanding of the aetiology of childhood infections.

The aetiology of childhood infections is significantly different from adults, with most infections being caused by respiratory or gastrointestinal viruses, *Streptococcus pneumoniae*, *H.influenza*e and in India, also includes common tropical infections like dengue, malaria, enteric fever and rickettsial infections. *Shigella* and EIEC (Enteroinvasive *E. coli*) are common causes of childhood dysentery, and amoebiasis is fairly uncommon in children. However, most children with dysentery are prescribed fixed drug combinations with fluoroquinolones and metronidazole, which are likely to be ineffective drugs in this condition. Children are less likely to have significant co-morbid illnesses, unlike adults and hence, less likely to have hospital exposures leading to colonisation by resistant bugs.

Hence, a lack of knowledge of standard treatment guidelines or expertise in dealing with children can contribute to a lot of antibiotic prescribing, especially in community-based settings.

3. Lack of protective factors like breastfeeding and childhood immunizations.

Breastfed infants are protected by the maternal antibodies and protective factors in breast milk against acute diarrhoeal and respiratory infections in particular. Hence, they are less likely to present to doctors' offices, and this protective effect has been shown to last even up to six years. On the contrary, formula feeding has been shown to be associated with higher antibiotic prescriptions.

Vaccines are an important tool in the fight against antimicrobial resistance. While DTP, Measles and MMR vaccines have helped to significantly reduce disease burden and associated morbidity, the introduction of protein conjugate vaccines like pneumococcal and H. Influenza (type B) vaccines and rotavirus vaccine in the national immunisation schedule has shown to further decrease rates of serious childhood infections by these pathogens significantly.

4. Perceived parental expectations regarding antibiotics.

Having a shared decision-making approach with parents is likely to lead to fewer antibiotic prescriptions. Parents often need reassurance after a consultation that the child's symptoms are not indicative of a serious infection. Delayed prescribing, where parents can collect antibiotics if the child's symptoms do not improve in seventy-two hours, has been shown to reduce antibiotic prescription by 80%. Parents often understand, when explained to, that antibiotics are often not required in common infections and may do a lot more harm in the long run.

What are the major issues with antibiotic prescribing in hospital settings?

1. Most children admitted to hospitals for viral infections like bronchiolitis, viral triggered wheeze, and diarrhoeal illness get parenteral broad-spectrum antibiotics like third-generation cephalosporins.
2. Neonates and young children (< 3 months of age) present a unique challenge as they often have non-specific clinical presentations, even in serious infections like sepsis and meningitis. The ESBL (extended-spectrum beta-lactamase) prevalence among gram-negative organisms in the community determines the choice of empirical antibiotics in this group of children at first presentation, but often unit policies fail to address this issue.
3. Children can get hospital-acquired infections much like adults, but often paediatric-specific data on the epidemiology of these infections and management guidelines are sparse. Much of the data and guidelines are extrapolated from adult studies.

4. Biomarkers like CRP and PCT are often used indiscriminately though they often fail to differentiate bacterial from viral infections or infectious from inflammatory conditions. While blood cultures lack sensitivity, the availability of reliable and cost-effective molecular diagnostics to reach a rapid identification of etiologic agents could play a major role in antibiotic stewardship.

What are the tools to evaluate antibiotic prescribing in children?

Days Of Therapy (DOT) is preferred over the Defined Daily Dose (DDD) in children due to the weight-based dose variation in children. Some useful metrics for benchmarking include:

- Total antibiotic use (DOT)
- Total parenteral antibiotic use (DOT)
- Total oral antibiotic use (DOT)
- Broad-spectrum parenteral antibiotic use (DOT)
- Combination parenteral antibiotic use (DOT)
- Antibiotic use for surgical prophylaxis (DOT)

Also, it is important that qualitative metrics like documentation of the reason for antimicrobial prescribing, adherence to standard treatment guidelines or hospital policy and appropriate dosing are also looked into.

How a paediatric antimicrobial stewardship team can help in a given setting?

1. Educate on the syndrome-based approach and standard treatment guidelines.
2. Help generate paediatric-specific microbiological surveillance data and its dissemination.
3. Guidance on appropriate diagnostic tests- what, when and how to do?
4. Develop antimicrobial dosing guidelines in children and neonates.
5. Monitor DOT and qualitative metrics to evaluate antimicrobial prescribing.

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Module: 4
Infection Control

CHAPTER

1

Hand Hygiene

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Effective hand hygiene is the single most important strategy in preventing healthcare-associated infections (HAIs). Ease of access to hand washing facilities (soap and water) and alcohol-based hand rubs can influence the transmission of HAIs.

Historical perspective on hand hygiene

Hand washing with soap and water has been used to improve personal hygiene for centuries. However, the link between hand washing and the spread of disease was only established in the mid-1800s.

Below is a summary of key historical events of relevance to hand hygiene and infection prevention and control:

- 1847: an Austrian doctor, **Ignaz Semmelweis**, is considered to be the first person who established that hospital-acquired diseases were transmitted via the hands of healthcare workers (HCWs).
- 1854-1856: Florence Nightingale champions hand hygiene in army hospitals during the Crimean War.
- 1980's: First national hand hygiene guidelines published in the USA.
- 2000: **Didier Pittet et al.** published a landmark study proving that a hand hygiene culture change program involving the introduction of alcohol-based hand rub, education of staff and hand hygiene promotion can significantly improve HCW hand hygiene compliance and, in turn, reduce HAIs.

- 2002: alcohol-based hand rub is defined as the gold standard of care for hand hygiene practices in healthcare settings, whereas hand washing is reserved for particular situations only.
- 2005: WHO released the Advanced Draft of the WHO Guidelines on Hand Hygiene in Health Care, based on the most extensive review of literature on hand hygiene in healthcare to date; in 2009, the final WHO Guidelines were released.
- 2009: Issuance of WHO Guidelines on Hand Hygiene in Health Care and launch of the global hand hygiene campaign Save Lives: Clean Your Hands and First World Hand Hygiene Day on 5 May, targeted at health care workers
- 2015: SDGs adopted by United Nations Member States. SDG Target 6.2 includes hygiene, with an indicator related to handwashing with soap
- 2019: Minimum requirements for infection prevention and control (IPC) programmes launched by WHO, with hand hygiene prominent
- 2020: The Hand Hygiene for All initiative launched by UNICEF, WHO and partners in response to the COVID-19 pandemic
- 2021: Launch of the first State of the World's Hand Hygiene report

Transmission of organisms by hands

Transmission of healthcare-associated organisms from one patient to another via healthcare workers (HCWs) hands requires five sequential steps:

1. Organisms are present on the patient's skin or have been shed onto inanimate objects immediately surrounding the patient
2. Organisms must be transferred to the hands of HCWs
3. Organisms must be capable of surviving for at least several minutes on HCWs' hands
4. Hand hygiene by the HCW must be inadequate or entirely omitted, or the agent used for hand hygiene must be inappropriate.
5. The contaminated hand or hands of the caregiver must come into direct contact with another patient or with an inanimate object that will come into direct contact with the patient.

Healthcare workers must perform hand hygiene before and after every patient contact to prevent patients from becoming colonised with healthcare-associated organisms from other patients and the hospital environment. Emphasis must also be placed on preventing the transfer of organisms from a contaminated body site to a clean body site during patient care. Hand hygiene should also be performed after contact with inanimate objects, including medical charts and equipment in the immediate vicinity of the patient.

The Five Moments for Hand Hygiene

The Five Moments for Hand Hygiene, developed by the World Health Organization, is based on a theoretical model of how infectious agents can be transferred between an HCW and a patient.

It is inclusive of all occasions where a patient's safety can be endangered by the care provided by an HCW, where opportunity exists for the transfer of infectious agents between the HCW, patient and the healthcare environment.

This approach recommends that healthcare workers clean their hands ((Figure 1).

Moment 1: before touching a patient,
Moment 2: before clean/aseptic procedures,
Moment 3: after body fluid exposure/risk,
Moment 4: after touching a patient, and
Moment 5: after touching the patient's surroundings.

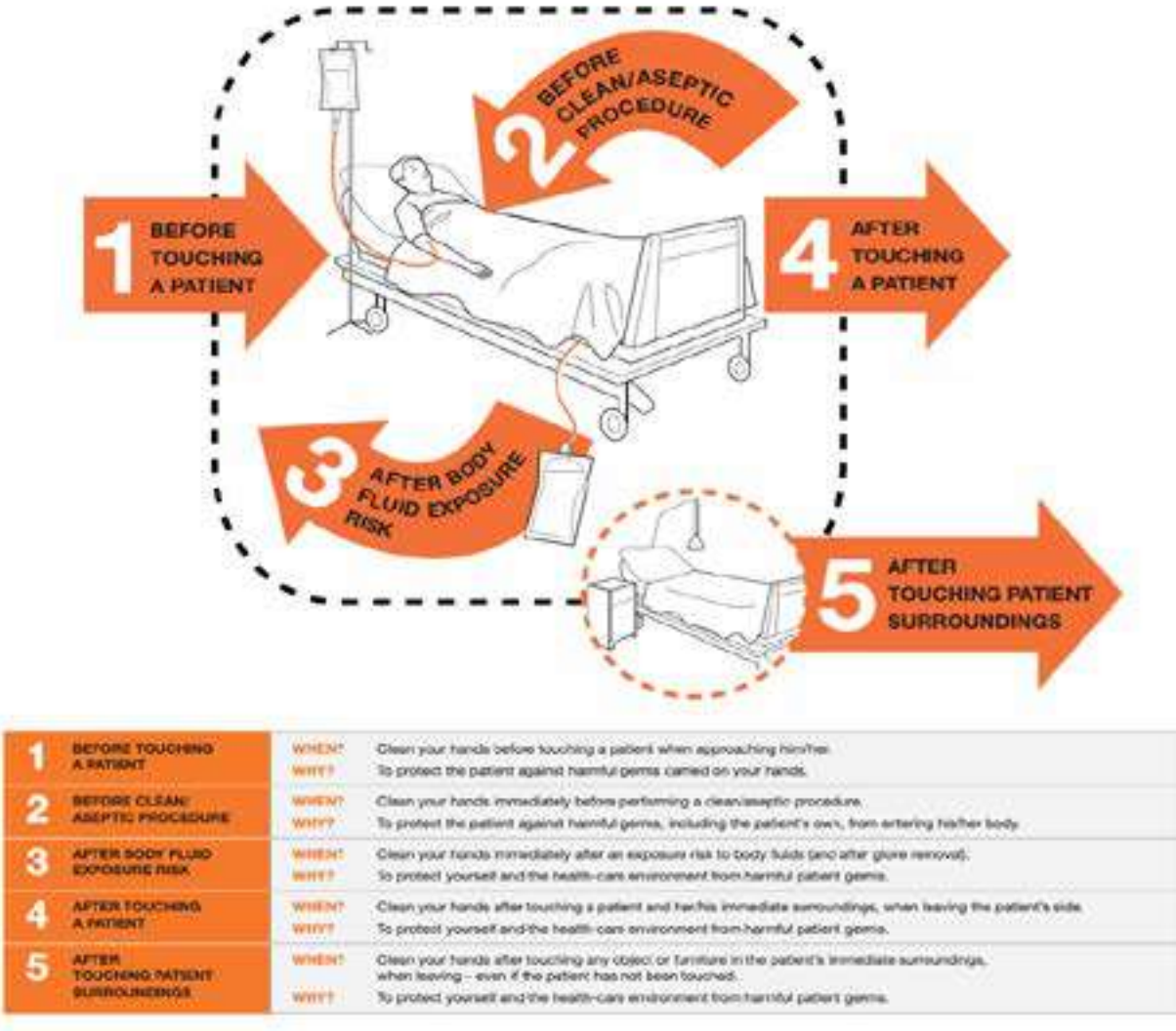


Figure 1: Moments for hand hygiene (WHO)

Technique

Effective hand hygiene relies on appropriate technique as much as on the selection of the correct product. The inappropriate technique can lead to the failure of hand hygiene measures to appropriately remove or kill microorganisms on hands, despite the superficial appearance of having complied with hand hygiene requirements.

Key factors in effective hand hygiene and maintaining skin integrity include

- The duration of hand hygiene measures.
- The exposure of all surfaces of hands and wrists to the preparation used.
- The use of rubbing to create friction.
- Ensuring that hands are completely dry.

Hand Hygiene methods:

There are three methods of Hand hygiene: hand rub, handwash and surgical hand scrub.

Figure 2: Steps of Hand rub (Source WHO)

Figure 3: Steps of Handwash (Source WHO)

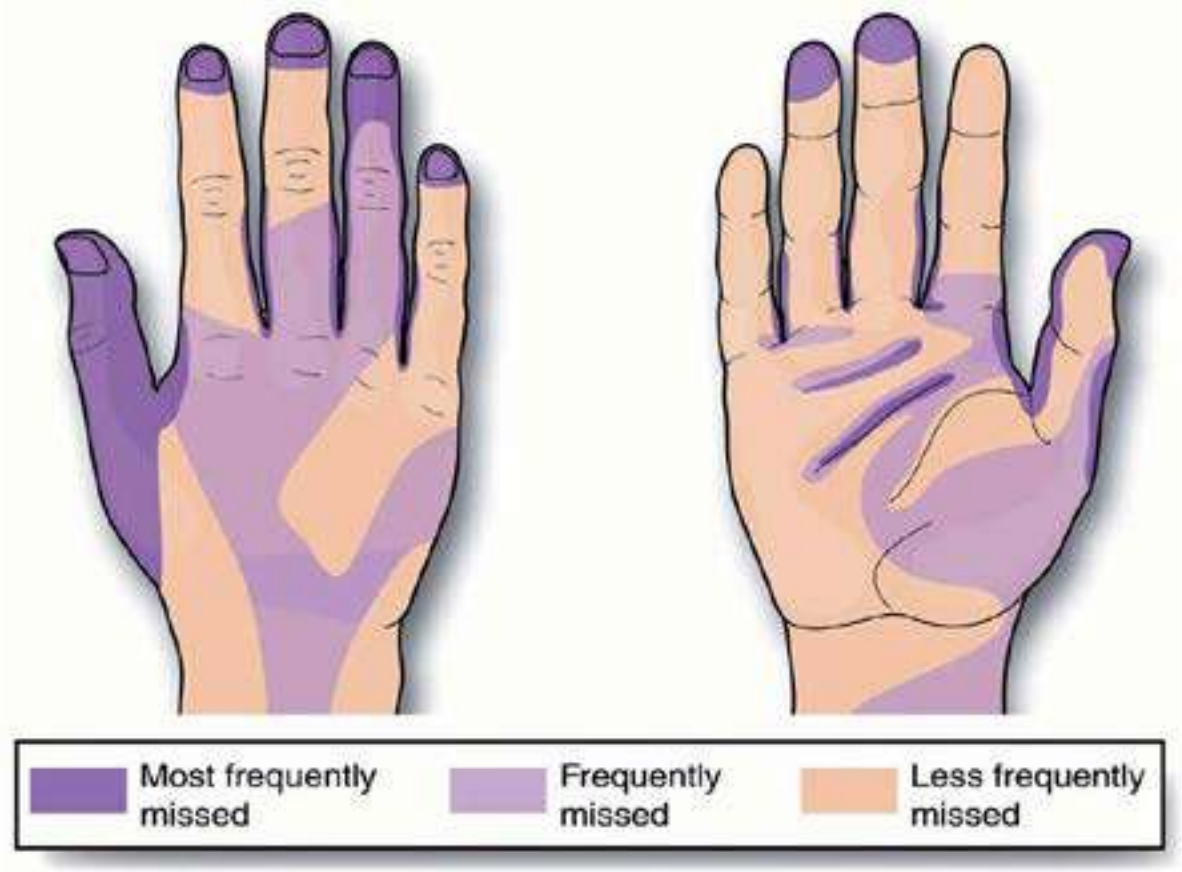


Figure 4: Areas of hand missed during hand hygiene.

Glove use

Inappropriate glove use often undermines efforts to sustain correct hand hygiene, according to the five Moments and has been shown to increase the risk of transmission of HAIs.

Wearing gloves does not replace the need for hand hygiene

Gloves do not provide complete protection against hand contamination. Microorganisms may gain access to the HCWs' hands via small defects in gloves or by contamination of the hands during glove removal. Microorganisms colonising patients may be recovered from the hands of approximately 30% of HCWs who wear gloves during patient contact. Gloves can protect both patients and HCWs from exposure to infectious agents that may be carried on hands.

As part of standard precautions single use gloves must be worn for:

- Contact with sterile sites and non-intact skin or mucous membranes.
- Any activity assessed as carrying a risk of exposure to blood, body substances, secretions and excretions.

CHAPTER

2

Healthcare-Associated Infection

Dr Yamunadevi VR

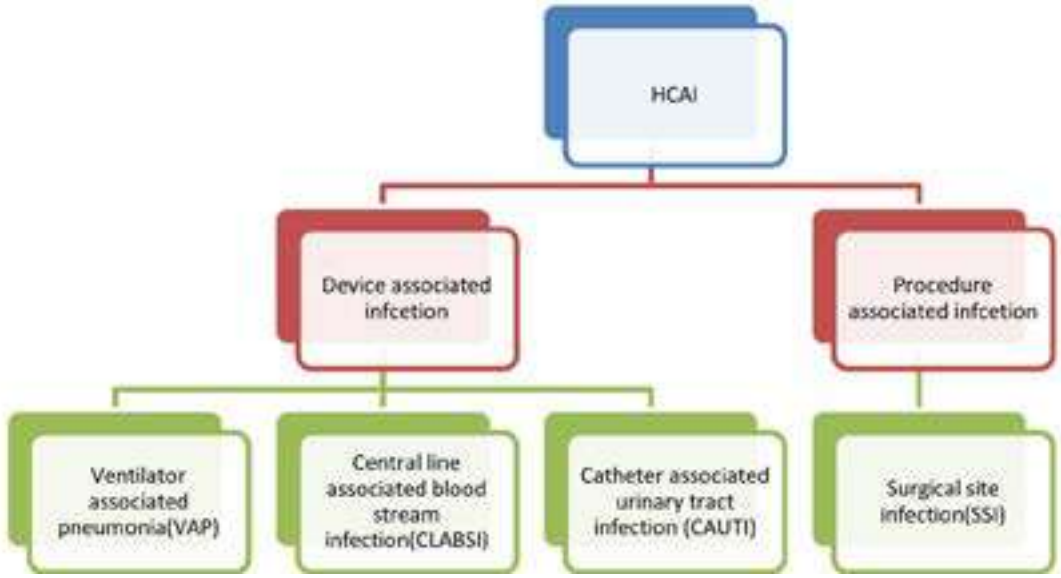
Introduction:

Healthcare-associated infections, or “nosocomial” and “hospital” infections, affect patients in a hospital or other healthcare facility and are not present or incubating at the time of admission. They also include infections acquired by patients in the hospital or facility but appearing after discharge and occupational infections among staff. Healthcare-associated infections (HAIs) are associated with increased morbidity and mortality and excess costs, and because a significant proportion of them are preventable, they are considered to be a marker of the quality of patient care. Continued improvements in patient safety depend on maintaining a comprehensive understanding of the epidemiology of healthcare-associated infections.

Many infections are caused by micro-organisms already present in or on the patient’s body. Such organisms only cause problems when the body’s defences are weakened or breached by surgery or other medical procedures.

Infections may also be caused by micro-organisms originating from another patient either by direct contact or through a contaminated hospital environment.

Major Types of HCAIs (Health care Associated Infections)



"If you cannot measure it, you cannot improve it."

Lord Kelvin

Epidemiology:

Healthcare-associated infections in high-income countries

- At any given time, the prevalence of healthcare-associated infection in developed countries varies between 3.5% and 12%. (Healthcare-associated infections FACT SHEET WHO)
- In 2016 and 2017, the ECDC coordinated point prevalence surveys to collect data on healthcare-associated infections (HAIs) in hospitals in EU/EEA countries, which showed a total of 8.8 million HAIs were estimated to occur each year in European hospitals
- In high-income countries, approximately 30% of patients in intensive care units (ICU) are affected by at least one healthcare-associated infection.

Healthcare-associated infections in middle and low-income countries

- At any given time, the prevalence of healthcare-associated infection varies between 5.7% and 19.1% in low- and middle-income countries
- The proportion of patients with ICU-acquired infection ranged from 4.4% to 88.9%, with a frequency of overall infections as high as 42.7 episodes per 1000 patient days.
- This is almost three times higher than in high-income countries.
- In the Asia-Pacific region, the risks of HAIs have been estimated to be 2–20 times higher than in developed countries, with up to 25% of hospitalized patients reported to have acquired infections.

- In 2006 a Multicenter prospective cohort surveillance of device-associated infection by the International Nosocomial Infection Control Consortium (INICC) in eight developing countries, including India, revealed an overall rate of 14.7% HAI corresponding to 22.5 infections per 1000 ICU days. In 2015 the INICC compilation data showed a reduction of device-associated infection by 70%.
- In 2007, the INICC conducted prospective surveillance in India to determine the rate of HAI. HAI rates in Indian ICUs against international standards. An overall HAI incidence rate of 4.4%, corresponding to 9.06 infections per 1000 ICU days, was reported.
- One of the studies published by our centre showed alarming incidence rates varying from 11% to 83% for different kinds of HAIs in India.

While urinary tract infection is the most frequent healthcare-associated infection in high-income countries, surgical site infection is the leading infection in settings with limited resources, affecting up to one-third of operated patients, up to nine times higher than in developed countries.

Risk factors:

Table 1: Risk associated with HCAI

S. no	HAI	Host related	Others
1.	**CAUTI**	older age, diabetes Females > males Immunosuppressive drugs	Catheterisation itself Duration of catheterization
2.	**CLABSI**	Males > females, Premature birth Parenteral nutrition, Neutropenia, infection at distal sites	Prolonged hospitalization before catheterization Duration of catheterization, Femoral > subclavian, Multi-lumen catheters, Skill of the inserter, Emergency > elective
3.	**VAP**	Older Age, Lung disease/ARDS, Immunosuppressant, Unconsciousness, Body position, Chest surgery	Re-intubation/prolonged intubation
4.	**SSI**	Extremes of age, morbid obesity, malnutrition, prolonged pre-operative stay, infection at distal sites, cancer, immunosuppression, ASA class > 3, diabetes mellitus, multiple transfusions, smoking, radiation treatment to surgical bed, multiple or repeat operations	the abdominal site, duration of surgery, hair removal with razors, improper choice of prophylactic antibiotics, surgeon's skill/ experience, poor hemostasis, use of drains, presence of dead space, hypothermia, tissue oxygenation, operating theatre/room traffic

Pathogenesis of CLABSI (Potential sources of infection of a Central line)

- Contaminated Catheter hub
  - Endogenous skin flora
  - Extrinsic (HCW hands)
- Insertion site
  - Skin Flora or Contaminated Disinfected or HCW Hands
- Contaminated Infusate
- Hematogenous (from distant infection)

Pathogenesis of CAUTI

Source of Micro-organisms

Endogenous (Meatal, Rectal or Vaginal)

Exogenous (usually contaminated hands of HCW during insertion or manipulation of collecting system)

Pathogenesis of Ventilator-associated Pneumonia

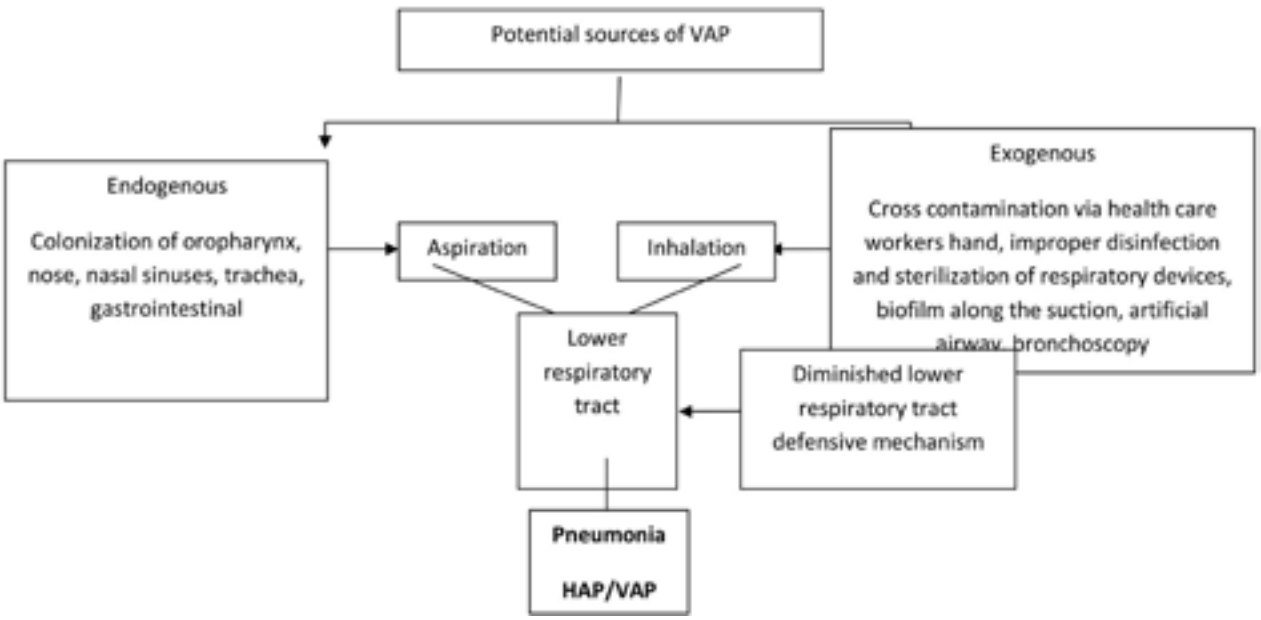


Figure3: Potential sources of infection in the ventilated patient

Pathogenesis of Surgical site infection

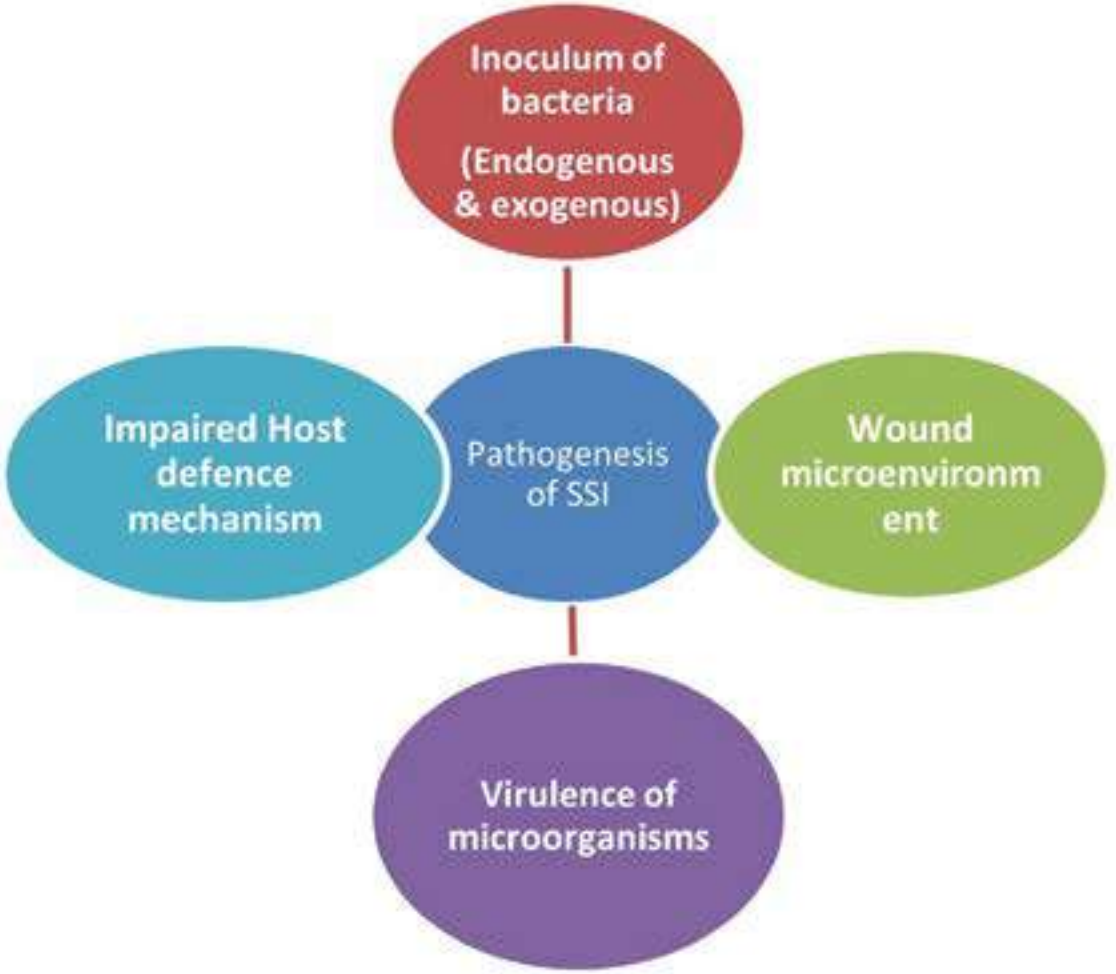


Figure4: Potential sources of SSI

Microbial Etiology:

Table 2: Distribution of microbial aetiology

S. no	HAI	Gram-positive organisms	Gram-negative organisms
1.	**CAUTI**	*Enterococcus sp*	*Escherichia coli* *Klebsiella (pneumoniae/oxytoca)* *Pseudomonas aeruginosa* *Other Enterobacteriaceae*
2.	**CLABSI**	*Staphylococcus aureus* *Coagulase-negative staphylococci,* *Enterococcus faecalis*	*Klebsiella (pneumoniae/oxytoca),* *Escherichia coli, Pseudomonas aeruginosa, Enterobacter sp,* *Acinetobacter sp, Serratia spp*
3.	**VAP**	**Early VAP** *Staphylococcus aureus* (Methicillin sensitive) **Late VAP** *Staphylococcus aureus* (Methicillin resistant)	**Early VAP** *Haemophilus influenza, Moraxella catarrhalis, non-resistant Klebsiella, Escherichia coli* **Late VAP** *Acinetobacter sp, Carbapenem resistant Klebsiella sp, Pseudomonas aeruginosa, Other Enterobacteriaceae*
4.	**SSI**	*Staphylococcus aureus* *Enterococcus faecalis (mostly abdominal surgeries)*	*Escherichia coli* *Klebsiella (pneumoniae/oxytoca)* *Pseudomonas aeruginosa* *Other Enterobacteriaceae*

Strategies to prevent infection:

Care bundle approach

Current strategies to prevent infection are based on the implementation of a ‘care bundle’. The care bundle approach was introduced by the Institute for Healthcare Improvement (IHI).

A care bundle is defined as the implementation of a set of evidence-based practices or interventions such that, when each element is executed individually, it improves the patient recovery process and outcomes; when all of the practices are executed together, they provide better outcomes than when implemented individually.

It helps the health care workers to remember and attribute the care in a systemic manner

1. CAUTI Bundle

Insertion Care Bundle
Hand hygiene Avoid unnecessary catheterisation or catheterise for appropriate indications Chose catheters of appropriate size Use sterile gloves, drape, and sponges; an antiseptic solution for cleaning the urethral meatus; and a sterile single-use packet of lubricant jelly for insertion Insert catheter using a strict aseptic non-touch technique Use a closed drainage system
Maintenance Care Bundle
Review the need for the catheter on a daily basis and remove the catheter promptly when no longer necessary Use an aseptic technique for daily catheter care (e.g., hand hygiene, sterile items/equipment, non-antiseptic solution) Maintain a closed drainage system Keep the catheter and collecting tube free from kinking. Keep the collecting bag below the level of the bladder at all times. Do not rest the bag on the floor. Keep unobstructed urine flow (If a urine specimen is required, take the specimen aseptically via the sampling port)
Appropriate indications for catheterization
Patient with acute and/or chronic urinary retention or bladder outlet obstruction Maintain a continuous outflow of urine for patients with voiding difficulties (as a result of neurological disorders that cause paralysis or loss of sensation affecting urination) Need for accurate measurements of urinary output in critically ill patients Peri-operative use for selected surgical procedures: • Patients undergoing urological surgery or other surgery on contiguous structures of the genitourinary tract • Anticipated prolonged duration of surgery (catheters inserted for this reason should be removed in the theatre recovery unit) • Patients anticipated receiving large-volume infusions or diuretics during surgery or need for intra-operative monitoring of urinary output To assist in the healing of open sacral or perineal wounds in selected incontinent patients The patient requiring prolonged immobilisation(e.g., potentially unstable thoracic or lumbar spine or multiple traumatic injuries such as pelvic fractures) To improve comfort for end-of-life care if needed

2. CLABSI Bundle

Insertion Care Bundle
Hand hygiene Maximal sterile barrier precautions (surgical mask, sterile gloves, cap, sterile gown, and large sterile drape). Skin cleaning with alcohol-based Chlorhexidine (rather than iodine). Avoidance of the femoral vein for central venous access in adult patients; use of subclavian rather than jugular veins. Use of a checklist and Use of ultrasound guidance for insertion of internal jugular lines if available Chlorhexidine-impregnated dressings with an FDA-cleared label to protect the insertion site of short-term, non-tunnelled central venous catheters.
Maintenance Care Bundle
Daily review of central line necessity. Prompt removal of unnecessary lines. Observe for evidence of infection, inflammation or pain at the site of insertion of the catheter, as well as mechanical problems with the catheter Scrub the hub, ports, connectors, etc., before using the catheter with 70% alcohol Replace dressings used on short-term CVC sites every seven days for transparent dressings Replace dressings used on short-term CVC sites every two days for gauze dressings. Replace administration sets not used for blood, blood products or lipids at intervals not longer than ninety-six hours Do not routinely replace Central venous catheters and haemodialysis catheters, or pulmonary artery catheters to prevent catheter-related infections.

3. VAP

Insertion Care Bundle
Use non-invasive positive pressure ventilation (NIPPV) whenever feasible Hand hygiene Clean Gloves(No need for sterile gloves) Use an aseptic technique during insertion(handling of the sterile endotracheal tube, bougie, laryngoscope blades Intubate with sub-glottic secretion drainage ports for patients likely to require greater than forty-eight or seventy-two hours of intubation
Maintenance Care Bundle
Hand hygiene **Daily assessment of the requirement of extubation** without contraindications Interrupt sedation once a day (spontaneous awakening and breathing trials) for patients without contraindications Elevate the head of the bed to thirty to forty-five degrees Intermittent or continuous drainage of sub-glottic secretions Change the ventilator circuit only if visibly soiled or malfunctioning Perform oral care with chlorhexidine

4. SSI

Pre-operative Care Bundle
Patient Education Avoid hair removal: use electric clippers if necessary Preoperative bathing with either plain soap or an antimicrobial soap Peri-operative intranasal applications of mupirocin 2% ointment with or without a combination of CHG body wash in patients undergoing cardiothoracic and orthopaedic surgery with known nasal carriage of *S. aureus* Glycemic control < 200 mg/dL in patients with and without diabetes Treat Remote Infection
Intra-operative Care Bundle
Surgical hand preparation by scrubbing with a suitable antimicrobial soap Administration of parenteral antibiotic prophylaxis within one hour before incision to maximize tissue concentration(surgical antibiotic prophylaxis) Surgical site skin preparation should be done with alcohol-based antiseptic solutions based on Chlorhexidine Maintain Peri-operative oxygenation Maintain Peri-operative normothermia Maintain Glycemic control < 200 mg/dL
Post-operative Care Bundle
Stop surgical antibiotic prophylaxis within twenty-four hours after surgery. Should not be continued even in the presence of a wound drain Maintain Peri-operative oxygenation Maintain peri-operative normothermia Maintain Glycemic control < 200 mg/dL

CHAPTER

3

Standard Precautions

Dr Rahul Garg

Standard precautions aim to protect both health workers and patients by reducing the risk of transmission of microorganisms from both recognized and unrecognized sources.

They are the minimum standard of infection prevention and control (IPC) practices that should be used by **all** healthcare workers, during the care of **all** patients, at **all** times, and in **all** settings. When applied consistently, **standard precautions** can prevent the transmission of microorganisms between patients, health workers and the environment.

Key elements of standard precautions include:

- Hand hygiene.
- Respiratory hygiene and cough etiquette.
- Patient placement.
- Personal protective equipment.
- Aseptic technique.
- Safe injections and sharps injury prevention.
- Environmental cleaning.
- Handling laundry and linen.
- Waste management.
- Decontamination and reprocessing of reusable patient care items and equipment.

Risk assessment

- Train health workers on early recognition and assessment of the risk of exposure to blood and body fluids – including secretions/excretions, splashes and/or sprays and contaminated surfaces.
- Train health workers on actions to reduce the risk of exposure to infectious agents.

- Perform a risk assessment within health care facilities related to the population they serve, the level of care they provide (including standard procedures) and available control measures and implement prevention measures and training based on this assessment.

TRANSMISSION BASED PRECAUTIONS

	Contact isolation	Airborne isolation	Droplet isolation
Definition	Intended to prevent transmission of infectious agents, including epidemiologically important microorganisms from patient	Intended to prevent transmission of pathogens that remain infectious over long distances when suspended in the air from respiratory secretions of the patient	Intended to prevent transmission of pathogens spread through close respiratory or mucous membrane contact with respiratory secretions from the patient
Mode of transmission	Direct or indirect contact with a patient or their environment	Inhalation of contaminated air with infectious particles	Inhalation of contaminated air with infectious particles, direct or indirect contact with a patient or their environment
Type of room	Private room with dedicated equipment No special ventilation	Private room with dedicated equipment Negative pressure room (-2.5 pascals) Visual air monitors	Private room with dedicated equipment No special ventilation
Personal protective equipment (PPE)	Gown, gloves Hand hygiene	N 95 mask Hand hygiene	Triple-layered mask, gloves Hand hygiene
Examples	CRE, VRE, MRSA, C.difficile, Candida auris, Carbepenem resistant Acinetobacter and Pseudomonas. Syndrome based isolation	Pulmonary, laryngeal, epiglottic, nasopharyngeal TB, Measles, Chickenpox and disseminated herpes zoster	Influenza, Rubella, Mumps, Group A streptococcal pharyngitis, Invasive N. meningitidis, Invasive H.influenza

CHAPTER

4 Personal Protective Equipment for Healthcare Personnel

Dr Rahul Garg

TYPES OF PPE USED IN HEALTHCARE

Gloves—Protect hands.
Gowns/Aprons—Protect skin and/or clothing.
Masks—Protect mouth/nose.
Respirators—Protect the respiratory tract from airborne infectious agents.
Goggles—Protect eyes.
Face shields—Protect the face, mouth, nose, and eyes.
Cap/Hair cover—To protect hairs.
Boots/Shoe cover—To protect feet.

HOW TO CHOOSE APPROPRIATE PPE

Selection of PPE is based on the type of patient interaction, known or possible infectious agents, and/ or likely mode (s) of transmission.

The following factors may be considered while choosing PPE:

- Probability of exposure to blood or body substances.
- Type of body substance involved.
- Probable type and probable route of transmission of infectious agents.

DO's AND DON'Ts WHILE USING PPE

- Always use PPE whenever blood or body fluids contact with patients is expected.
- Always use PPE most '**appropriate**' for the task.

Using PPE should not replace basic infection control procedures, like hand hygiene.

- Do not share the PPE.
- Avoid contact with contaminated (used) PPE and surfaces.
- Change the PPE completely and wash your hands each time you leave a patient to attend to another patient or another duty.
- Discard the used PPE inappropriate disposal bags.

Gloves

- Wear gloves when touching blood, body fluids, secretions, excretions or mucous membranes.
- Don't touch your face or adjust PPE with contaminated gloves.
- Don't touch environmental surfaces except as necessary during patient care.
- Change gloves:
  - During use, if torn and when heavily soiled.
  - Between contacts with different patients to prevent transmission of infectious material.
  - Between tasks/procedures on the same patient to prevent cross-contamination between different body sites.
  - If the patient interaction involves touching portable computer keyboards or other mobile equipment that is transported from room to room.
- Remove gloves immediately after use and before attending to another patient.
- Discard used/ contaminated gloves in the red colour waste bin.
- Perform hand hygiene by hand washing with soap and water or by alcohol-based hand rubs before and after removing gloves.

Masks

Masks are used to protect patients from the respiratory secretions of healthcare workers as well as to protect healthcare staff while caring for patients with airborne infections or when performing any procedures with anticipated splashes of blood or body fluids.

Do's and Don'ts of Wearing a Mask

- Surgical masks are preferred over cotton or gauze masks.
- Do not reuse disposable masks.
- Change masks whenever they are soiled or wet.
- Do not reapply the same mask after they have been removed.
- Masks should not be left dangling around the neck.
- Do not touch the mask from the front while wearing it.
- Use specifically designed masks for children, and their oxygen saturation should be monitored.

When to Use Surgical Mask

- Use surgical masks on coughing patients to limit the potential dissemination of respiratory pathogens.
- Use surgical masks as a part of standard precautions to keep splashes or sprays from reaching the mouth and nose of the person exposed.
- While caring for patients on droplet precautions.

Using N95 Respirator/Any Particulate Respirator

Indication for Use

When dealing with patients infected with highly transmissible respiratory pathogens while following droplet precautions (e.g. HCW dealing with open tuberculosis cases/influenza patients)

Wearing the Respirator

- Select a fit-tested respirator.
- Place over nose, mouth and chin.
- Fit a flexible nose piece over the nose bridge. Secure on the head with elastics.
- Adjust to fit.
- Perform a fit check.
    - Inhale—Respirator should collapse.
    - Exhale—Check for leakage around the face.

Removing the Respirator

- Always remove it just outside the patient's room. Lift the bottom elastic over your head first, then lift off the top elastic.
- Discard and perform hand hygiene.

For a better understanding of How to Don and Doff PPE, please scan the QR code from your smartphone (Source CDC YouTube channel)

(Demonstration of Donning (Putting On) Personal Protective Equipment (PPE)

Demonstration of Doffing (Taking Off) Personal Protective Equipment (PPE)

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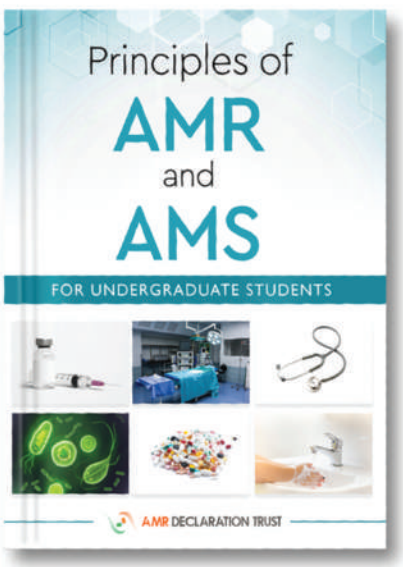
Principles of AMR and AMS

Antimicrobial resistance (AMR) is one of the biggest challenges the world faces today. In 2019 alone, 4·95 million deaths were estimated to be due to resistant bacterial infections. The burden of drug-resistant infections and associated morbidity and mortality remains high in low- and middle-income countries (LMICs), including India. Tackling AMR requires a multi-pronged approach; the education of our future doctors is one of those. This book covers all the fundamental aspects of AMR, AMS (Antimicrobial Stewardship) and IPC (Infection Prevention & Control). This book has been written in Q n A format so that students can grasp it quickly. It will form a foundation and familiarise students with day-to-day activities in this field.



This book has been prepared by practising Infectious Diseases (ID) physicians, clinical microbiologists and clinical ID pharmacists from all over India. This book is a work of AMR Declaration Trust, an organisation founded on the principles of the Chennai Declaration - one of the landmark policy documents in the history of AMR. This book fulfils one of the many objectives of the trust, which is to educate various stakeholders, such as the medical community and the public, on the importance of rational antibiotic usage and other measures to tackle the challenge of Antimicrobial Resistance (AMR). More details about the trust can be found at:

https://amrdeclaration.com

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