Treatment Guidelines for Antimicrobial Use in Common Syndromes

2019

New Delhi, India

ICMR, New Delhi

Treatment Guidelines for Antimicrobial Use in Common Syndromes. 2nd edition.

Publications of the ICMR can be obtained from ICMR-HQ,
Indian Council of Medical Research
Division of ECD, Ansari Nagar, New Delhi, India

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सत्यमेव जयते
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FOREWORD

Antimicrobial resistance (AMR) is a serious global concern. The incidence rate of AMR is gradually rising in many pathogens that threaten our ability to treat and cure common infections. Irrational use of antibiotics, unregulated over the counter sale of antibiotics and lack of guidance and awareness on antibiotic use are major drivers of AMR incidences. Lack of monitoring and inappropriate use of antimicrobials is a major contributor for the development of AMR and its spread.

In recognition of this growing problem, ICMR developed evidence based treatment guidelines for treatment of common syndromes in 2017. The second edition reflects the updated information on guidelines for treatment of bone and joint infections, skin & soft tissue and central nervous system infections with their dosing, route of administration and duration of therapy. We gratefully acknowledges the infectious disease physicians and clinical microbiologists who contributed to the compilation of this document.

We hope that this document will serve as a practical guide for the health care professionals in guiding the treatment and proper usage of antimicrobials. This document will benefit in prescribing and dispensing antimicrobials effectively thus improving the quality of patient care and bringing down the AMR burden in the country.

Prof. Balram Bhargava
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Instructions to Users of Antimicrobial Guidelines

The "Treatment guidelines for antimicrobial use in common syndromes" aims to rationalize the usage of antibiotics on National List of Essential Medicines (NLEM) and to establish consistency in the treatment of various infectious conditions. ICMR established AMR surveillance network in 2012 to collect nationally representative data on trends and patterns of AMR to the commonly used antibiotics in pathogens of public health importance. The data emanating from this network has been used to guide the treatment of various syndromes.

The country's leading infectious disease physicians and clinical microbiologists from leading medical organizations have contributed to this compilation. All recommended therapies are either evidence-based as per universally accepted standards. These are general guidelines; treatment of individual patients may vary depending upon local conditions and experience. The antimicrobial susceptibility data given in this guideline are from selected leading tertiary care hospitals in India and does not represent the community data. Antimicrobial resistance data is known to differ between different healthcare institutes and between different clinical departments of same institute. Hence each healthcare institute and each clinical department must customize their respective guideline accordingly using ICMR guideline as rational format. ICMR had brought out the first edition of the guideline in 2017. This guideline builds up on the first edition and has additional chapters on skin & soft tissue, bone & joint and CNS infections.

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CHAPTER: 1

Introduction To Antibiotic Use

1.1 Introduction

Antimicrobial resistance (AMR) is a global threat today and has overshadowed the potential gain in reducing deaths due to infections. It is estimated that by the year 2050, Asia will have 4.7 million deaths that could be directly attributed to AMR. Antimicrobial resistance is rampant in India with up to 12-59 % of *E. coli* being extended beta lactamase (ESBL) producers and up to 30% being carbapenemase producers (CP). *Klebsiella pneumoniae* has emerged over the last few years as a highly resistant pathogen with up to 50% resistance to carbapenems and rapidly increasing resistance to polymyxins. In addition, methicillin resistance in *Staphylococcus aureus* is seen in up to 30% of *S. aureus* isolates nationally. It is well documented that antibiotic abuse is one of the major drivers of antibiotic resistance and thus optimising usage of antibiotics is the need of the hour. India is the largest consumer of antibiotics in the world i.e., 13 billion standard units in 2010 and from 2000 to 2010 the per capita consumption increased by 66%. In May 2015, the World Health Assembly adopted a resolution to endorse a global action plan on antimicrobial resistance.

1.1.1 The plan set out five objectives:

- To improve awareness and understanding of antimicrobial resistance; To strengthen surveillance and research; To reduce the incidence of infection;
- To optimise the use of antimicrobials
- To ensure sustainable investment in countering antimicrobial resistance.

In India antibiotics are prescribed by physicians irrationally, dispensed over the counters without a prescription and used in livestock and poultry as growth enhancers. Hence a concerted effort at all levels is required to prevent transmission of antimicrobial resistance.

The strategic objectives of the Indian National Action Plan –Antimicrobial resistance (NAP-AMR) are aligned to the Sustained Developmental goals (SDGs) and the Global action plan on antimicrobial resistance adopted by the World Health Assembly in 2015. The main objectives put forth by the World Health Assembly were adopted and in addition, a 6^{th} priority was identified –strengthening India's leadership on AMR.

1.1.2 Principles of rational antibiotic use

Human antimicrobial misuse or overuse is one of the main drivers of AMR and in the presence of a dry antibiotic pipeline, it becomes imperative that we learn to use antibiotics judiciously and responsibly. In 2010, India was adjudicated to be the world's largest consumer of antibiotics and hence curbing injudicious use of antibiotics is a must.

Antibiotic abuse happens due to common fallacies such as a belief that broad spectrum antibiotics are "safer" and failure to distinguish between bacterial infections and non-bacterial infections and non-infectious syndromes. In addition, antibiotics for durations longer than necessary, redundant cover (like double gram negative or double anaerobic over) or treatment of colonizers or contaminants also constitute inappropriate antibiotic use. A stewardship program implementing rational antibiotic use is mandatory to curb irrational antibiotic use.
Antimicrobial stewardship is defined as a set of coordinated interventions designed to measure and improve the appropriate use of antibiotics by promoting the selection of the optimal choice, dose, duration and route of the antibiotic which in turn lead to improved patient outcomes and decreased adverse effects.

1.1.3 Steps of rational antibiotic use

Step 1: Making a clinical diagnosis is often not given enough importance leading us to most often stumble upon a diagnosis while sending multiple lab tests. A clinical diagnosis most often helps us to predict causative pathogens fitting in to a clinical syndrome which would tailor the correct antibiotic rather than blindly relying on fever, procalcitonin levels, WBC counts, cultures or radiology to make a diagnosis of infection. Our thought process here should be

Diagnosis of infection
- Is it an infection?
- A risk assessment of how likely is it that the patient has an infection?
- What are the possible non-infectious mimics?
- Have we taken the appropriate cultures to confirm the final diagnosis?

Step 2: **Limiting empiric antibiotic therapy** to genuine seriously ill patients. Generally, empiric antibiotic therapy is ONLY recommended for a select group of patients as described below after taking appropriate cultures
- Febrile neutropenia
- Severe sepsis and septic shock
- Community acquired pneumonia
- Ventilator associated pneumonia
- Necrotizing fasciitis

Hence, it is important to start smart and then focus, i.e., evaluate if empiric therapy can be justified or de-escalated and then make a plan with regard to the duration of therapy.

Step 3: Know your bugs
Approach includes
- Identify the clinical syndrome
- Elucidate possible sources of infection

- Predict possible microbial pathogens
- Predict the local resistance pattern based on institutional antibiogram

Step 4: Choose the appropriate antibiotic

- Based on the spectrum of the antibiotic taking into account possible resistant patterns
- Use the correct dose, route and duration
- Ensure chosen antibiotic has adequate tissue penetration at the site of infection
- Optimize PK-PD parameters according to co-morbidities

Step 5: De-escalation/modification

- Modify empiric broad spectrum antibiotics depending on culture and antimicrobial susceptibility reports and patient status
- Stop polymyxins and glycopeptides if no carbapenem resistant organisms (CRO) or methicillin resistant *Staphylococcus aureus* (MRSA) identified on cultures
- Avoid double or redundant gram negative or anaerobic coverage
- Discontinue antibiotics if a non-infectious mimic identified
- De-escalate combination therapy to a single agent
- Change a broad spectrum antibiotic to a narrow spectrum one
- Change IV to oral antibiotics

De-escalation is safe in all patients including febrile neutropenia and septic shock and reduces mortality and length of hospital stay.

Step 6: Stop antibiotics in the following clinical situations

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

Step 7: Reduce the duration of therapy

Duration of therapy should be optimized to minimum possible to reduce selection pressure. Practice guidelines and recommendations for optimum duration of therapy for various infectious disease syndromes suggest the following durations:

Community acquired pneumonia: 5 days

Hospital acquired pneumonia: 8 days
Skin and Soft tissue infections: 5 days
Urinary tract infections

- cystitis: 3-5 days
- Pyelonephritis: 5-14 days
- Catheter associated: 7 days
- *Staphylococcal aureus* bacteraemia – low risk of complications = 2 weeks
- high risk of complications = 4-6 weeks

Intra-abdominal infection: 4-7 days
Surgical antibiotic prophylaxis: 1 dose

A stop date should be planned and recorded in advance to ensure antibiotic is not given beyond the recommended duration.

Step 8: Optimize PK-PD parameters

We cannot influence how a drug gets metabolized but we can influence drug administration for maximum efficacy. Age and co-morbidities like renal failure, sepsis and burns also influence the outcomes of the patients. Overall, exposure of the infective agent to the unbound antibiotic drug fraction at the relevant effect site seems to be the most important factor. Optimizing Pk-PD parameters include loading doses when needed, therapeutic drug monitoring for toxicity and efficacy and optimization of drug infusion or administration. For e.g.,

- Loading dose of Colistin 9 million units stat and then followed by 3 million units Q8H or 4.5 million units Q12H [to target Colistin Average Steady State Plasma Concentration ($C_{ss,avg}$ = 2-2.5 mg/L)
- Inj vancomycin 1g IV Q12H and dose to be adjusted to maintain a trough level between 15-20 µg/ml [however there are increasing recent data that suggests that AUC/MIC may be a better indicator of clinical efficacy than a trough level]
- Extended infusion of β lactams

Conclusion

Antimicrobial stewardship is a pressing need and is the only proven strategy to prevent human antimicrobial over use and abuse which is one of the main drivers of antimicrobial resistance. Rational use of antibiotics needs to be taught at all levels in the medical school curriculum.

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CHAPTER: 2

Management of Acute Fever

2.1 Management of community-onset acute undifferentiated fever in adults

2.1.1 Outline

The purpose of the guidelines is to ensure appropriate antimicrobial treatment while at the same time limiting the inappropriate use of antibiotics in the management of infections by addressing issues like antibiotic selection, dosing, route, duration, adverse drug events, and cost and prevention of unintended collateral damage.

2.1.2 Some general principles

- Antibiotic use will need to be classified with respect to type (high- and low-risk) and the patient's place in the treatment pathway (untreated, treated, and post-treatment).
- The choice of medication may vary depending on differences in the case mix of patients, various drugs (of same or different class) listed in the formulary or clinical practice guidelines already in place at different institutions in similar patient care locations.
- Timely use of diagnostic tests or documentation of symptoms supporting the presence of infection would be best. Cultures (two sets of blood cultures and other appropriate samples as clinically indicated e.g. normally sterile body fluids, deep pus etc.) should be taken before starting empiric antibiotic treatment.
- Empiric antibiotic treatment for common infections should be limited to conditions where early initiation of antibiotics has been shown to be beneficial, e.g. severe sepsis and septic shock, acute bacterial meningitis, community acquired pneumonia, necrotizing fasciitis, etc.
- Re-assessment of the situation within 48 hours based on the test results and examination of the patient is required. If needed, the drug's dosage and duration can be adjusted or the antibiotic regimen should be de-escalated (to the narrowest spectrum, least toxic and least expensive antibiotic) based upon patient response and culture and susceptibility reports.

2.1.3 Case Definition

- Previously healthy (non-immunosuppressed) community (urban or rural) dwelling adult (ages 19-64 yrs.) reporting no previous medical illness or recent hospitalization (in the preceding 30 days) presenting with acute onset of fever > 38.3° C (101.0° F) for >2 days and lasting up to 14 days and having received no specific treatment for this current illness with antimalarials or antibiotics.

- Seen in ambulatory care settings at the primary level (PHC), doctor's office/clinic, an emergency room in a Community Hospital, including referrals from primary health care or community physicians.
- With history of no localizing symptoms (except accompaniments of fever such as – chills, headaches, retro-orbital pain, myalgia, malaise, nausea or vomiting). On examination found to have normal vital signs (excepting fever) and lacking organ or system specific physical signs*.

** A complete and thorough physical examination is mandatory. Record of vital signs is essential. A search is required for hidden foci such as throat examination, sinus tenderness, renal or hepatic tenderness, heart murmurs, chest examination, lymph nodes and splenomegaly. Fundus examination (if headache or bleeding tendency) and examination of the skin for eschar and petechiae or purpura must be made.*

2.1.4 Common pathogens causing "tropical fevers", "seasonal fevers" "endemic /epidemic /outbreak fever", "monsoon fever":

- Suspect malaria in all cases of acute undifferentiated fever (there are no key differentiating features between this and other causes (see below). Despite historical claims, fever patterns are not especially helpful in establishing a specific diagnosis. Malaria is especially to be suspected after a visit to high malaria endemic zone.
- Viruses cause febrile illness or specific viral "influenza-like- illness" (with mild sore throat and cough).
- If rash or exanthem is present without drug exposure (rule out drug allergy), consider mononucleosis syndrome (EBV, CMV, HIV) or an exanthematous viral illness (measles, rubella, etc).
- Primary or secondary dengue may be accompanied by maculo-papular rash or polyarthralgia. Tourniquet test may be inappropriate as a general discriminating test without hemorrhagic manifestations or the shock syndrome. Consider hemorrhagic fever with two or more hemorrhagic symptoms - hemorrhagic or purpuric rash, epistaxis, conjunctival haemorrhage, bleeding gums, bleeding at puncture sites, hematuria, hematemesis, hemoptysis, blood in the stool.
- Scrub typhus or murine typhus may present with skin eschar, regional lymphadenopathy, and maculopapular rash.
- Leptospirosis can present with conjunctival suffusion, muscle tenderness and jaundice (ask for flood water or sewage exposure).
- Typhoid should be suspected in the presence of continuous fever, gastro intestinal symptoms and splenomegaly.
- Community acquired secondary bacteremia: Primary source may be occult. In most instances, it is either from underlying pneumonia, intra-abdominal infection or urosepsis. Symptoms related to these systems may not be manifest, especially in the elderly.

- Hepatitis A or E can cause fever that usually subsides with the onset of jaundice.
- Chikungunya presents with fever and polyarthralgia /polyarthritis.
- Consider rheumatic fever caused by Group A beta hemolytic streptococci if there is migratory arthritis with preceding significant sore throat.
- Tuberculosis should be considered in any patient with prolonged undifferentiated fever, especially if there is weight loss.

2.1.5 Diagnostic Investigations (where facilities are available)

- One blood smear and/or RDT at least is required for malarial parasite detection (repeat blood smear once more if the initial smear is negative in an endemic region).
- Complete blood count:Anemia, leucopenia /leukocytosis, elevated hematocrit or thrombocytopenia are all helpful in diagnosis.
- Diagnostic blood cultures (at least two sets) are to be drawn prior to the start of empiric antibiotics.
- Liver enzymes and bilirubin
- Urinalysis – white blood cells, proteinuria and hematuria.
- Chest roentgenogram (if chest findings are present, to rule out early pneumonia or TB)
- Ultrasonography of abdomen if fever persists to rule out hepatic, renal or intraabdominal sources of infection.
- Within 96 hours of onset of fever, antigen based serological tests are likely to be positive whereas antibody tests are generally positive after at least 5-7 days of illness.
  a. Dengue rapid NS1 antigen
  b. IgM ELISA for Dengue, Scrub typhus and Leptospira

2.1.6 Prevalent AMR status in common pathogens

Malaria: *P. vivax* is susceptible to chloroquine which remains the drug of choice. *P. falciparum* resistance to chloroquine is seen in at least 25% of cases nationwide, and therefore artemisinin-based combination therapies (ACT) should be the first line treatment for *P. falciparum* malaria and where species is unclear. Artemisinin (especially oral) monotherapy should be strongly discouraged as it leads to resistance to this class.

Typhoid fever: Quinolone resistance is increasing and is as high as 69% for *Salmonella* Typhi and 23% for *Salmonella* Paratyphi A. Resistance rates are low for co-trimoxazole, chloramphenicol and third generation cephalosporins. Though sensitivity testing is not validated for azithromycin, the response is good in most clinical studies. However,

defervescence times are significantly longer with third generation cephalosporins compared with other classes and bone marrow depression is a concern with chloramphenicol.

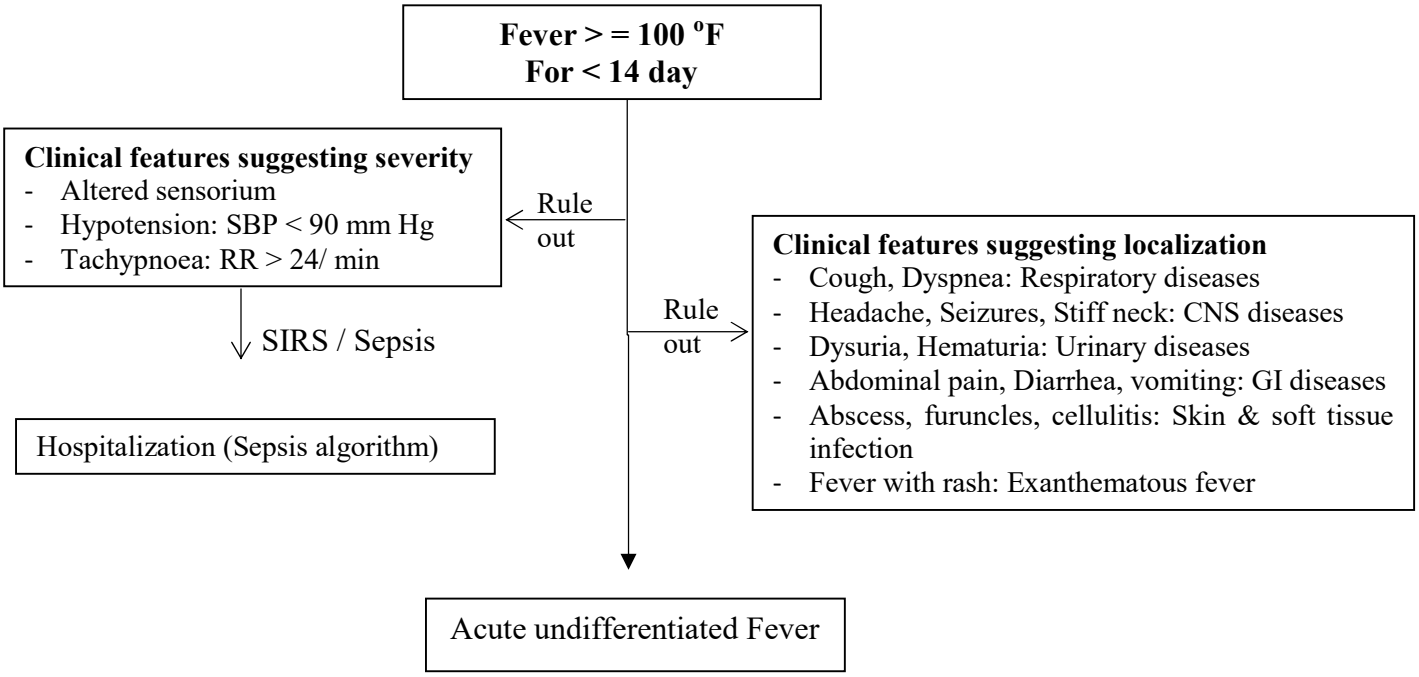
Gram negative organisms: There is increasing resistance among Enterobacteriaceae (*E. coli* and *Klebsiella*) to both quinolones (up to 80%) and third generation cephalosporins (up to 75% on account of ESBL production). Initial empiric therapy for infections caused by these organisms {pyelonephritis, severe intraabdominal infections (IAI), etc} should be with an agent active against ESBL producers e.g.a carbapenem or with a beta-lactam/beta-lactamase inhibitor forless severely ill patients.

Gram positive organisms: Community acquired organisms such as *S. aureus* are usually susceptible to methicillin i.e. standard anti staphylococcal drugs such as cloxacillin and first cephalosporins may be used. Penicillin still remains the drug of choice for pneumococcal infection.

2.1.7 Principles of empiric therapy

a. Supportive: Acetaminophen 650 mg every 6 hours round the clock is advisable, accompanied by tepid sponging for fever $>103^0$ F. Replace fluid and electrolytes as required.
b. No antibiotics are required for the majority of patients with acute febrile illness without an obvious clinical diagnosis.
c. Start antibiotics for a presumed bacterial infection promptly, but adjust the drug's dosage and duration, switch to a new drug, or end antibiotic therapy when results do not support or justify the need to continue.
d. Reassess the situation within 48 hours based on test results and patient status.
e. Corticosteroids are not recommended in the treatment of acute undifferentiated fever.
f. In patients with fever and thrombocytopenia, platelet transfusions are not recommended in general.
g. Consider platelet transfusion when platelet counts are <10,000 cu mm or in the presence of clinical bleeding in cases of dengue hemorrhagic fever.
h. Empirical treatment with doxycycline for patients with undifferentiated fever and negative rapid diagnostic tests for malaria and dengue is an option for the clinician.

Protocol for the management of adult patients with acute undifferentiated fever



A. Day 1 or 2: Defer investigation and anti-microbials

B. Day 3 or 4: Total leukocyte count with differential, Malaria parasite slide and rapid diagnostic kits, may test for Dengue if suspicion high.

C. > 5 days: As per (B) plus paired blood cultures. May test for Dengue, Chikungunya, Scrub typhus, Leptospirosis if suspicion high.

D. > 7 days: As per (C) plus X-ray chest and USG abdomen

Table 2.1: Antimicrobial choice for disease conditions

S. No	Type of disease	Organisms	Initial Treatment/ Preferred	Alternatives Comments	Comments
1	Typhoid fever	*Salmonella* Typhi, *Salmonella* Paratyphi A	Oral: cotrimoxazole or azithromycin Parenteral: ceftriaxone	Cefixime or chloramphenicol or ciprofloxacin	Change the empiric regimen based on susceptibility testing. Duration of treatment: 10-14 days.
2	Empiric therapy of suspected Gram positive infections	*S. pneumoniae*, *Streptococcus pyogenes*, *S. aureus*	Cefazolin or Cloxacillin	Amoxicillin clavulanate or Vancomycin (if anaphylactic penicillin allergy or MRSA clinically possible)	Adjust regimen after receipt of culture and susceptibility data.

3	Empiric therapy for suspected Gram negative infections (e.g. pyelonephritis or intra-abdominal infections)	*E. coli*, *Klebsiella pneumoniae*, anaerobes especially Bacteroides sp in IAI	Piperacillin-tazobactam or Cefoperazone - sulbactam	Imipenem or Meropenem or Ertapenem (carbapenems preferred for more seriously ill patients)	Separate anaerobic coverage unnecessary for IAI, when using BL-BLIs or carbapenems. De-escalate to ciprofloxacin, cotrimoxazole or third generation cephalosporin if the isolate is sensitive.
4	Rickettsial infections	*Orientia tsutsugamushi*,*Rickettsia conorii, R. typhi*	Doxycycline	Azithromycin chloramphenicol	Duration of treatment: 7 days
5	Leptospirosis	*Leptospira* sp	Penicillin G or doxycycline	Ceftriaxone	Duration of treatment: 7 days
6	Vivax malaria	*P. vivax*	Oral Chloroquine	Artemether-lumefantrine	Followed by primaquine
7	Falciparum malaria	*P. falciparum*	If the patient is able to take orally: Except for North eastern states: Oral Artesunate and Pyrimethamine on the first day. In Northeastern states: Artemether-Lumefantrine should be used. If the patient is unable to take orally: IV Artesunate. Switch over to oral therapy when as soon as possible. Add a second agent such as doxycycline or clindamycin	Artemether-lumefantrine	Followed by primaquine single dose. All mixed infections should be treated with full course of ACT and primaquine 0.25 mg per kg daily for 14 days.

** All these regimens need to be tailored according to susceptibility patterns at individual centres.*

Table 2.2: Standard doses of antimicrobials

Antibiotics	Doses, duration and route of administration
Cotrimoxazole	1 DS tab bd
Azithromycin	20 mg/kg/day)
Ceftriaxone	2 g IV od
Cefixime	20 mg/kg/day
Chloramphenicol	500 mg qid
Ciprofloxacin	750 mg bd
Cefazolin	2 g IV q8h
Cloxacillin	2 g IV q6h
Amoxicillin clavulanate	1.2 g IV q8h
Piperacillin-tazobactam	4.5 g IV q6h
Cefoperazone -sulbactam	3 g IV q12h
Imipenem	1 g IV q8h
Meropenem	1 g IV q8h
Ertapenem	1 g IV od
Doxycycline	100 mg PO or IV bd
Azithromycin	500 mg PO or IV od
Penicillin G	20 laks IV q4h
Oral Chloroquine	25 mg/kg body weight divided over three days i.e. 10 mg/kg on day 1, 10 mg/kg on day 2 and 5 mg/kg on day 3.
Artemether-lumefantrine	1 tab bd for 3 days
Primaquine (For vivax malaria)	0.25 mg/kg daily for 14 days
Primaquine (for falciparum malaria)	0.75 mg/kg single dose
Oral Artesunate	4mg/kg for 3 days plus sulfadoxine (25 mg/kg body weight)
Pyrimethamine	1.25 mg/kg body weight) on the first day
Artesunate	IV 4.2 mg/kg at 0 hr, 12 hr followed by every 24 hourly

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2.2 Malaria

Around 2 million laboratories confirmed cases of malaria are reported in the country annually of which 40-50% are *P. falciparum*, which may lead to complications in 0.5% to 2% of cases and mortality in about 30% of such cases if timely treatment is not given. All malaria should be treated after confirmation only, with the exception of an initial dose of antimalarial till the smear report is ready.

2.2.1 Treatment of uncomplicated *Plasmodium falciparum* malaria

The five artemisinin-based combination therapy (ACTs) recommended for treatment of uncomplicated *P. falciparum* malaria are:

(a) artemether + lumefantrine
(b) artesunate + amodiaquine
(c) artesunate + mefloquine
(d) artesunate + SP
(e) dihydroartemisinin + piperaquine

ACT regimens should provide 3 days treatment with an artemisinin-derivative.

Table 2.3: ACT regimens as per body weight

Body weight (kg)	Artemether + lumefantrine dose (mg) given twice daily for 3 days
5 to < 15	20 + 120
15 to < 25	40 + 240
25 to < 35	60 + 360
= 35	80 + 480
Body weight (kg)	Artesunate + amodiaquine dose (mg) given daily for 3 days
4.5 to < 9	25 + 67.5
9 to < 18	50 + 135
18 to < 36	100 + 270
= 36	200 + 540
Body weight (kg)	Artesunate + mefloquine dose (mg) given daily for 3 days
5 to < 9	25 + 55
9 to < 18	50 + 110
18 to < 30	100 + 220
= 30	200 + 440
Body weight (kg)	Dihydroartemisinin + piperaquine dose (mg) given daily
5 to < 8	20 + 160
8 to < 11	30 + 240
11 to < 17	40 + 320
17 to < 25	60 + 480
25 to < 36	80 + 640
36 to < 60	120 + 960
60 < 80	160 + 1280
>80	200 + 1600

Body weight	Artesunate dose is given daily for 3 days (mg)	Sulfadoxine/ pyrimethamine dose (mg) given as a singledose on day 1
5 to < 10	25 mg	250 / 12.5
10 to < 25	50 mg	500 / 25
25 to < 50	100 mg	1000 / 50
= 50	200 mg	1500 / 75

The recommended second-line treatment is an alternative ACT known to be effective in the region. Recurrence of fever and parasitaemia > 4 weeks after treatment may be due to either recrudescence or a new infection. The distinction can be made only by PCR. As PCR is not routinely used in patient management, all presumed treatment failures after 4 weeks of initial treatment should be considered new infections and be treated with the first-line ACT. However, reuse of mefloquine within 60 days of first treatment is associated with an increased risk for neuropsychiatric reactions, and an alternative ACT should be used.

2.2.2 Reducing the transmissibility of *P. falciparum* infections

In low-transmission areas, give a single dose of 0.25 mg/kg body weight (BW) primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required.

Table 2.4: Primaquine regimens as per body weight

Body weight (kg)	A single dose of primaquine (mg base)
10a to < 25	3.75
25 to < 50	7.5
50 to 100	15

2.2.3 Treating uncomplicated *P. falciparum* malaria in special risk groups

a) The first trimester of pregnancy- Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with either ACTs (there is increasing evidence of safety in this population) or the conventional regimen of 7 days of quinine + clindamycin.
b) Infants less than 5 kg body weight- Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with ACT at the same mg/kg body weight target dose as for children weighing 5 kg.
c) Patients co-infected with HIV- In people who have HIV/AIDS and uncomplicated *P. falciparum* malaria, avoid artesunate + SP if they are also receiving co-trimoxazole, and avoid artesunate + amodiaquine if they are also receiving efavirenz or zidovudine.
d) Non-immune travelers- Treat travelers with uncomplicated *P. falciparum* malaria returning to non endemic settings with an ACT.
e) Uncomplicated hyperparasitaemia (People with *P. falciparum* hyperparasitaemia are at increased risk of treatment failure, severe malaria and death so should be closely monitored, in addition to receiving ACT.

2.2.4 Treating uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria

2.2.4.1 Blood stage infection- If the malaria species is not known with certainty, treat like uncomplicated *P. falciparum* malaria. In areas with chloroquine-susceptible infections, treat adults and children having uncomplicated *P. vivax, P. ovale, P. malariae* or *P. knowlesi* malaria with either ACT (except pregnant women in their first trimester) or chloroquine (Strong recommendation, high-quality evidence).

2.2.4.2 In areas with chloroquine-resistant infections, treat adults and children having uncomplicated *P. vivax, P. ovale, P. malariae* or *P. knowlesi* malaria (except pregnant

women in their first trimester) with ACT. (Strong recommendation, high-quality evidence). Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.

2.2.4.3 Preventing relapse in *P. vivax* or *P. ovale* malaria- The G6PD status of patients should be used to guide administration of primaquine for preventing relapse. To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known no to be G6PD deficient, and people with G6PD deficiency) with a 14-day course (0.25-0.5 mg/kg bw daily) of primaquine in all transmission settings.

2.2.4.4 In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced adverse haematological effects. When the G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine. Pregnant and breast feeding women- consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse (Conditional recommendation, moderate-quality evidence).

2.2.5 Treating severe Malaria

Children: The signs and symptoms in children are a history of high fever, plus at least one of the following:-

- Prostration (inability to sit), altered consciousness lethargy or coma;
- Breathing difficulties;
- Severe anaemia;
- Convulsions;
- Inability to drink/ vomiting

Patients with prostration and/or breathing difficulties should, if at all possible, be treated with parenteral antimalarials and antibiotics. If the clinical condition permits, other patients may be treated with oral antimalarials.

Adults: The same symptoms and signs in children are valid for adults, with the addition of dark and/ or limited production of urine

2.2.5.1 Who is at risk for severe complications?

- In areas of low transmission – all age groups are vulnerable but adults develop more severe and multiple complications. The transmission pattern in most parts

of India is usually low, but the intense transmission is seen in north-eastern states and large areas of Orissa, Chattisgarh, Jharkhand, and Madhya Pradesh.

- In areas of high transmission – children below 5 years, visitors, migratory labours.
- Association of pregnancy

2.2.6 Treatment of severe and complicated malaria

Semiconscious or comatose patients of severe *P. falciparum* infection should be treated with parenteral artemesinin based regimens. It is essential that full doses of effective parenteral (or rectal) antimalarial treatment be given promptly in the initial treatment of severe malaria. This should be followed by a full dose of effective ACT orally. Two classes of medicine are available for parenteral treatment of severe malaria: artemisinin derivatives (artesunate or artemether) and the cinchona alkaloids (quinine and quinidine). Parenteral artesunate is the treatment of choice for all severe malaria. There is substantial reduction in mortality with intravenous or intramuscular artesunate as compared with parenteral quinine. Artesunate is simpler, safer and reduces mortality significantly than quinine.

The dose of artesunate is 2.4 mg/kg bw at 0, 12 and 24 hr. Then it is repeated once in every 24 hr.

Treat adults and children who have severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT (add single dose primaquine in areas of low transmission).

Note: *Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.*

If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria. Artemether is two to three times less active than its main metabolite dihydroartemisinin.

The initial dose of artemether is 3.2 mg/kg bw intramuscularly (to the anterior thigh). The maintenance dose is 1.6 mg/kg bw intramuscularly daily.

This should be followed by a full dose of effective ACT orally.

2.2.7 Chemoprophylaxis

- Chemoprophylaxis is recommended for travelers, migrant labourers and military personnel exposed to malaria in highly endemic areas. Use of personal protection

measures like insecticide-treated bednets should be encouraged for pregnant women and other vulnerable populations.

- For short-term chemoprophylaxis (less than 6 weeks):- Doxycycline- 100 mg daily in adults and 1.5 mg/kg for children more than 8 years old. The drug should be started 2 days before travel and continued for 4 weeks after leaving the malarious area. (Note: Doxycycline is contraindicated in pregnant women and children less than 8 years).
- For long-term chemoprophylaxis (more than 6 weeks) Mefloquine: 5 mg/kg bw (up to 250 mg) weekly and should be administered two weeks before, during and four weeks after leaving the area.

Table 2.5: Antimicrobials dosage as per chemoprophylaxis

Chemoprophylaxis	**Antimicrobial**	**Dose duration**	**Remark**
Short-term (less than 6 weeks	Doxycycline Contraindicated in pregnant women and children < 8 years	100 mg daily in adults and 1.5 mg/kg for children >8 years old.	Started 2 days before travel and continued for 4 weeks after leaving the malarious area
Long-term (More than 6 weeks	Mefloquine*	5 mg/kg bw (up to 250 mg) weekly	Administered two weeks before, during and four weeks after leaving the area

** Mefloquine is contraindicated in cases with history of convulsions, neuropsychiatric problems and cardiac conditions*

Table 2.6: Standard doses of antimicrobials

Name	**Mechanism of action**	**Elimination half Life**	**Action**	**Advantage**	**Disadvantage**
Chloroquine	• ? Inhibits plasmodial heme polymerase • Toxic drug-heme complex form • Dg. Intercalation of Pl. DNA • Intravacuolar pH alteration	10 days	• Schizonticidal for all species • Gametocidal for Pv. PO.PM. • No action on hypnozoites	a) Highly potent against sensitive strains b)Long half life c)Effective at once a week dose as a prophylactic agent	The rapid development of resistance
Quinine	(Same as Chloroquine)	11 hrs.	• Primary blood schizonticide • Little effect on sporozoite • Gametocidal to PV and PM	The rapid development of resistance not yet seen	Higher toxicity
Artesunate / Artemether / Arteether	• Activated by heme/ molecular iron to produce carbon centered free radicals • Membrane damage by free radical	< 1 hr. 3-11 hrs > 20 hrs.	• Blood schizonticide • Gametocidal action recently described	a)Broader window period of effectiveness b)Little/ no cross resistance c)Resistance not yet recorded	High recrudescence rate when used as monotherapy (10-50%) when used for <5 days
Mefloquine	Formation of toxic subs. with heme	20 days	• Strong schnizonticidal action against all species. • Gametocidal l against PV, PM, PO • Sporonticidal act	a)Useful as a prophylactic agent for non-immune travellers b)Single dose sufficient c) Good alt. To quinine in MDR Pf.	a)Only oral prep. available. So cannot be used in sev. Pf malaria b)High chances of cross-resistance, might lead to quinine resistance as well
Halofantrine	Concentrates and combines with ferri protop orphyrin IX, leading to memb. Damage1	10-90 hrs.	• Schizonticidal to all species • No action on latent tissue form of PV and gametocytes	Good alternative to mefloquine/ quinine in chloroquine/ MDR Pf.	a)Oral absorption erratic b)High chances of cross resistance with mefloquine c)Cardiotoxicity

Atovaquone	Inhibits parasite mitochondrial electron transport chain (complex III)	70 hrs.	Blood schizonticide (used primarily for MDR Pf.)		a)Erratic absorption b)High recrudescence rate when used alone
Pyronaridine	Inhibits vacuolar degradation, leading tot impaired Hb degradation	60 hrs.	• Schizonticide for PF, PV, MDR, PF	a)Good oral absorption b)Cross resistance not yet documented c)Well tolerated	
Sulfadoxine - Pyrimethamine	Acts against the parasite dihydrofolate reductase enzyme	Sulfadoxine – 180 hrs. Pyrimethamine – 95 hrs	Active against blood schizonts of P. *falciparum.* Less active against other species	a) Can be used against chloroquine resistant P. *falciparum*. b) No cross resistance with the 4 aminoquinolines, mefloquine, quinine, artemisinin derivatives	Risk of severe skin reactions
Primaquine	May get converted to electrophiles that act as redox mediators	6 hrs.	• Destroys late hepatic stage and latent forms of PV and PO • Gametocidal to all sp., mainly Pf. • No action on the erythrocyte stage of Pf., though active against the hepatic stage	Useful for the terminal prophylaxis and radical cure of PV and PO	Cannot be used in a patient with G-6PD deficiency.
Proguanil	Selective inhibition of the bi-functional dihydrofolate reductase-thymidylate synthetase of Pl.	16 hrs.	Weak schizonticidal action against all species.	Good prophylactic agent for Pf or mixed infection, when used with chloroquine	Can not be used alone in the treatment of malaria

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2.3 Dengue

2.3.1 Introduction

Dengue virus infection is an acute febrile illness caused by dengue viruses (DEN-1 to 4) belonging to the family Flaviviridae. Dengue viruses are transmitted to humans through the bite of infected *Aedes* mosquitoes, principally *Aedes aegypti*.

2.3.2 Symptoms

The incubation period varies from 4 to 7 days. Patients with dengue infection may not have specific localizing symptoms at the time of presentation. Moderate to a high-grade fever which is sudden in onset is a universal complaint, which lasts for up to 6 days. Patients usually experience an abrupt onset of a severe headache, retro-orbital pain, and as the name "break-bone fever" suggests is associated with a backache, severe myalgias. Pain in abdomen in dengue fever may be as a warning sign and suggests the need for admission and close monitoring. Causes of pain abdomen in dengue infection include stretching of liver capsule due to hepatitis, pancreatitis, acalculous cholecystitis and peptic ulcer.

2.3.3 WHO grading system

The classification helps decide regarding admission, close monitoring, providing supportive care and prognosticate.

1. **DF without warning signs**: defined as fever along with two of the following criteria: nausea/vomiting, rash, aches and pains, leukopenia, positive tourniquet test.
2. **DF with warning signs**: defined as fever with abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation (ascites or pleural effusion), mucosal bleeding, lethargy or restlessness, liver enlargement >2 cm, or when a laboratory parameter includes an increase in hematocrit with concurrent rapid fall in platelet count.
3. **DF is severe dengue:** defined as fever with evidence of plasma leakage leading to shock (dengue shock syndrome) or fluid accumulation with respiratory distress, severe bleeding (as evaluated by a clinician), and /or severe organ involvement (i.e., AST or ALT 1000 or greater, impaired consciousness or organ failure).

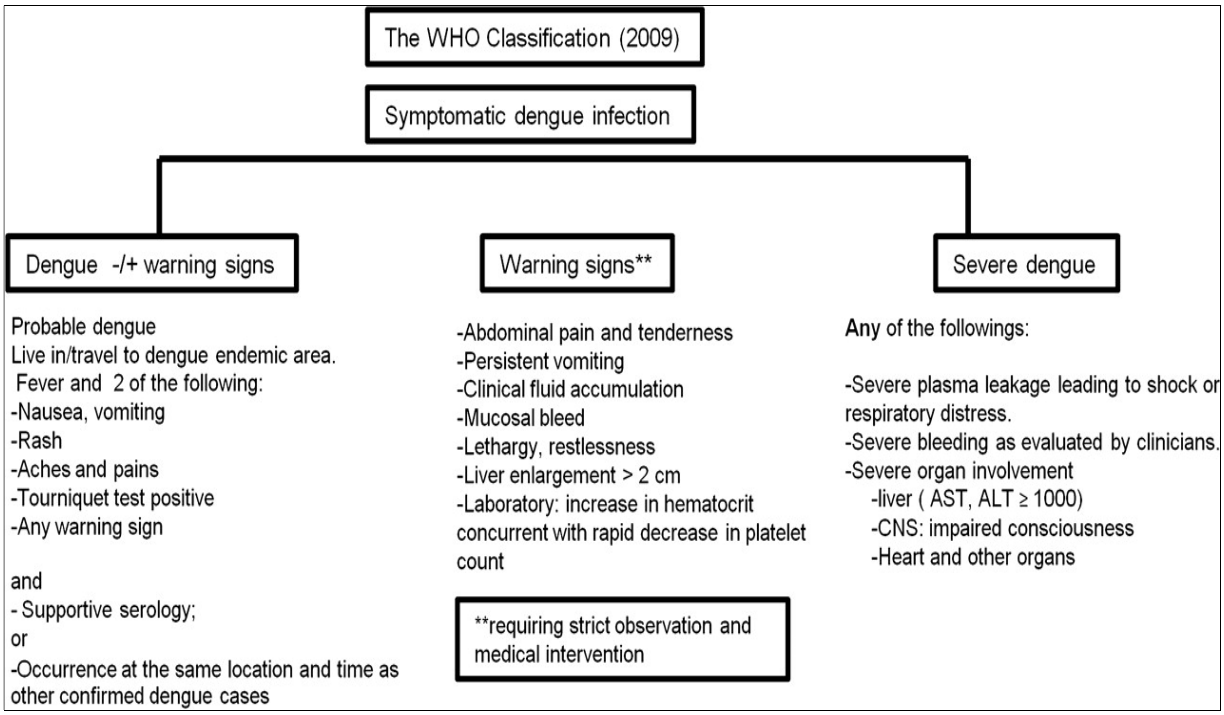

Fig 2.1 WHO Classification 2009

WHO developed terminology "expanded dengue" in the year 2012 to describe unusual manifestations in the form of severe organ involvement such as liver, kidneys, brain or heart. These unusual manifestations may be associated with co-infections, co-morbidities like diabetes mellitus, COPD, pregnancy, extremes of age and other immunocompromised states or complications of prolonged shock and consequent organ failure.

2.3.4 Signs

Cutaneous manifestations are another important clue to the diagnosis of dengue fever. In patients with dengue infection, initially, there is transient flushing of the face due to capillary dilatation. After 3-6 days of onset of fever, blanchable maculopapular rash associated with itching appears. Some patients develop hemorrhagic manifestations such as petechiae, subconjunctival haemorrhages and ecchymoses with positive tourniquet test, particularly in severe dengue infection. In some cases, individual lesions may coalesce and are seen as generalized confluent erythema with rounded islands of sparing described as "white islands in a sea of red". Hepatomegaly of more than 2 cm is a warning sign of dengue according to WHO. This is an important clue in the outpatient department to admit a patient of suspected dengue.

2.3.5 Complications

In severe dengue patients develop bleeding manifestations, out of which gastrointestinal bleeding in the form of melena is the commonest bleeding manifestation. Neurological manifestations are uncommon as dengue is a non-neurotropic virus, though occasional cases of dengue encephalopathy, encephalitis, myelitis, Guillain Barre (GB) syndrome and myositis are reported. A high index of suspicion is required in patients with dengue fever during convalescence about intracranial bleed when they present with altered sensorium. Serious bleeding manifestations in the form of subdural hematoma (SDH) and intracerebral bleed are also described. Increased menstrual flow (menorrhagia) as a bleeding complication in dengue infection is described in the literature as case reports.

2.3.6 Diagnosis

2.3.6.1 Dengue-specific

During the early part of dengue infection, it can be diagnosed by virus isolation in cell culture, by detection of viral RNA by nucleic acid amplification tests (NAAT), or by detection of viral antigens i.e. non-structural protein 1(NS1) by ELISA or rapid tests. Currently, dengue infection can be diagnosed in the clinical setting during the first one week of illness with the detection of NS1 antigen. Rapid dengue antigen detection tests can be used in field settings to detect infection in less than an hour. During the primary infection with dengue virus, IgM antibody is the first immunoglobulin isotype to appear and will rise to detectable levels at around 7 days followed by IgG antibody rise. In contrast during secondary dengue infection, IgG antibody titers rise rapidly during the first week with lower titers of IgM, though detectable levels.

2.3.6.2 Rouitne blood investigations

Routine investigations help in suspecting dengue fever before the confirmatory test results. Raised haemoglobin level, raised hematocrit, low total leucocyte count and mildly low platelet counts are initial indicators for dengue infection. Low haemoglobin occasionally can be seen due to preexisting nutritional anaemia or due to bleeding manifestations. Leucocytosis should not be ignored in a case of diagnosed dengue infection as it may indicate a secondary bacterial infection. Severe cases with dengue shock have coagulopathy, manifested by a prolonged activated partial thromboplastin time (aPTT).

2.3.6.3 LFT & RFT

Hepatic dysfunction is a well-recognized feature of dengue infection due to the direct involvement of liver cells by dengue virus and by the unregulated host immune response against the virus. It is characterized by hepatomegaly and mild to moderate increase in transaminase levels although jaundice and acute liver failure are uncommon. Clinicians should advise a liver function test in a case of acute pyrexia. Significant hypoalbuminemia observed in severe forms of dengue. Complete urine examination may

reveal hematuria and albuminuria in some patients. Renal involvement and elevated serum creatinine are rare in dengue patients.

2.3.6.4 Chest X-Ray

Chest radiographic abnormalities include pleural effusions and bilateral infiltrates suggestive of ARDS in severe dengue grades.

2.3.6.5 ECG

Electrocardiography may show bradycardia and prolonged PR interval. Myocarditis in dengue infection can manifest with complete AV block or ventricular arrhythmias, which manifest as syncope or palpitations. ECG changes in dengue fever include sinus bradycardia, PR prolongation, ST-segment elevation and non-specific ST-T changes. Most of these changes are transient and usually revert to normal.

2.3.6.6 USG Abdomen

Ultrasonogram of the abdomen may show gall bladder wall thickness of more than 5 mm (acalculous cholecystitis), fatty liver, ascites and pleural effusions depending on the severity of dengue.

2.3.7 Management

2.3.7.1 General principles of management

Abnormal hemostasis and plasma leakage are the pathophysiologic hallmarks of dengue infection which are represented by thrombocytopenia and haemoconcentration. General principles management of dengue include

- Treatment of dengue is dynamic involving initial treatment and reassessment periodically till patient completes critical phase.
- Fever can be treated with paracetamol and the dosing should not be less than six hours. Tepid sponge if the patient still has a high fever.
- Do not give acetylsalicylic acid (aspirin), ibuprofen or other non-steroidal anti-inflammatory agents (NSAIDs) as these drugs may aggravate gastritis or bleeding.
- Antibiotics are not needed.
- Plenty of oral fluids should be given if there are no warning signs.
- Daily monitoring of temperature, the volume of fluid intake, urine output (volume and frequency), warning signs, signs of plasma leakage and bleeding, haematocrit, and white blood cell and platelet counts should be done.
- Look for warning signs and manage accordingly.

2.3.7.2 WHO recommendations

Group A Dengue fever without warning signs: need not be admitted and should be advised home care with close daily monitoring for disease progression in the form of decreasing white blood cell count, defervescence and warning signs of dengue until they are out of the critical period. These are patients who are able to tolerate adequate volumes of oral fluids and pass urine at least once every six hours and do not have any of the warning signs, particularly when the fever subsides. Adequate oral fluid intake to patients initially may be able to reduce the number of hospitalizations. Oral fluids should contain electrolytes and sugar to replace losses from fever and vomiting. Patients who are sent home should be monitored daily by health care providers for temperature pattern, the volume of fluid intake and losses, urine output (volume and frequency), warning signs, signs of plasma leakage and bleeding, haematocrit, and white blood cell and platelet counts. If a patient does not show any clinical improvement and deteriorates around the time of defervescence, should be referred for in-hospital management and follow the action plan.

Group B Dengue patients with warning signs: The warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation (ascites or pleural effusion), mucosal bleeding, lethargy or restlessness, liver enlargement >2 cm, or when a laboratory parameter includes an increase in hematocrit with concurrent rapid fall in platelet count. Patients need to be admitted to a secondary health care centre for close observation, particularly as they approach the critical phase. These include patients with warning signs, those with co-existing conditions such as pregnancy, infancy, old age, obesity, diabetes mellitus, renal failure and other comorbid conditions.

Start intravenous administration of 0.9% saline or Ringer's lactate, or Hartmann's solution. Start with 5–7 ml/ kg/hour for 1–2 hours, then reduce to 3–5 ml/kg/hr for 2–4 hours, and then reduce to 2–3 ml/kg/hr or less according to the clinical response. If the vital signs are worsening and haematocrit is rising rapidly, increase the rate to 5–10 ml/kg/hour for 1–2 hours. Reassess the clinical status, repeat the haematocrit and review fluid infusion rates accordingly. Sometimes patients receive intravenous fluids elsewhere and present with complications like myocarditis and fluid overload. Fluids containing glucose may exacerbate hyperglycaemia of physiological stress from dengue and in patients with diabetes mellitus. WHO guidelines suggest that the intramuscular injections are contraindicated in patients with dengue as they can result in large intramuscular hematoma.

Group C: Severe dengue includes severe plasma leakage leading to dengue shock or fluid accumulation with respiratory distress, severe haemorrhages or severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis). All patients with severe dengue should be admitted to a hospital with access to intensive care facilities and blood transfusion. Judicious intravenous fluid

resuscitation is essential and usually, the sole intervention required. Plasma losses should be replaced immediately and rapidly with isotonic crystalloid solution. It is important to monitor haematocrit levels before and after fluid resuscitation. Start with isotonic crystalloid solutions at 5-10 ml/kg/hr over 2-4 hours. If the patient improves intravenous fluids can be reduced to 2-3 ml/kg/hr. But if hematocrit increases IV crystalloid or colloid solution at 20 ml/kg as a bolus for 15 minutes needs to be administered. If hematocrit increases a second bolus of IV fluid may be given. If hematocrit falls below 40% in females and <45% in males suspect bleeding. Packed red cell transfusion in case of bleeding recommended. Platelet transfusion is required only if there is clinical evidence of bleeding.

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2.4 Scrub typhus

2.4.1 Introduction

Scrub typhus is caused by *Orientia tsutsugamushi* (*O.tsutsugamushi*) an obligatory intra-cellular gram-negative bacterium but it is not easily stained with gram's stain. It is transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*. Primary reservoir and vector for the disease is *Leptotrombidium deliense*, a trombiculid mite. Rattus is a common reservoir. During wet season the mites lay eggs on vegetation. That is why transmission is seasonal, and the peak of scrub typhus occurs during monsoon and continues in to cooler months in India.

Incubation period of scrub typhus is 6 to 21 days.

Pathogenesis involves focal or disseminated vasculitis and perivasculitis, involving the lungs, heart, liver, spleen, kidney and central nervous system (CNS).

2.4.2 Clinical manifestations

The symptoms may be mild and the clinical course self-limited, with spontaneous recovery after a few days in some cases. But in some patients, the disease may be more severe and protracted, and may be fatal.

Initial clinical features of scrub typhus patients include fever, headache, myalgia, cough and loose motions.

In severe cases encephalitis and interstitial pneumonia are seen.

- The classic case description of scrub typhus includes an eschar at the site of chigger feeding, regional lymphadenopathy, and a maculopapular rash. An eschar at the wound site is the single most useful diagnostic clue. Though eschar was pathognomic of scrub typhus, it was noted in less percentage of patients in Indian studies.
- Respiratory tract involvement is a common manifestation of scrub typhus. Cough and breathlessness are seen in majority of patients. Atypical pneumonia, consolidation, respiratory failure and acute respiratory distress syndrome (ARDS) requiring ventilator support are the common complications in patients with scrub typhus.
- Gastrointestinal system symptoms in the form of vomiting and loose motions are common presenting features of scrub typhus. Clinicians should suspect scrub typhus in a case of fever and diarrhea if accompanied by symptoms of respiratory or central nervous system in an endemic area.
- Acute renal failure is another important complication in scrub typhus and may need dialysis occasionally.
- Scrub typhus, as the name suggests is characterized by fever with altered sensorium in some cases. CNS involvement ranges from aseptic meningitis to frank meningoencephalitis.
- The existence of myocarditis in scrub typhus is easily ignored; because the symptoms of myocardial involvement are usually subclinical. Cardiac conduction abnormalities in the form of bradycardia can be seen on electrocardiogram.

2.4.3 Investigation

- In scrub typhus complete blood counts show anemia, thrombocytopenia and occasionally leukocytosis.
- Liver function tests show elevated hepatic transaminases in which ALT is found to be more than AST and physicians need to pay attention to these observations in endemic areas.
- Elevation in serum creatinine can also be seen in some patients of scrub patients.
- Chest radiograph abnormalities in the form of reticulonodular opacities, air space consolidation, peribronchial infiltration, pulmonary congestion. and pleural effusion.

2.4.4 Diagnostic tests

- Serological testing using IgM ELISA continues to be the mainstay in the laboratory diagnosis of scrub typhus. Indirect immunoflourescence test is the gold standard diagnostic test for scrub.
- Weil-Felix agglutination test is not a very sensitive test, it has high specificity and a positive predictive value. Weil felix can be a useful tool when used and interpreted in correct clinical context.

2.4.5 Treatment:

Table 2.7: Treatment guideline for Scrub typhus

Etiology	Primary treatment	Alternative regimen	Remarks
Scrub typhus infection	Doxycycline 100mg per dose administered twice daily (orally or intravenously) for adults or 2.2mg per Kg for children less than 45.5 Kg for 7 days to a maximum of 15 days	chloramphenicol (500 mg 4 times a day orally for 7days in adults or 150 mg per kg per day for 5 days in children (been proven effective in treating scrub typhus and preventing relapse) Rifampicin or azithromycin or clarithromycin are effective in doxycycline resistant strains of scrub typhus	India where tuberculosis is endemic monotherapy with rifampicin is strongly discouraged

Conclusion

Scrub typhus clinically mimics infections like dengue viral infection, leptospirosis, malaria, pneumonia as all of them may be associated with sudden onset fever, mild hepatitis and thromocytopaenia. In patients in the endemic areas, presenting with fever, respiratory symptoms and hepatitis, scrub typhus should be considered in the differential diagnosis. As delay in treatment may lead to complications and higher mortality, empiric treatment with doxycycline or macrolides may be given in cases where scrub typhus is suspected if facilities for diagnosis are not available.

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CHAPTER: 3

Management of Sepsis

3.1 Introduction

Sepsis and septic shock are the major causes of morbidity and mortality in the intensive care unit patients worldwide. Indian data shows a severe sepsis or septic shock incidence of 28% with a mortality of 18% in the adult ICU population. Early identification of sepsis and septic shock patients and appropriate management in the initial hours has seen a nearly 50% reduction in mortality during the last decade.

3.2 Definitions

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The organ dysfunction is represented by an acute increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more (with the baseline assumed to be 0 in patients without any known pre-existing organ dysfunction).

Septic shock is a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Clinically they are identified by a vasopressor requirement to maintain mean arterial pressure of ≥ 65 mmHg and serum lactate level greater than 2 mmol/L (>18mg/dL) in absence of hypovolemia.

Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly.

3.3 When to suspect

Adult patients with suspected infection can be quickly screened for likelihood of having poor outcomes typical of sepsis if they have at least 2 of the following 3 clinical criteria:

1. Respiratory rate of 22/minute or greater
2. Altered mentation
3. Systolic blood pressure of 100 mmHg or less.

These together constitute a bedside clinical score termed quick SOFA (qSOFA). It is a simple risk stratification tool that can be used to identify patients at risk of sepsis in out-of-hospital, emergency department and general hospital ward settings.

Infection-induced organ dysfunction may be occult; therefore, all patients with infection should be carefully evaluated. Conversely, any unexplained acute onset of organ dysfunction should also raise the possibility of an underlying infection.

3.4 Diagnosis

In patients with suspected sepsis or septic shock, appropriate routine microbiologic cultures should be obtained before initiation of antimicrobial therapy from all potential sites of infection. These may include blood, respiratory secretions, urine, cerebrospinal fluid, wounds, and other body fluids. If it is not logistically possible to obtain cultures promptly (45 minutes), the appropriate antimicrobials should be administered.

In sepsis or septic shock patients, the diagnosis includes identification of a specific anatomic site of infection requiring emergent source control.

Clinical experience with molecular diagnostic methods for the diagnosis of infection is still limited and needs further verification before they can be recommended for use in clinical practice.

3.5 Management

Sepsis and septic shock are medical emergencies requiring urgent assessment, aggressive management and repeated revaluation of the response to treatment. Sepsis management is simplified using the "bundle" approach. A bundle is a selected set of elements of care that, when implemented as a group, effects the outcomes beyond implementing the individual elements alone. Lower mortality has been observed in hospitals with higher compliance of sepsis bundle.

The 1st hour of the patient with sepsis and septic shock within the healthcare facility is the GOLDEN HOUR and appropriate management can make a significant difference to patient outcomes (box 1).

Box 1: Hour-1 Surviving Sepsis Campaign Bundle of Care: The Golden Hour

1. Measure lactate level. Re-measure if initial lactate level > 2 mmol/L.*
2. Obtain blood cultures before administering antibiotics.**
3. Administer broad-spectrum antibiotics.
4. Begin rapid IVadministration of 30mL/kg crystalloid for hypotension or lactate level ≥ 4 mmol/L.***
5. Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg. ****

"Time zero" or "time of presentation" is defined as the time of triage in the emergency department or, if presenting from another healthcare facility, from the earliest time-point in the treatment chart wherein, the patient had all the features consistent with sepsis.

***Two or more sets of blood cultures are recommended before initiation of any new antimicrobial in all patients with suspected sepsis.*

****Hydroxyethyl starches (HESs) are not recommended for intravascular volume replacement in patients with sepsis or septic shock.*

***** Norepinephrine is the first-choice vasopressor.*

Circulatory shock is possible with normal arterial blood pressure, and not all patients with arterial hypotension have a circulatory shock. Resuscitation aims to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion. A targeted central venous pressure (CVP) alone is not recommended to guide the fluid resuscitation. IV hydrocortisone can be used in the treatment of septic shock if hypotension is persisting even after adequate fluid resuscitation and vasopressor use. IV immunoglobulins are not recommended for the management of sepsis or septic shock.

3.6 Antimicrobial therapy

Intravenous antimicrobials must be initiated as soon as possible after recognition for both sepsis and septic shock. In absence of a definitive diagnosis at presentation, which is common (in the Golden hour), empiric broad-spectrum therapy should be initiated to cover all likely pathogens (including bacterial, potentially fungal or viral coverage). Selection of an optimal empiric antimicrobial regimen in sepsis and septic shock is one of the central determinants of outcome. Various factors which must be taken into consideration for deciding the choice of empiric antimicrobial therapy are shown in box 2.

Box 2: Factors determining the selection of antimicrobials for sepsis and septic shock

1. Clinical syndrome/site of infection
2. Prevalent pathogens and their resistance patterns
3. Severity of illness
4. Age and concomitant underlying diseases, chronic organ failures, medications, indwelling devices
5. Immunosuppression or other form of immunocompromise
6. Recent infections, intake of antimicrobials within the previous 3 months

Sepsis can originate from community locations as well as a healthcare facility. About 80% of hospital-treated sepsis cases arise in the community. The common sites of infection leading to sepsis include lungs followed by abdomen, bloodstream, renal and genitourinary tracts.*Refer to the appropriate sections in this guideline for the empirical antibiotic therapy for a different site of infection*. The table below gives empirical therapy for sepsis when the source is unclear.

Table 3.1: Antimicrobial choice for disease conditions

Diagnosis	**Suggested regimens**		**Remarks**
	Preferred	**Alternative**	
Sepsis or septic shock with focus unclear Rule out common tropical infections (chapter 1) Refer to appropriate sections for empirical antibiotic therapy for different sites of infection	Imipenem-Cilastatin +/- Amikacin **+/-** Vancomycin Teicoplanin +/- doxycycline +/- Colistin or polymyxin B *If risk factors for candida add an echinocandin (Caspofungin or micafungin or anidulafungin)	Meropenem or Cefoperazone –Sulbactam +/- Amikacin +/- Vancomycin or Teicoplanin	• Septic shock patient must receive empiric combination therapy with at least two antibiotics of different antimicrobial classes. • Add MRSA or CR-GNB coverage or antifungals in patients with appropriate risk factors. • Avoid piperacillin-tazobactam in septic shock till bacteremia with cephalosporin resistant organisms is excluded, as mortality increases (MERINO trial)[6] • De-escalation of antimicrobials should be considered daily and at the earliest stage when the clinical situation permits/ once culture susceptibility reports are available** • Treatment duration of 7 to 10 days is adequate for most cases. • Longer courses appropriate in slow clinical response, undrainable foci of infection, bacteremia with *S. aureus*, some fungal and viral infections, or immunologic deficiencies. • Measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy.

**Risk factors for invasive Candida infections include immunocompromised status (neutropenia, chemotherapy, transplant, diabetes mellitus, chronic liver failure, chronic renal failure), prolonged invasive vascular devices (hemodialysis catheters, central venous catheters), total parenteral nutrition, necrotizing pancreatitis, recent major surgery (particularly abdominal), prolonged administration of broad-spectrum antibiotics, prolonged hospital/ICU admission, recent fungal infection, and multisite colonization. Triazoles are acceptable in hemodynamically stable, less ill patients who have not had previous triazole exposure and are not known to be colonized with azole-resistant species.*

***If the infection is subsequently proven not to exist, then antimicrobials should be discontinued. De-escalation includes discontinuation of combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution.*

3.7 Metabolic, ventilation therapy and other adjunct therapy

Other important aspects of care of the patients with sepsis and septic shock include the use of blood products, mechanical ventilation, sedation and analgesia, glucose control, renal replacement therapy, venous thromboembolism prophylaxis, stress ulcer prophylaxis, and nutrition.

Table 3.2: Standard doses of antimicrobial agents

Antibiotics	Doses, duration and route of administration
Imipenem-Cilastatin	500 mg IV q6h or 1g q8h
Amikacin	15 mg/kg IV q24h
Meropenem	1gm IV q8h
Cefoperazone – Sulbactam	3g IV q12h
Vancomycin	15 mg/kg IV q8–12h
Teicoplanin	400mg IV every 12h for 3 doses followed by 400mg IV q24h
+/- doxycycline	100 mg iv q12h
+/- Colistin	9mu iv stat, then 4.5 mu iv q12h
Polymyxin B	15-20 lak units iv stat, then 7.5-10 laks iv q12h
Caspofungin	70 mg IV on day 1, then 50 mg IV q24h
micafungin	100 mg iv od
anidulafungin	200 mg iv stat then 100 mg iv od

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CHAPTER: 4

Management of Respiratory tract infections (RTI) & Community Acquired Pneumonia (CAP)

4.1 Upper respiratory tract infections (URTI)

4.1.1 Definition

- The term upper respiratory tract infections (URTI) include acute rhinitis/ rhinosinusitis, acute pharyngitis/ tonsillopharyngitis, acute epiglottitis, acute laryngitis and acute otitis media.
- These infections are the commonest reasons for outpatient visits as well as antibiotic misuse in both adults and children.

4.1.2 Causative Agents

The usual causative agents of URTI are viruses including rhinovirus, influenza, parainfluenza, RSV, human metapneumovirus, enterovirus, adenovirus, Ebstein Barr virus and herpes simplex virus.

Non-viral causes include *Streptococcus pyogenes*, Pneumococcus, Moraxella, *H. influenzae*, *S. aureus*, *B. pertussis*, Mycoplasma, gonorrhoea and *C. diphtheriae*.

4.1.3 Resistance pattern

Group A beta-hemolytic streptococci (GABHS) is universally sensitive to penicillin. Pneumococcal resistance in non meningeal isolates is very low in our country and hence standard doses of amoxicillin generally suffice. Conversely, pneumococcal resistance to co-trimoxazole and macrolides is widespread. Resistance to amoxicillin by production of beta lactamase in *Hemophilus influenzae* is around 30% and that in *Moraxella* is 90%.

4.1.4 Signs and Symptoms

The usual presenting features of URTI include sore throat, runny/ blocked nose; cough with or without systemic symptoms including fever and malaise. The term influenza like illness is used when there are systemic signs such as fever and malaise along with the upper respiratory symptoms.

4.1.5 Management: Investigation and diagnosis

4.1.5.1 Viral URTI

- These illnesses are best treated with symptomatic therapy including paracetamol, nasal saline drops, rest, oral fluids, humidification and certain home remedies such as honey, ginger etc.

- In selected cases oral and nasal decongestants and anti-tussives such as dextromethorphan/ codeine may be used.
- Antimicrobial therapy is not indicated for viral URTI. The patients should be warned about symptoms which indicate complications like breathing difficulty, persistent fever beyond 4-5 days or ear pain.
- The use of oseltamivir in patients with influenza when started within 48 hours of onset reduces duration of symptoms by 1 day, viral shedding/ infectiousness and may reduce the risk of development of complications.
- Empiric therapy with oseltamivir may be considered in patients with influenza like illness during an ongoing outbreak if they are at high risk of complications such as pregnant women, those with co-morbidities and the immunocompromised.

4.1.5.2 Bacterial Pharyngitis

- Group A beta haemolytic streptococcal pharyngitis (GABHS) usually affects children between 5 and 15 years of age and is characterized by sudden onset of fever, sore throat with pain during swallowing.
- Examination findings include tonsillo-pharyngeal erythema and exudates, palatal petechiae, tender anterior cervical adenopathy and sometimes scarlatiniform rash. The positive predictive value of these signs for streptococcal sore throat is around 60%.
- The centor score (3 of 4 criteria) can be used to predict a bacterial etiology: exudative pharyngitis, tender cervical lymphadenopathy, fever, absence of cough.
- Confirmation of diagnosis by rapid antigen test or throat swab culture is desirable but not always possible.
- Treatment is with penicillin V/ amoxicillin is for 10 days.
- Presence of features indicative of viral etiology including coryza, conjunctivitis, cough, hoarseness, diarrhea, ulcerations and viral exanthema have high negative predictive value for GABHS pharyngitis and here diagnostic testing and antimicrobial therapy is not indicated.

4.1.6.1 Bacterial sinusitis should be suspected in the following situations.

a) Persistence and non-improvement of symptoms and signs of acute rhinosinusitis beyond 10 days.
b) Worsening of symptoms or signs including new onset fever, headache or increase in nasal discharge following a typical viral URI that lasted 5-6 days and was initially improving (double sickening).
c) Acute onset of high fever with facial pain or purulent nasal discharge for at least 3-4 days.
d) The recommended treatment for patients with mild disease is amoxicillin and for severe cases/ history of prior antibiotic use or non response to first line therapy is

co-amoxiclav. Treatment duration in adults is for 5-7 days and in children 10-14 days.

4.1.6.2 Acute otitis media (AOM) is defined as either moderate or severe bulging of the tympanic membrane/new onset otorrhoea not due to otitis media OR mild bulging of the tympanic membrane AND recent onset of ear pain/ erythema of the tympanic membrane. Further AOM should not be diagnosed in the absence of middle ear effusion as demonstrated by pneumatic otoscopy or tympanometry.

Pain assessment and relief by using paracetamol or ibuprofen is crucial. Factors that determine need for antimicrobial therapy include the age of the child, whether the disease is unilateral or bilateral, and whether disease is severe (temperature 39 ^{0}C or higher OR severe otalgia OR otalgia persisting for more than 48 hours).

Antibiotic therapy is definitely indicated in any child with otorrhea or severe disease or bilateral AOM in children below the age of 24 months. All other situations (children older than 24 months with non severe AOM whether unilateral or bilateral) or children between 6-24 months with non severe unilateral AOM can be managed with watchful waiting for 48-72 hours or use of antibiotics either upfront or if there is failure to improve with conservative management.

The first line drug for patients who have not received penicillin in the past one month and those with absence of purulent conjunctivitis is amoxicillin. Co- amoxiclav should be used in others and if the patient fails to respond to amoxicillin. The duration of therapy for severe disease and children less than 2 years is 10 days. Children between 2 and 5 years with mild disease can be treated for 7 days and those above 5 years with 5-7 days of therapy.

Table 4.1: Antimicrobial therapy in URTI

Condition	Preferred drug	Alternative	Penicillin allergy
Streptococcal pharyngitis	Penicillin V (not easily available in India, Penicillin G not a substitute since oral absorption is poor	Amoxicillin Benzathine penicillin single dose	Anaphylactic: clindamycin/ clarithromycin/ azithromycin Non-anaphylactic: cephalexin/ cefadroxil
Bacterial sinusitis	Amoxicillin Co-amoxiclav	Ceftriaxone Cefpodoxime (adults)	Adults: doxycycline/ resp quinolones Children: Anaphylactic resp quinolones, Non-anaphylactic: cefixime and clindamycin

Acute otitis media	Amoxicillin Co-amoxiclav	Cefpodoxime, cefuroxime, cefdinir, Ceftriaxone	Anaphylactic: azithromycin/ clarithromycin Non-anaphylactic: cephalosporins

4.2 Lower respiratory tract infections (LRTI)

4.2.1 Acute bronchitis

Acute tracheobronchitis is characterized by cough and phlegm production. The predominant etiology is viral. Antibiotics are not indicated even if sputum is purulent. Treatment is symptomatic; if cough lasts more than 14 days, suspect pertussis and TB. Use macrolides for pertussis and work up for AFB.

4.3 Community acquired pneumonia (CAP)

Community acquired pneumonia (CAP) is one of the most common causes of morbidity and mortality in both adults and children.

CAP is characterised by as

- Symptoms of an acute lower respiratory tract illness (cough with or without expectoration, shortness of breath, pleuritic chest pain) for less than 1 week.
- At least one systemic feature (temperature >37.7°C, chills, and rigors, and/or severe malaise).
- New focal chest signs on examination (bronchial breath sounds and/or crackles); with no other explanation for the illness.
- When a chest X-Ray is available, CAP is defined as the above with new shadows on the X-Ray with no other defined cause.

4.3.1 Etiology and causative agents

The etiology of CAP includes bacteria (*S. pneumoniae*, *H. influenzae*, *S. aureus*, S. *pyogenes*, gram negative bacilli), respiratory viruses (influenza, parainfluenza, RSV, human metapneumovirus, adenovirus, coronavirus), the atypical pneumonia pathogens (*Mycoplasma pneumonia*, *Chlamydophilia pneumonia*, *Legionella* sp) and tropical pathogens (scrub typhus, leptospirosis, melioidosis). The percentage contribution of viruses reduces as age advances and the relative contribution of mycoplasma increases. Gram negative bacteria are mainly seen in newborns and in the elderly. The etiology of CAP in various studies has been established in only 40-70% of the cases. Worldwide including India, *S. pneumoniae* (3-51%) is the commonest organism followed by *H. influenza (5-21%)*, *Mycoplasma pneumoniae* (4-24%) and respiratory viruses (influenza, parainfluenza, RSV, coronavirus, human metapneumovirus 10-36%). Other agents include Legionella species (1-6%) *S. aureus* (1-2%) and in some predisposed individuals *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Mycobacterium tuberculosis should also be considered a possible etiology in some individuals with a slightly protracted illness.

4.3.2 Resistance Pattern

Review of recent studies addressing the problem of pneumococcal resistance reveal the very low prevalence of resist*ance to penicillin i*n *non meningeal isolate*s (< 1%, with revised CLSI breakpoints), but high level of resistance to macrolides (25-30%) and cotrimoxazole (> 90%). Since penicillin resistance is very low, standard doses of amoxicillin (30-40 mg/ kg/day or 500 mg thrice daily in adults)suffice. Resistance in Hib to ampicillin in a recent study evaluating lower respiratory tract isolates was 10%. Resistance in invasive Hib isolates to ampicillin, macrolides and cotrimoxazole in the IBIS study conducted two decades ago was around 40%.

4.3.3 Treatment guideline

- All patients with CAP should be risk stratified for site of care as outpatients, or inpatients based on scores such as CURB -65/ CRB-65, clinical assessment and pulse oximetry. Further triage for inpatients for ICU/ WARD admission can be based on applying the ATS/ IDSA criteria.
- Antibiotics should be administered as early as possible in severe CAP. In the outpatient setting the diagnosis should be confirmed before starting therapy.
- The choice of antibiotics depends on various factors including severity of disease, presence or absence of co-morbidities, likely pathogen, likely resistance pattern and previous antibiotic use.
- Overall the antibiotic therapy is geared towards covering *S. pneumoniae* the commonest pathogen in CAP. Several studies have looked at the benefit of including an atypical cover in the regime and the consensus is that atypical cover/ combination therapy is not routinely required in outpatient CAP since the disease is mild, the benefit of treatment for mycoplasma/ Chlamydia is controversial and macrolides may be associated with cardiac abnormalities in the elderly.
- Combination therapy with beta-lactam and macrolide is indicated in outpatient CAP in the presence of co-morbidities or antibiotic use in previous three months and in all inpatient CAP. The rationale for combination therapy in these settings is to expand the spectrum and covering atypical pathogens (especially legionella in severe CAP), immunomodulation and also that combination therapy has been seen to reduce mortality in some studies.
- The role of fluoroquinolones is well established in CAP and all western guidelines where the baseline prevalence of TB is low endorse them. However, in India where there is a high burden of TB and where TB may present as CAP, use of empiric fluoroquinolone therapy may lead to masking and delayed diagnosis of TB and promotion of drug resistance. **Therefore, fluoroquinolines are best avoided**. Similarly, drugs with anti-tubercular activity including linezolid and aminoglycosides should not be used.

- The empiric addition of oseltamivir should be considered in patients with CAP if there is an ongoing outbreak.
- If CA MRSA is suspected than vancomycin/ teicoplanin may be added empirically (sputum cultures/ endotracheal aspirates have a high yield here); linezolid should be used only once the diagnosis is confirmed and TB is ruled out.
- The duration of therapy in outpatients is 5 days. Therapy in hospitalized patients with CAP can be switched from parenteral to oral after clinical improvement and is 7 days. Patients can be considered for discharge if they are afebrile, accepting orally and hemodynamically stable for 48 hours. Longer duration of therapy should be considered in patients with bacteremic pneumococcal pneumonia, S. *aureus* pneumonia, *Legionella* pneumonia, lung abscess, empyema, pneumonia with enteric gram negative bacilli (*Klebsiella*) or non fermentative gram negative bacilli (*Pseudomonas/ Acinetobacter*) or if there is endocarditis/ meningitis complicating pneumonia.
- CAP in children is classified as pneumonia, (age related tachypnea) severe pneumonia (tachypnea and recessions) and very severe pneumonia (severe pneumonia with hypoxemia, dullness or inability to drink). Severe or very severe pneumonia are ideally treated as inpatients. There is some data that severe CAP can also be treated on an outpatient basis in certain situations. No investigations including CXR are needed for outpatients. Blood cultures and CXR should be performed for inpatients. CBC and CRP may not always help differentiate bacterial from viral CAP. Other investigations to determine etiology are not routinely indicated. Empiric antimicrobial therapy is discussed in Table 2. Salient difference from adult CAP is the selective use of macrolides only if clinical features suggest mycoplasma. Complications such as empyema should be watched out. Duration of therapy for outpatients is 5 days and for uncomplicated pneumonia in inpatients is 7 days.

Table 4.2: Choice of empiric antimicrobial therapy in adult CAP

Type of CAP	Preferred drug	Alternative	Comments
Outpatients without co-morbidities	Co amoxiclav	Macrolides** Cefuroxime Cefpodoxime	Beta lactam preferred over macrolides due to high prevalence of macrolide resistance in *S. pneumoniae* in India. Doxycycline monotherapy 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, empyemas

4.3.4 Empyema

- Empyema is a common complication of bacterial CAP. The common pathogens causing empyema include *Pneumococcus*, *S. aureus*, *S. pyogenes* and sometimes *Klebsiella* or other gram negative bacilli. It should be suspected if there is persistent fever, leukocytosis and effusion on the CXR. USG can be done to confirm the diagnosis. The pleural fluid should be tapped and if it is purulent/ has organisms on the gram stain or culture, empyema is confirmed. It should also be suspected in complicated para-pneumonic effusions (pH < 7.0/ sugar <40 mg/dl/ LDH> 1000 IU/l/ lactate > 45 mg/dl).
- Drainage of the infected fluid is paramount and can be done by chest tube with or without fibrinolytics. VATS or thoracotomy may be needed in certain cases with organized empyema.

Table 4.3: Antimicrobial therapy for Pediatric CAP

	Outpatient	**Inpatient**
Newborns < 1 month	Cefotaxime and gentamicin, add macrolides if Chlamydia suspected (afebrile, staccato cough)	
Age less than 5 years	Amoxicillin Co-amoxiclav	Ceftriaxone Cefotaxime

	Cefuroxime	Co-amoxiclav
Age more than 5 years	Amoxicillin Macrolide only if clinical features suggestive of mycoplasma	Ceftriaxone Ampicillin Co-amoxiclav with/ without macrolide
Suspected MRSA: add vancomycin/ teicoplanin /(linezolid only if TB ruled out)		
Suspected influenza: Add oseltamivir		

Table 4.4 : Drug doses, duration and route

Drug	**Adult dose**	**Pediatric dose**
Penicillin V	500 mg twice daily	250 mg twice daily
Benzathine penicillin	<27 kg 6,00,000 units IM single dose ≥ 27 kg 1.2 million units IM single dose	
Amoxicillin	500 – 1000 mg thrice daily (PO or IV)	15-20 mg/kg twice daily oral 30-35 mg/kg thrice daily IV
Co-amoxiclav	1 gm twice daily/ 625 mg thrice daily oral 1.2 gm IVq8h	15-20 mg/kg of amoxicillin twice daily PO 25-30 mg/kg of amoxicillin component thrice daily IV
Azithromycin	500 mg daily (PO or IV)	10 mg/kg once daily
Clarithromycin	500 mg twice daily	7.5 mg/kg twice daily
Oseltamivir	75 mg twice daily PO	≤15 kg 30 mg twice daily 16-34 kg 45 mg twice daily 35 -44 kg 60 mg twice daily 45 kg and more 75 mg twice daily
Doxycycline	100 mg twice daily	1.5-2 mg/kg twice daily
Clindamycin	300 mg four times a day PO 600 mg thrice daily IV	7 mg/kg thrice daily
Cephalexin	750 mg twice daily PO	20 mg/kg twice daily PO
Cefadroxil	1 gm once daily	30 mg/kg once daily
Levofloxacin	750 mg once daily PO or IV	10-15 mg/kg in one or two divided doses PO or IV
Moxifloxacin	400 mg once daily PO or IV	10 mg/kg once daily PO or IV
Cefpodoxime	200 mg twice daily	5 mg/kg twice daily
Cefuroxime	500 mg twice daily oral 1.5 gm twice daily IV	10 mg/kg twice daily oral 35 mg/kg twice daily IV
Ceftriaxone	2 gm once daily IV	50 mg/kg twice daily
Cefotaxime	2 gm thrice daily IV	30-35 mg/kg thrice daily IV
Cefepime	2 gm twice daily IV	50 mg/kg twice daily
Piperacillin tazobactam	4.5 gm thrice daily	100 mg/kg piperacillin thrice daily
Cefoperazone sulbactam	3 gm twice daily	50 mg/kg of cefoperazone twice daily

Imipenem	1 gm thrice daily or 500 mg four times daily IV	15-25 mg/kg four times daily IV
Meropenem	1 gm thrice daily IV	20-40 mg/kg thrice daily
Vancomycin	1 gm twice daily	10 mg/kg four times daily
Teicoplanin	400 mg twice daily for 3 doses and then 400 mg once daily	12 mg/kg twice daily for 3 doses and then 12 mg/kg once daily
Linezolid	600 mg twice daily PO or IV	10 mg/kg thrice daily PO or IV

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CHAPTER: 5

Management of Intra-abdominal Infections

5.1 Classification

Intra-abdominal infections are broadly classified as uncomplicated and complicated. Generally, if the infection remains confined to the viscus, it is considered uncomplicated and if infection spreads from the organ into the peritoneum causing localized or diffuse peritonitis, it is termed as complicated intra-abdominal infection.

For the purpose of management of complicated intra-abdominal infections, take into consideration the suspected point of origin of infection, i.e., community acquired or healthcare associated infections and severity of infection.

- Community acquired
  a. Mild to moderate severity
  b. High severity or high risk patients
- Hospital acquired infections /Health care associated infections

5.1.1 Disease Overview:

Classification of bacterial peritonitis is based upon the source of the infectious bacteria.

5.1.1.1 Primary or spontaneous peritonitis*:* refers to an extraperitoneal etiology, in which the infectious bacteria enter the peritoneal cavity through the circulatory or lymphatic system. In these cases, the patient usually has an underlying comorbidity that can lead to bacterial migration into the peritoneum. Such comorbidities may include ascites and indwelling peritoneal dialysis catheters. Primary peritonitis is estimated to occur in 10% to 30% of patients with alcoholic cirrhosis. Additionally, patients on chronic ambulatory peritoneal dialysis (CAPD) have, on average, one incidence of peritonitis every 33 months.

5.1.1.2 Secondary peritonitis*:* this most common etiology is the result of infectious bacteria from a source within the peritoneum. Considering the plethora of microflora existing within the abdominal organs, migration of the bacteria from any of the organs into the sterile peritoneum can lead to an inflammatory response, resulting in secondary peritonitis. Dispersion of bacteria from their host organs may result from puncture due to trauma, surgery, or perforation. Ulceration, ischemia, or obstruction may cause the perforation of abdominal organs.

5.1.1.3 Tertiary peritonitis: is persistent or recurrent peritonitis that reappears at least 48 hours after apparent resolution of a primary or secondary peritonitis. Data on the incidence of secondary and tertiary peritonitis are limited. Classification of peritonitis is useful in clinical practice as it can facilitate appropriate diagnosis and treatment.
Since numerical scores for severity assessment may be as good as clinical judgement. One good guide may be as suggested in the Socie´ te´ franc¸aise d'anesthe´ sie et de re´animation (Sfar) guidelines would be presence of 2 or more of the following features

- Hypotension attributed to sepsis
- Serum lactic acid higher than the laboratory's normal values
- Diuresis < 0.5 ml/kg/h for more than 2 hours despite appropriate IV fluid therapy
- PaO_2/FiO_2 ratio < 250 mmHg in the absence of pneumonia
- Serum creatinine > 2 mg/dL (176.8 mmol/l)
- Serum bilirubin > 2 mg/dL (34.2 mmol/l)
- Thrombocytopenia < 100,000/mm

In addition to this, it is important to identify patients who may be at a higher risk of treatment failure. Some of the identified risk factors at the time of admission are

- High APACHE score
- Immunocompromised /immunosuppressed state
- In the Socie´ te´ franc¸aise d'anesthe´ sie et de re´animation (Sfar) guidelines would be presence of 2 or more of the following features

  -Prolonged hospital stay (> 5 days)
  -Prolonged preoperative antibiotic therapy (>2days)
  -diffuse peritonitis

Acute pancreatitis constitutes a separate group by virtue of the nature of disease, progression and management. Broad principles of management of intra-abdominal infections include the following:

- Early initiation of antimicrobials. While culture and sensitivity from intra-op cultures may not be essential for management of an individual case, it would help in formulating empiric antimicrobial policy, particularly for community acquired intraabdominal infection. For hospital acquired infection, culture and sensitivity testing may be useful for guiding empirical therapy.
- For patients requiring hemodynamic support, fluid management should be initiated and done as needed.
- Adequate source control is the backbone of management of patients with intra-abdominal infections. Laparotomy, laparoscopy or percutaneous drainage as appropriate is various options for source control.

5.1.2 Organisms involved

The commonly isolated organisms in IAI include facultative and aerobic Gram negative bacilli (*E.coli, Klebsiella, Pseudomonas, Proteus, Enterobacter spp*), Gram positive aerobic cocci (*Streptococcus species, Enterococcus fecalis, Enterococcus fecium*) and anaerobes (*Bacteriodes* being isolated in most cases). *Enterococcus* may not be an important issue in cholangitis and cholecystitis. Candida species, usually *Candida albicans* are important healthcare associated pathogens in patients who have received antibiotics.

5.1.3 Selecting an antibiotic regimen for empiric therapy

- For community acquired infections, the prevalence of enterobacteriaceae with extended spectrum beta-lactamases (ESBL) is more than ten percent or in patients with severe infection, then it would be advisable to include a beta-lactam- beta-lactamase inhibitor (BL-BLI) or a carbapenem in the regimen. If the prevalence is less than ten percent, then third generation cephalosporin may be used. For patients receiving third generation cephalosporins, additional administration of metronidazole would be needed.
- Double anaerobic cover is now recognized as a redundant practice world over. Empiric cover for *Enterococcus*, methicillin resistant *Staphylococcus aureus* or *Candida* is not necessary in patients with community acquired intra abdominal infection.
- For health care associated infections, the empiric regimen would largely be determined by the profile of organisms found in the hospital settings. A reasonable choice would be imipenem or meropenem (depending on the susceptibility pattern in hospital setting). Covering for enterococci may be needed for healthcare associated infections particularly for postoperative patients, immunosuppressed patients or those who have been on antibiotics which select out enterococci such as cephalosporins.
- In health care associated infections, carbapenem resistant gram negative organisms may be present and may need coverage. An intraoperative culture is usually of benefit in patients with healthcare associated infections.
- Empiric coverage for *Candida* may be needed in immunosuppressed patients, patients with perforated gastric ulcer on acid suppressants, presence of malignancy, recurrent intra-abdominal infection and if the intra-op cultures showing candida. Either an echinocandin or fluconazole can be used.

5.1.4 Duration of therapy

Therapy for complicated intra-abdominal infections should be continued till signs of infection have settled. In select cases a shorter duration of treatment may suffice such as – acute stomach and proximal jejunal perforations without malignancy receiving intervention for source control within 24 hours, bowel injury due to trauma that are

repaired within 12 hours, acute appendicitis sans abscess, perforation or peritonitis. Recently some data suggests that in those patients who are not severely ill and have achieved good source control a shorter duration of treatment may be as good (3-5 days).
For healthcare associated infections, particularly with carbapenem resistant organisms, a longer duration (10-14 days) of treatment may be needed, assuming adequate source control and resolution of clinical symptoms and signs.
For patients receiving antifungal treatment, generally 2 weeks of therapy may be needed, assuming adequate source control and resolution of clinical symptoms and signs.

Table 5.1: Antibiotics regimen for various IAIs

Conditions	First Choice ABs	Alternative	Comments
Community acquired intra-abdominal infection of mild to moderate severity	Cefoperazone-sulbactam	Piperacillin-tazobactam	
Community acquired intra-abdominal infection with high severity	Imipenem or meropenem		
Healthcare associated intra-abdominal infections	Imipenem/ Meropenem + vancomycin	Colistin, Tigecyline	-Based on the findings of intra-operative cultures cover for *Enterococcus* may either be stopped or changed. If multi-drug resistant organism is isolated, based on susceptibility patterns, colistin, tigecyline may be used. -Echinocandins or fluconazole if risk factors for Candida.
Infected pancreatic necrosis, pancreatic abscess	Imipenem-cilastatin and vancomycin		Therapy to be adjusted as per the culture and sensitivity results from pancreatic aspirate or necrosectomy. Antifungal cover with fluconazole, or echinocandins may be added if risk factors for disseminated candidiasis. For nosocomial infections, depending on the culture and sensitivity data, colistin/ tigecycline may be used.
Cholangitis, cholecystitis	As for community associated complicated intra-abdominal infections		
Liver Abscess	Cefoperazone-sulbactam or piperacillin-		The treatment should be changed as per culture report and amoebic serology

	tazobactam with metronidazole to cover for possible bacterial and amoebic etiology		subsequently.

5.2 Spontaneous Bacterial Peritonitis (SBP)

- Spontaneous bacterial peritonitis (SBP) refers to ascitic fluid infection with no recognizable source and occurs commonly in patients with cirrhosis. Among patients with ascites who were followed up for one year, SBP developed in 10-30% with an in-hospital mortality rate of 20%. SBP results from translocation of bacteria from the intestinal lumen.
- Risk factors associated with SBP include cirrhosis, ascitic fluid protein less than 1g/dl, total serum bilirubin greater than 2.5 mg/dl, variceal bleeding and a previous episode of SBP.
- Indications for diagnostic peritoneal fluid aspiration to rule out SBP include emergency visit, hospital admission, local signs or symptoms of peritonitis (abdominal pain, vomiting, diarrhea, paralytic ileus), systemic signs and symptoms of infection (fever, hypotension, leukocytosis, acidosis, hypothermia), hepatic encephalopathy, renal failure and worsening liver function.
- **Diagnosis** of spontaneous bacterial peritonitis requires an ascitic fluid absolute polymorphonuclear leukocyte (PMN) count > 250 cells/mm^3 and a positive ascitic fluid bacterial culture without an intra-abdominal surgically treatable source of infection. Culture-negative neutrocytic ascites refers to patients who have a PMN count of at least 250 cells / mm^3 but with a negative bacterial culture in the absence of pancreatitis or recent receipt of antimicrobial therapy.
- For an initial diagnostic paracentesis, other tests should be performed as clinically warranted on the remaining ascitic fluid which includes albumin, total protein, glucose, lactate dehydrogenase, amylase, and bilirubin.
- Prior to administering antibiotics, ascitic fluid (at least 10 ml) should be obtained and then directly inoculated into a blood culture bottle at the bedside, instead of sending the fluid to the laboratory in a syringe or container. The practice of immediate inoculation in blood culture bottles improves the yield on bacterial culture from approximately 65 to 90%. Separate and simultaneous blood cultures should also be obtained, as up to 50% of patients with SBP have concomitant bacteremia.
- It is important to distinguish SBP from secondary bacterial peritonitis because of the critical need to determine whether surgical intervention is needed.
- Treatment: Empirical antibiotic therapy which targets the likely organisms must be initiated immediately after the diagnosis of SBP. SBP is usually caused by gram negative organisms, *Escherichia coli* and *Klebsiella pneumoniae*. However, *Staphylococcus, Enterococcus* or *Streptococcus* may be implicated. Increasing

numbers of resistant bacteria in the community and multidrug resistant organisms (MDROs) in hospitals has complicated the empiric treatment of SBP.

- Patients with advanced cirrhosis are highly susceptible to the development of infections caused by MDROs, because they require repeated hospitalizations, are often submitted to invasive procedures and are frequently exposed to antibiotics, either as prophylaxis or as treatment.
- As the prevalence of ESBL in the community is more than 10%, we suggest using piperacillin/tazobactam or cefoperazone-sulbactam for the empiric management of SBP. For patients with a possibility of harboring multi-drug resistant organism imipenem or meropenem may be more reasonable.
- Antibiotics should be tailored as per the culture and sensitivity data.
- Patients with risk factors such as ascitic fluid protein concentration less than 1g/dl, variceal bleed or a history of SBP have benefited from prophylaxis with trimethroprim-sulfamethoxazole (one double strength tablet once daily), ciprofloxacin (500 mg b.i.d) or norfloxacin (400 mg o.d) in the western literature. However these antibiotics are unlikely to be useful for prophylaxis in India as the prevalence of resistance is >20% even for community acquired isolates, and may drive further resistance.

Table 5.2: Antibiotics regimen for SBP

Conditions	First Choice ABs	Alternative	Comments
Commonly caused by gram negative organisms, *Escherichia coli* and *Klebsiella.* Occasionally, *Staphylococcus, Enterococcus* or *Streptococcus* may be implicated.	Piperacillin/tazobactam or cefoperazone-sulbactam	For multi-drug resistant organism imipenem or meropenem may be more reasonable.	Antibiotics should be tailored as per the culture and sensitivity data.

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5.3 Acute Diarrhea

5.3.1 Introduction

Every year over ten million cases and over 1000 deaths are reported due to diarrhoea in India. The diarrheal diseases represent one of the five leading causes of death worldwide and are the second leading cause of death in children under five years of age.

5.3.2 Definition

Diarrhea is defined as the passage of loose or watery stools, typically at least three times in a 24-hour period [3]. Acute diarrhea is defined as diarrhea of ≤14 days in duration, in contrast to persistent (>14 days and ≤30 days) or chronic (>30 days) diarrhea.

Table 5.3 Types of Acute Diarrhea

Acute watery diarrhea	**Acute bloody diarrhea**
In a non-epidemic situation, enterotoxigenic *Escherichia coli* (E. coli). Epidemic disease; Vibrio cholera **seasonal out breaks:** Norovirus, Campylobacter species, nontyphoidal Salmonellae, Aeromonas species, and enteroaggregative. *E. coli, Giardia lamblia*	Shigella species, particularly Shigella flexneri, are the most important. Other causes include Campylobacter jejuni, enteroinvasive and enterohemorrhagic E. coli, nontyphoidal Salmonella species, *Entamoeba histolytica*.

5.3.3 Clinical features-

- The onset, duration, severity, and frequency of diarrhea should be noted, with particular attention to stool character (e.g., watery, bloody, mucus-filled, purulent, bilious).
- The patient should be evaluated for signs of dehydration, including decreased urine output, thirst, dizziness, and change in mental status.
- Vomiting is more suggestive of viral illness or illness caused by ingestion of a preformed bacterial toxin.
- Symptoms more suggestive of invasive bacterial (inflammatory) diarrhea include fever, tenesmus, and grossly bloody stool.
- A "rice-water" appearance of stool flecked with mucous is suggestive of cholera. Furthermore, diarrhea caused by V. cholera may present very suddenly with vomiting and abdominal cramping but not frank pain or tenesmus. Fever is uncommon in cholera.

In contrast, shigellosis is typically characterized by the frequent passage of small liquid stools that contain visible blood, with or without mucous.

- Abdominal cramps and tenesmus are common, along with fever and anorexia. Infection with *Entameba histolytica* presents with frequent passage of small liquid stools that contain visible blood and mucous associated with tenesmus.

Occasionally candida species may be the causative agent for diarrhea.

- Symptoms ascribed to Candida-associated diarrhea in the literature include prolonged secretory diarrhea with abdominal pain and cramping but without blood, mucus, fever, nausea, or vomiting.
- Non infective causes of diarrhea must be explored in case of chronic diarrhoea.

The physical exam should focus on characterizing the degree of volume depletion:

- Early hypovolemia – signs and symptoms may be absent
- Moderate hypovolemia – thirst, restless or irritable behavior, decreased skin turgor, sunken eyes
- Severe hypovolemia – diminished consciousness, lack of urine output, cool moist extremities, rapid and feeble pulse, low or undetectable blood pressure, peripheral cyanosis

5.3.4 Diagnostic testing

- Because most watery diarrhea is self-limiting, testing is usually not indicated in general.
- A stool culture is indicated if the patient has grossly bloody stool, severe dehydration, signs of inflammatory disease, symptoms lasting more than three to seven days, or is immunuosuppressed [6].
- Routine microscopy of fresh stool is inexpensive and can identify the presence of numerous fecal leukocytes, suggesting an invasive bacterial infection.

Microscopic evidence of *Entamoeba* trophozoites containing red blood cells provides sufficient basis for treating for amoebic dysentery instead of shigellosis. Notably, finding cysts or

trophozoites without red blood cells in a bloody stool does not indicate that Entamoeba is the cause of illness, since asymptomatic infection is frequent among healthy persons.

5.3.5 Treatment

Adequate fluid and electrolyte replacement and maintenance are essential to the management of diarrheal illness Rehydration.

None to moderate hypovolemia — can be effectively treated with oral rehydration solution (ORS). An improved, reduced osmolarity. ORS solution, containing 75 mEq/L of sodium and 75 mmol/L of glucose.

Severe hypovolemia- should receive intravenous fluids. Ringer's lactate is preferred, but normal saline can also be used.(Normal saline is less preferable because it does not contain potassium to replace losses nor a base to correct acidosis).

- Antimicrobial therapy is not typically indicated for the treatment of acute watery diarrhea in adults. An important exception is the treatment of severe cholera in outbreak settings, for which antibiotics can decrease the duration of illness and the volume of fluid losses.

- The use of probiotics or prebiotics for the treatment of acute diarrhea in adults is not recommended, except in cases of postantibiotic-associated illness.

- In patients receiving antibiotics for traveler's diarrhea, adjunctive loperamide therapy can be administered to decrease duration of diarrhea and increase chance for a cure [7]. Loperamide should be avoided in dysentery.

- In contrast to the treatment of watery diarrhea, adults with bloody diarrhea should be treated promptly with an antimicrobial that is effective against Shigella. Antibiotics reduced the duration of diarrhea and fever in infections caused by Shigella, which is the most common cause of dysentery in resource-limited settings and can otherwise be associated with severe complications.

- Stool microscopy and cultures has to be sent routinely in dysentery syndromes and antibiotics should be selected based on the microscopy and sensitivity testing.

Table 5.4 Antibiotic Treatment for Diarrhea

Suspected Cause	**Antibiotic**
V. Cholerae	Doxycycline (Not recommended in children and pregnant women) 300mg once Azithromycin 1 g as a single dose
Shigella	Ciprofloxacin 500 mg b.d for 3days Alternatively, Ceftriaxone 2g i.v as single dose
Amoebiasis	Metronidazole 500 mg t.i.d for 5 days
Giardiasis	Metronidazole 250 mg t.i.d for 5 days
Campylobacter	Azithromycin 500 mg for 3days
Aeromonas	Ciprofloxacin 500 mg b.i.d for 3days Alternatively, Norfloxacin 400 mg, b.i.d for 3 days

*The antibiotic of choice is Flouroquinolones or Azithromycin. Ampicillin or TMP-SMX are no longer drugs of choice in India in view of high resistance. As the resistance of shigella to Azithromycin and cefixime is nearing 20 percent.

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CHAPTER: 6

Management of Skin and Soft Tissue Infections

6.1 Introduction

Skin and soft-tissue infections (SSTIs) include infections of the skin, subcutaneous tissue, fascia, and muscle. They can present with a wide spectrum of clinical presentations, ranging from simple cellulitis to rapidly progressive necrotizing fasciitis. The major challenge lies in the diagnosis of the exact extent of the disease to institute appropriate management.

6.2 Definitions

6.2.1 Cellulitis: Cellulitis is an acute spreading infection that involves subcutaneous tissue; most commonly caused by Group A *Streptococcus* and *Staphylococcus aureus*. Trauma, underlying skin lesions and spread from adjacent infections such as osteomyelitis can lead to the development of cellulitis. Clinically rapidly intensifying pain and redness is a common presentation. Fever and lymphadenopathy may be present. The borders in cellulitis are not well demarcated. Rarely organisms like *H. influenza* and *Pneumococcus* may also cause cellulitis.

6.2.2 Furunculosis: Furunculosis is a deep infection of the hair follicle leading to abscess formation with an accumulation of pus and necrotic tissue. Furuncles appear as red, swollen, and tender nodules on hair-bearing parts of the body. The most common infectious agent is *S. aureus*, but other bacteria may also be causative. Furunculosis often tends to be recurrent and may spread among family members.

6.2.3 Carbuncle: It is a coalescence of several inflamed follicles into a single inflammatory mass with purulent drainage from multiple follicles.

6.2.4 Erysipelas: It is characterized by abrupt onset of fiery red swelling of the face or extremities. The distinctive features of erysipelas are well defined indurated margins, particularly along the naso-labial fold, rapid progression and intense pain. The most common cause of erysipelas is beta-haemolytic streptococci.

6.2.4 Necrotizing fasciitis: Necrotizing fasciitis is an infection of the deep soft tissues that result in progressive destruction of the muscle fascia and the overlying subcutaneous fat. This condition is notorious for rapid progression. Early and aggressive surgical debridement and treatment with appropriate antibiotics are important to reduce mortality.

Table 6.1: Antibiotics guidelines for skin and soft-tissue infections (SSTIs)

Condition	Organism	Antibiotic	Duration	Comments
Cellulitis	*S.pyogenes* *S.aureus*	Cefazolin Or cephalexin Or Amoxicillin-clavulanate +/- Clindamycin	5-7 days (longer if clinically indicated)	-Obtain blood/ pus cultures before starting antibiotics -Consider poly-microbial pathogens in diabetics -Consider risk factors for MRSA and presence of TSS before using clindamycin
Necrotizing fasciitis	*S. pyogenes* *S.aureus*, anaerobes, Gram negative organisms (polymicrobial)	Piperacillin-tazobactam + Clindamycin	Generally, 14 days if adequate source control achieved	Early surgical debridement essential Send blood and intraoperative specimens for bacterial cultures. Consider use of IVIG for streptococcal NF/TSS
Necrotizing fasciitis	*Aeromonas*/ *V.vulnificus* (suspect when history of exposure to fresh water or salt water respectively)	Ciprofoxacin + Doxycycline	Generally, 14 days if adequate source control achieved	
Erysipelas	*Propionibacterium acnes*/MSSA	Amoxicillin-clavulanate	5-7 days	
Abscess	*S. pyogenes, Oral anaerobes*	Clindamycin **OR** Ampicillin-sulbactum **OR**Amoxicillin-clavulanate	5-7 days	
	S.aureus, facultative gram negative anaerobes	Linezolid **OR** Vancomycin **PLUS** Ciprofloxacin	Generally, 14 days	

Table 6.2: LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) Score (>6 favours NF):

Parameter	Units	Score
CRP	mg/dL	
<15		0
≥15		4
WBC	cells/mm^3	
<15000		0
15000-25000		1
>25000		2
Hemoglobin	g/dL	
>13.5		0
11-13.5		1
<11		2
Sodium	mmol/dL	
≥135		0
<135		2
Creatinine	mg/dL	
≤1.6		0
>1.6		2
Glucose	mg/dL	
≤180		0
>180		1

Table 6.3: Clinical signs which favour NF>cellulitis

Symptoms	**General examination**
High grade fever	Toxic look
Delirium	Hypotension
Lethargy	Tachycardia
Severe pain disproportionate to clinical signs	Pallor
Limb examination	
Skip areas (Areas of normal skin surrounded by infection)	Edema/tenderness extending beyond the cutaneous erythema
Dishwater-like pus discharge	Probe sign* positive
Hypoesthesia over the skin	Bullous lesions
Crepitus	Skin necrosis/ecchymoses
Wooden hard induration of subcutaneous tissue extending beyond the area of apparent skin involvement	

*: After infiltrating the involved area, a 2 cm incision is made down to the deep fascia. Gentle probing is performed with a blunt instrument or index finger and if the tissue dissects with minimal resistance, then probe test is considered to be positive.

6.3 Deep neck space infections

6.3.1 Introduction

Deep neck space infections usually arise from an infected dental source or the tonsils, parotid gland, deep cervical lymph nodes, middle ear, or sinuses. They often progress rapidly and may develop a life-threatening complication. Thus, clinicians must be aware of such infections and should not underestimate their potential extent or severity.

6.3.2 Principles of management

Adequate antibiotics with surgical source control in case of loculated collections are essential for successful management of these infections.

Patients with risk factors for MRSA infection should be treated empirically with linezolid (600 mg orally or IV every 12 hours) or vancomycin (15 to 20 mg/kg IV every 12 hours). Risk factors for MRSA include a history of healthcare exposure, indwelling lines/ devices, intravenous drug use, co-morbid disease (e.g., diabetes mellitus, CKD on dialysis), prior history of MRSA infection and residing in a community or hospital where there is a substantial incidence of MRSA.

Table 6.4: Antibiotics guidelines for deep neck space infections

Site of infection	Organisms	Immunocompetent	Immunosuppressed
Peri-tonsillar abscess (Quinsy)	*S.pyogenes, Oral anaerobes*	Clindamycin **OR** Ampicillin-sulbactum **OR**Amoxicillin-clavulanate	Piperacillin-tazobactam
Suppurative parotitis	*Streptococci, oral anaerobes*	Clindamycin **OR** Ampicillin-sulbactum**OR** Amoxicillin-clavulanate	Piperacillin-tazobactam **plus**Clindamycin
		Note: Urgent ENT reference in case of obstructed salivary duct	
Ludwig's angina	*Streptococci, oral anaerobes*	Clindamycin OR Ampicillin-sulbactum OR Amoxicillin-clavulanate	Piperacillin-tazobactam Plus Clindamycin
Odontogenic	Viridians and other streptococci, *Peptostreptococcus* and other oral anaerobes	Clindamycin OR Ampicillin-sulbactum OR Amoxicillin-clavulanate	Piperacillin-tazobactam Plus Clindamycin
Rhinogenic	*S.pneumoniae*, *H.influenzae*, streptococci, anaerobes	Ceftriaxone + linezolid	Piperacillin-tazobactam + Clindamycin
Otologic	*S.pneumoniae*, *H.influenzae*, streptococci,	Ceftriaxone Plus Metronidazole	Piperacillin-tazobactam + Clindamycin

	anaerobes		
Prevertebral abscess	*S.aureus*, facultative gram negative anaerobes	Linezolid **OR**Vancomycin **PLUS** Ciprofloxacin	Piperacillin-tazobactam + Clindamycin
Lemierre syndrome (Septic jugular thrombophlebitis)	*Fusobacterium necrophorum*, *Streptococcus*, anaerobes	Piperacillin-tazobactam Plus Clindamycin	Piperacillin-tazobactam Plus Clindamycin

#Enterobacteriaceae must be considered as potential pathogens in immunosuppressed hosts (neutropenics, diabetics, critically ill, postoperative infections & trauma)
**Drainage of abscess/ collection where possible should be carried out

Table 6.5: Standard doses of antimicrobials for SSTIs

Antibiotics	**Doses, duration and route of administration**
Cefazolin	1-2 g IV q8h
Cephalexin	750 mg bd, 500 mg TID
Amoxicillin-clavulanate	Oral: 1g bd/ IV 1.2gm TDS
Clindamycin	600-900 IV 8hourly
Piperacillin-tazobactam + Clindamycin	IV 4.5 gm 6 hourly (P-T) + IV 600 mg TDS (Clinda)
Ciprofoxacin	IV 750 mg q12h
Doxycycline	IV200 mg stat f/b 100 mg 1-0-1
Amoxicillin-clavulanate	1g bd

Table 6.6: Standard doses of antimicrobials for Deep neck space infections

Antibiotics	**Doses, duration and route of administration**
Clindamycin	600 mg 6-8 hourly for 2-3 weeks
Ampicillin-sulbactum	3 gm 6 hourly
Amoxicillin-clavulanate	1.2 g 8 hourly (for **Peri-tonsillar abscess)**
Piperacillin-tazobactam	4.5 gm 6-8 hourly 2-3 weeks
Amoxicillin-clavulanate	625 mg 8 hourly
Ceftriaxone	1gm 12 hourly
Linezolid	600 mg 12 hourly
Metronidazole	500 mg 8 hourly
Vancomycin	15 mg/kg 12 hourly
Gentamicin or	1.7 mg/kg IV Q 8 h
Tobramycin	5 mg/kg IV Q 24 h
Ciprofloxacin	400 mg IV Q 12 h

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CHAPTER: 7

Management of Bone and Joint Infections

7.1 OSTEOMYELITIS

7.1.1. Introduction

- Osteomyelitis is an infection of the bone.
- Osteomyelitis is characterized by sequestra formation.

7.1.2 Classification

7.1.2.1 Based on the duration of illness –

a) Acute osteomyelitis (days-weeks)
   Absence of sequestra
b) Chronic osteomyelitis (months-years)
   Presence of sequestra&/or sinus tract

7.1.2.2 Based on the mechanism of infection

a) Contiguous e.g Trauma, soft tissue infection, decubitus ulcer
b) Hematogenous– Most often affects long bones and vertebral bones
c) Vascular insufficiency e.g Diabetes mellitus

7.1.2.3 Based on anatomical stage and host factors -Cierny-Mader staging system

Table 7.1: Classification of Osteomyelitis

Cieny- Mader staging system –Anatomic and Physiologic	
Anatomic stage	Anatomic type
1	Medullary
2	Superficial
3	Localized
4	Diffused
Physiologic host	Physiologic type
A	Normal host
Bs	Systemic compromise
BI	Local compromise
Bis	Systemic compromise and local compromise
C	Treatment worse than the disease

7.1.3 Common organisms causing osteomyelitis

- Hematogenous osteomyelitis is usually monobacterial, Contiguous osteomyelitis may be polymicrobial.
- *Staphylococcus aureus,* Enterobacter species, *Streptococcus* species, *Pseudomonas* species, gram negative bacilli.

7.1.4 Clinical features

- Diagnosis of osteomyelitis should be based on clinical presentation.
- Symptoms can be vague, pain over the site of infection being the most common symptom.
- Typical signs and symptoms of infection like fever, swelling, and tenderness are uncommon.
- Draining sinus tract may be present over infected bone.
- Osteomyelitis following fracture may present with fracture non union.
- Vertebral osteomyelitis can cause cord compression.
- "Probe to bone" test is useful bed side test for diagnosis of osteomyelitis especially in the diabetic foot.

7.1.5 Investigations

7.1.5.1 Blood investigations:

- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often abnormal.
- White blood cell count can be normal or elevated and anaemia can be a feature of chronic osteomyelitis.
- Investigations directed towards identification of systemic illness like blood sugars, renal and liver function tests should be done.

7.1.5.2 Radiology :

- X-ray should be first radiological investigation for a suspected case of osteomyelitis even though is it insensitive test for acute osteomyelitis. However, X-ray finding will be positive in the majority of patients with chronic osteomyelitis. Common finding includes osteopenia, periostitis and Brodie abscess.
- Contrast enhanced MRI is the most sensitive and specific radiological investigation for both acute and chronic osteomyelitis.
- Tracer scan with Tc99 or Gallium 67 citrate has high sensitivity for the diagnosis of acute osteomyelitis in non traumatized bone.
- F-Fluorodeoxyglucose Positron emission tomography (PET) scan can be used if MRI is contraindicated as it has high diagnostic accuracy.

7.1.5.3 Cultures:

- Preferable to collect specimen prior to initiation of therapy and only from wounds that are clinically infected. In case the patient is currently on antibiotics which appear to be ineffective it is advisable to discontinue for 1-2 weeks if possible. Use standard techniques to collect sample.
- Swab cultures and sinus tract cultures may be unreliable

Container**:** Sterile screw-capped container / sterile swabs in the screw capped tubes

A swab from wounds: (generally discouraged as they often grow skin colonizers)

-Collect swabs only when tissue or aspirate cannot be obtained.

-Sinus tract

- Samples should be collected using a syringe and needle.
- It should be placed in a sterile container.
- A portion of the sample should also be placed in a sterile tube containing anaerobic medium like RCM if an anaerobic culture is required.

-Blood culture

- Blood culture should be obtained along with wound and bone culture for all patients presenting with acute Osteomyelitis.

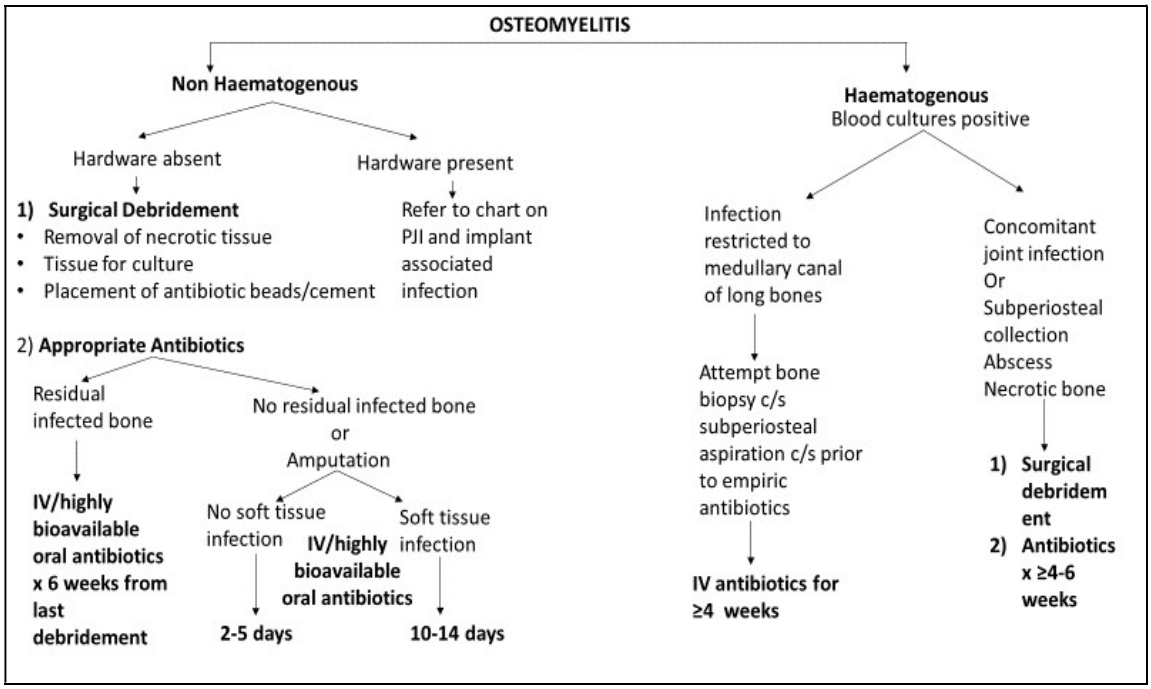
7.1.6 Management

A brief approach to management has been shown in the flowchart below.

(Details of epidemiology & directed antibiotic choices have been discussed in the section on management of B&J Infections.)

In the chart: Placement of antibiotic beads depending on the organism that is suspected or detected earlier

Fig. 7.1 Approach to management of osteomyelitis



7.2 Joint Infections

Infection of the joint can occur in native joint or prosthetic joint.

7.2.1 Septic arthritis of native joint

7.2.1.1 Introduction

- Infection of native joint is most often due to bacteremia, occasionally can also result due to direct injury to joint e.g Trauma, therapeutic joint injections.
- Most common bacteria causing septic arthritis are gram positive, *Staphylococcus aureus* being the commonest. gram negative septic arthritis is seen in the setting of gastrointestinal or urogenital bacteremia.

7.2.1.2 Risk factors

1) Previously damaged joint • Rheumatoid arthritis • Gout Osteoarthritis • Recent joint surgery 2) Diabetes mellitus	3)Intravenous drug abuse 4) Cirrhosis 5) Chronic kidney disease 6) Steroids 7) Skin diseases like Psoriasis

7.2.1.3 Clinical features

- Classic symptoms include acute onset high grade fever with tender swollen joint. Classic symptoms may be masked if the patient is NSAID's or immunosuppressive drugs like steroids.
- The knee joint is the most common site for septic arthritis. Hip, ankle and elbow joints can also be involved.
- Gonococcal or pneumococcal septic arthritis can be polyarticular.

7.2.1.4 Investigations

- Leucocytosis, high ESR and CRP are features of septic arthritis.
- Synovial fluid from the infected joint should send for WBC counts, gram stain, and culture before starting antibiotics.
- In septic arthritis synovial WBC counts are more 50000 cells /mm^3.
- Blood cultures should be obtained for all suspected cases of septic arthritis before starting antibiotics.
- Radiology of infected joint in early stages will show periarticular soft tissue swelling, fat pad oedema with normal periarticular bone. As the infection worsens loss of joint space, periarticular osteoporosis and periosteal reaction will happen. CT and MRI are very sensitive techniques to pick up early changes of septic arthritis.
- Ultrasound is not only useful for assessing the amount of joint effusion but also to guide synovial fluid aspiration.

7.2.1.5 Prosthetic joint infection (PJI)

- Prosthetic joint infection is the worst complication of joint replacement surgeries.
- Presence of biofilm on prosthesis makes diagnosis and treatment of prosthetic joint infections very challenging.

7.2.2 Definition of prosthetic joint infection by infectious disease society of America (IDSA), 2012

PJI is present when one of the following criteria is present:

- Sinus tract communicating with a prosthesis
- Presence of pus
- Acute inflammation on histopathologic evaluation of periprosthetic tissue
- Two or more positive cultures with the same organism (intraoperatively and/or preoperatively)
- Single positive culture with the virulent organism.

Type of infection	Time of PJI	Likely Source of infection
Early	Less than 3 months	Intraoperative
Delayed	3-12 months	Intraoperative
Late	More than 12 months	Haematogenous or Intraoperative

7.2.3 Clinical presentation

- Clinical presentation of PJI is based on time of implantation, organism virulence, and host immunity.
- A detail history and examination will not only help in choosing appropriate investigation but also its interpretation.
- Joint pain and signs of joint inflammation are features of PJI.
- Presence of sinus almost always suggests PJI.

7.2.4 Common organism:

- *Staphylococcus aureus*- common in western literature
- Coagulase-negative Staphylococci common in western literature
- Enterococci
- Gram negative aerobic bacilli quite common in the Indian setting
- *Propionibacterium acnes* for shoulder

7.2.5 Investigations

7.2.5 Preoperative

- Total counts, ESR (>30) and CPR (>10). If ESR and CRP are normal PJI is unlikely.
- Synovial fluid cell counts with percentage of polymorphonuclear (PMN) leucocyte and synovial culture have a high sensitivity and specificity for the diagnosis of septic arthritis and PJI. Cut off values for cells and % of PMN cells for diagnosis of PJI is based on the joint & time after surgery.

7.2.5.2 Intraoperative

- At least 3 and optimally 5-6 samples of periprosthetic tissue must be obtained for:
  a. Histopathology of periprosthetic tissue.
  b. Periprosthetic tissue/pus culture.
  c. Sonication of the prosthetic implant will detect biofilm organisms &improve microbiological yield especially in patients with prior receipt of antimicrobials.
- Molecular methods and synovial fluid biomarkers are newer diagnostic modalities for culture negative PJI.

7.2.6 Management

A brief approach to management has been shown in the flowchart below.

(Details of epidemiology & directed antibiotic choices have been discussed in the section on management of B&J Infections.)

IV treatment has been traditionally recommended, however switching to oral treatment after 2 weeks in selected cases appears to be equally successful

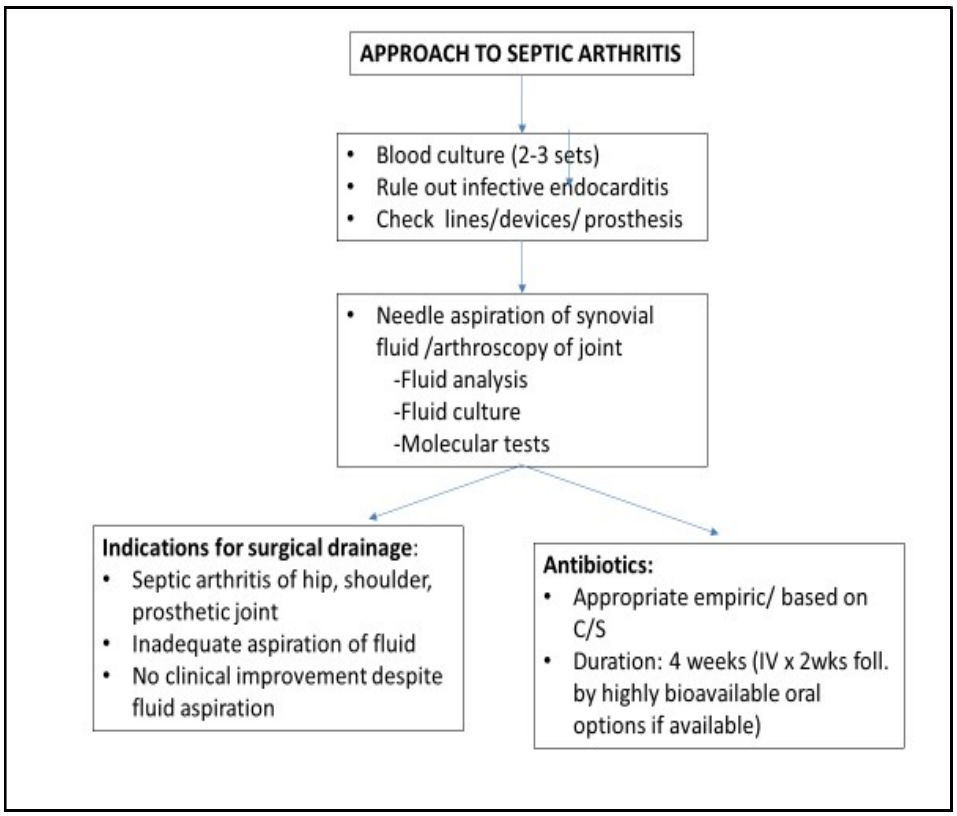


Fig. 7.2 Approach to management of septic arthritis

7.2.7 Management of Bone & Joint infections

7.2.7.1 Principles of management of Bone & Joint (B&J) infections:

a. Cure in the first attempt is essential for B&J infections. Each episode of treatment failure leads to significant tissue damage and loss of functional integrity.
b. The cure is defined as long-term, pain free functional joint/limb with complete eradication of infection. This requires **a combination of an appropriate surgical procedure and long-term directed antimicrobials.** *(Although this is an antimicrobial guideline, we have included and emphasized on appropriate surgical debridement with removal of implants if possible, as this is an integral part of the successful management of B&J infections).*

c. The most important consideration in the management of bone & joint infections is the presence of biofilm associated with implants and prosthesis. The implications of biofilm formation are:
   - Antibiotic penetration into biofilm is poor
   - Antibiotics that penetrate may not act on biofilm organisms (non-replicating, stationary phase)
   - Biofilm organisms are protected from immune processes like phagocytosis
   - Biofilm organisms can acquire resistance patterns from one another

Hence, the antimicrobial regimen used to treat B&J infections should have the following properties:

a. Bactericidal drugs are preferred for deep seated infections e.g. osteomyelitis
b. Agents with good bone penetration
c. Drugs with biofilm activity (penetration into biofilm, action against biofilm organisms)
d. Least toxic and most affordable regimen should be used in view of prolonged duration of treatment

The use of local antibiotic cement spacer/antibiotic impregnated beads is a useful adjunctive treatment option along with systemic antibiotics, especially in drug resistant, difficult to treat B&J infections. It provides high concentrations of the drug locally which elute over a period of days-weeks, without increasing systemic toxicity.

7.2.7.2 Empiric management of B&J infections

Patients with B&J infections, especially chronic osteomyelitis and implant-associated infections often undergo multiple incomplete procedures and receive several courses of empiric antibiotics.

Whereas this practice should be strongly discouraged and every attempt should be made at a tissue diagnosis, fashioning empiric treatment based on the most likely cause is sometimes inevitable when cultures fail to isolate the organism or the patient is clinically unstable.

If ongoing/ recent receipt of empiric antimicrobials, surgery may be deferred for ≥ 2 weeks (antibiotic-free interval), to increase diagnostic yield in a stable patient.

The likely organisms may be predicted based on several factors:

a. Source of infection (haematogenous, contiguous, traumatic, post-surgical)
b. Open or closed injury
c. Immunocompetence of the host
d. Recent contact with health care, the presence of lines, devices, prosthetic valves, implants

e. The time interval between surgery and infection in PJI/ implant associated infection

Table 7.2: Likely organisms after orthopaedic implant surgery/ PJI based on the interval between surgery and infection

Time of Onset- post implant	Likely Organisms	Clinical features
Very early infection (<2 days)	Group A *Streptococcus* *Clostridium perfringens*	High fever, shock, bullae, necrosis, gangrene
Early Infection (<2 wks)	*S.aureus* Gram-negative bacilli	Fever, inflammation, poor wound healing
Delayed Infection (3-10 wks)	CONS NTM, *Propionibacterium acnes*	Persistent pain, low grade fever, mechanical instability, sinus tract
Late Infection (>10 Weeks) **1. Acute** **2. Chronic**	*S. aureus* GNB CONS NTM Polymicrobial Fungal	-Hematogenous seeding - sepsis, local inflammation -Inadequately treated early infection -signs of infection after bridging symptoms: pain, wound healing disturbances, nonunion

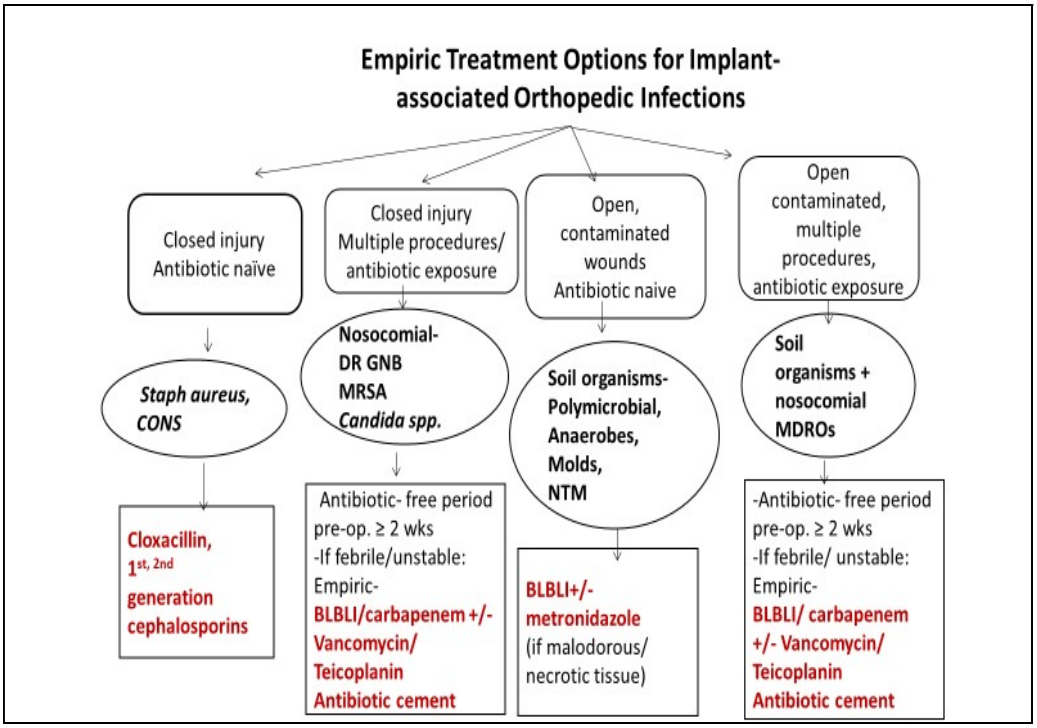


Fig 7.3. Empiric choices for B&J infections

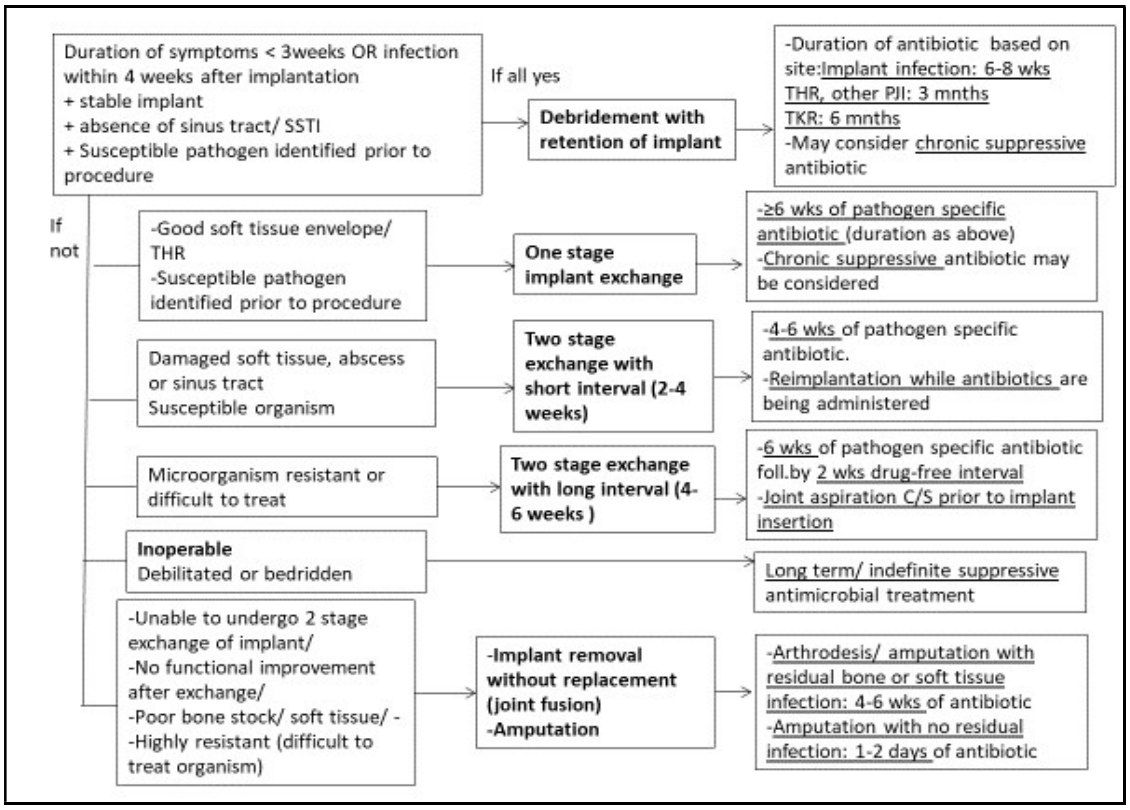


Fig 7.4 Approach to Prosthetic Joint & Implant-associated Infections

Table 7.3: Pathogen-specific Antibiotics for B&J Infections

Organism	Drugs of Choice	Alternative Drugs	Remarks
MSSA	-Cloxacillin -Flucloxacillin -Cefazolin	-Ceftriaxone -Daptomycin	Rifampicin 300-450mg PO/day may be added in presence of hardware Possible antagonism with Beta-lactams. Best results if along with FQN (FQN use is unlikely in India due to widespread resistance)
MRSA	-Vancomycin -Teicoplanin	-Daptomycin - Linezolid	-Rifampicin 300-450mg PO/day (as above) -High dose of vancomycin used 15-20mg/kg q8-12h (max. 2g/dose) Monitor trough levels, renal function
B-hemolytic *Streptococcus*	-Penicillin G - Ampicillin -Ceftriaxone	Vancomycin (if immediate hypersensitivity to Pen)	Monitor vancomycin trough levels

Enterococcus spp. **Penicillin-susceptible** **Penicillin resistant**	-Penicillin G - Ampicillin Vancomycin -Teicoplanin	-Vancomycin -Teicoplanin -Daptomycin - Linezolid	-Combination therapy with aminoglycoside not proven superior in PJI -May use BLBLI (piperacillin-tazobactam) for BLase producers - VRE to be treated as per individual susceptibility (daptomycin, linezolid) are options
Pseudomonas spp.	Ceftazidime Cefepime	-Piperacillin tazobactam -Meropenem (for ESBL producers) -Polymyxin / Colistin	Ciprofloxacin 750mg PO BD may be used upfront if susceptible (good penetration & bioavailability) -Renal dose adjustment for colistin only (Polymyxins have poor B&J penetration, use antibiotic laden spacer/ beads)
Enterobacteriaceae	Beta-lactam based on in vitro susceptibility	Piperacillin-tazobactam Meropenem (for ESBL producers) -Polymyxin / Colistin	Ciprofloxacin 750mg PO BD may be used upfront if susceptible (good penetration & bioavailability) -Renal dose adjustment for colistin only (Polymyxins have poor B&J penetration, use antibiotic laden spacer/ beads)
Propionibacterium acnes	Ceftriaxone	-Vancomycin -Clindamycin	Monitor vancomycin trough levels Higher risk of CDAD with clindamycin prolonged use
Gram- neg. Anaerobes	Metronidazole		Metronidazole need not be added for additional anaerobic cover in presence of BLBLI/ carbapenems

**Parenteral antibiotics are generally recommended for at least the 1st 2 weeks, may step down to oral antibiotics with good bioavailability if susceptible to complete the course of treatment*

*** Antibiotic-impregnated cement spacers/beads must be considered in addition to systemic antibiotics especially in resistant infections with few drug options/ drugs which have poor B&J penetration/ drug toxicity.*

Table 7.4: Directed Oral Antibiotic Options for Treatment of B&J Infections

Organism	Antibiotic	Dosage	Chronic Suppression
MSSA	Cloxacillin/ Flucloxacillin Cephalexin	1000 mg TDS/QDS 1000 mg QDS	500 mg TDS 500 mg TDS
MRSA	Linezolid TMP-SMX Doxycycline	600 mg bd 800/160 mg BD 100 mg BD	Linezolid Difficult for a prolonged period 800/160 mg BD 100 mg BD
B- haemolytic *Streptococcus*	Cephalexin Amoxicillin	1000 mg QDS 500 mg QDS	500 mg TDS 500 mg TDS
Enterococcus spp.	Amoxicillin	500 mg QDS	500 mg TDS
Pseudomonas spp.	Ciprofloxacin	750 mg BD	500 mg BD
Enterobacteriaceae	Ciprofloxacin TMP SMX Doxycycline	750 mg BD 800/160 mg BD 100 mg BD	500 mg BD 800/160 mg BD 100 mg BD

After initial IV antibiotics for 2-3 weeks, high dose oral antibiotics may be used for susceptible isolates for the remaining duration of therapy.

Table 7.5: Etiology of osteomyelitis, septic arthritis, prosthetic and implant-associated infections

Study Centre	GP Organisms	GN Organisms	Enterobact-eriacaceae	Non fermenters	Resistance
ICMR (includes SSTI, B&J data)	53.9%	53%	22.2%	30.9%	-
Tummala et al AP 2017	74%	40%	14% of GNB	21% of GNB	MRSA 31.57%
Mishra et al Bhopal 2016	21%	77%	59%	18%	MDR- 35% ESBL- 65% CRE- 58%
Chhabra et al Himachal Pradesh 2015	26%	74%	61%		
Rajkumari et al Delhi 2014	22%	78%	50%	50%	CRE-72%
Fernandes et al Mangalore 2013	60.9%	37.5%			ESBL-31.7%

Table 7.6: Likely etiology of B&J Infections based on Host and Environment

Open Injuries-Soil contamination	**Recent health-care contact/ lines/ devices etc.**	**Special hosts (neutropenic, immunosuppressants, HIV, post-transplant, CKD)**
Gram-negative Enterobacteriaceae	*S. aureus* (MSSA/ MRSA)	*Nocardia spp.*
Pseudomonas spp.	CONS	*Salmonella* spp.(sickle cell, thalassemias)
Acinetobacter spp.	*Enterococcus* spp.	*Burkholderia pseudomallei* (diabetics, alcoholics)
Clostridium spp. (anaerobes)	Drug resistant GNB	*Candida* spp. *Cryptococcus* spp.
Nocardia spp.	*Burkholderiacepacia*	Endemic mycoses *(Histoplasma spp.)*
NTM	NTM	Opportunistic moulds (*Aspergillus* spp., Mucor)
Environmental moulds	*Candida* spp.	(Above organisms must be kept in mind in addition to other routine causes of B&J infections)

Table 7.7: Standard doses of antimicrobial agents

Drugs of Choice	**Doses**
Cloxacillin	2 g q4-6h
Flucloxacillin	2 g q4-6h
Cefazolin	2 g q8h
Ceftriaxone	2-4g q24h
Vancomycin	1 5mg/kg q12h
Teicoplanin	12 mg/kg q12h x 3 doses; foll. by 12 mg/kg/d
Daptomycin	8-10 mg/kg/d (MRSA)
Linezolid	600 mg q12h
Penicillin G	20-24mu/day (divided into 6 doses)
Ampicillin	2 g q4-6h
Ceftazidime	2 g q8h
Cefepime	2 g q 12h
Piperacillin tazobactam	4.5 g q6-8h
Meropenem	1g q8h
Polymyxin	15L IV loading dose, 5L IV q8h
Colistin	9 mU loading dose, 3mU IVq8h
Clindamycin	600-900 mg q8h
Metronidazole	500 mg q8h

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CHAPTER: 8

Management of CNS Infections

8.1 Acute Febrile Encephalopathy (AFE)/ Acute Encephalitis Syndrome (AES)

- A case of AFE/ AES is defined as the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures).
- The causes of AFE/AES are listed below
  - Acute bacterial meningitis
  - Acute viral encephalitis
  - Tubercular meningitis
  - Sepsis associated encephalopathy (due to systemic infections including UTI, pneumonia, enteric fever etc)
  - Cerebral malaria
  - Other pathogens: *Mycoplasma, Rickettsia, Leptospira*
- Non infectious causes: Reye's syndrome, acute disseminated encephalomyelitis, metabolic/toxic encephalopathy, non convulsive status epilepticus (NCSE) and autoimmune encephalitis.
- Acute febrile encephalopathy is a medical emergency. The algorithm below details the approach towards diagnosis and management of a case of AFE/ AES in children but applies similarly to adults as well.
- Initial management includes resuscitation and stabilization based on the clinical condition followed by clinical evaluation, imaging and investigations to establish the diagnosis. Empiric therapy (may include ceftriaxone, acyclovir, doxycycline and artesunate) should be started immediately after drawing blood cultures pending results of tests. Supportive care should be continued and then therapy narrowed based on the results of investigations.

8.1.1 Evaluation and management of AFE/AES case

Step I: Rapid assessment and stabilization

- Establish and maintain airway: Intubate if GCS<8, impaired airway reflexes, abnormal respiratory pattern, signs of raised ICP, oxygen saturation <92% despite high flow oxygen and fluid refractory shock.
- Ventilation, Oxygenation

- Circulation: Establish IV access, take samples (CBC, Blood sugar, KFT, LFT, electrolytes, blood gas, lactate), fluid bolus if in circulatory failure (20 ml/kg NS), inotropes if required
- Identify signs of cerebral herniation or raised ICP
- Temperature: treat fever and hypothermia
- Treat ongoing seizures- benzodiazepine, followed by phenytoin loading

Step II: Clinical evaluation: History and examination establish etiology (Table 8.1)

Table 8.1: Causes of AFE with pointers to diagnosis and recommended tests

Cause	Pointers to diagnosis	Diagnostic test
Meningococcus	Petechial rash, adrenal hemorrhage	Blood and CSF cultures Latex/PCR in CSF for meningococcus
Herpes simplex virus 1 and 2	PLEDS on EEG, MRI showing temporal lobe involvement, CSF rbc	CSF HSV PCR for HSV-1 and II
HHV6, HHV 7	Rash	Specific PCR in CSF
EBV	Rash, generalized adenopathy, tonsillitis, organomegaly	EBV VCA IgM in blood EBV PCR in CSF
Varicella zoster	Antecedent rash	Varicella IgM in blood CSF varicella PCR
HIV	Fever, adenopathy, rash	HIV ELISA in blood HIV PCR in blood
Japanese encephalitis	Epidemiology, dystonic and extrapyramidal movements MRI shows changes in thalami, basal ganglia, substantia nigra	IgM antibody in serum and CSF
Measles	Antecedent or concurrent rash History of vaccination	Measles IgM in blood and CSF
Mumps	Antecedent/ concurrent parotitis, high amylase,low sugar in CSF	Mumps IgM in blood Mumps virus in CSF by PCR
Influenza	Respiratory prodrome, ongoing outbreak	Influenza PCR in throat swab
Dengue	Ongoing outbreak, rash, low WBC and platelets, biochemical hepatitis	Dengue specific PCR in CSF Dengue IgM, NS1 antigen in blood
Chikungunya	Ongoing outbreak, Rash, severe joint pains	Chinkungunya PCR in CSF Chinkungunya PCR in blood, IgM in blood
Enterovirus	Vesicular lesions in the mouth, GI symptoms, brain stem involvement	Specific PCR in CSF
Rabies	Animal bite, hydrophobia, brain stem involvement	Specific IgM antibody in CSF Nuchal skin biopsy/ conjunctival smears for direct fluorescent antibody Brain biopsy
Chandipura	Epidemiology	PCR in CSF, saliva/ IgM

		ELISA in CSF
Nipah	Epidemiology, contact with animals, fruit bats	PCR/ IgM ELISA in CSF
Mycoplasma	Respiratory illness, skin rash, haemolytic anemia	Mycoplasma IgM in blood Mycoplasma PCR in throat swab
Rickettsia	Epidemiology, rash, eschar, multisystem involvement	IgM & IgG antibodies in serum Scrub typhus DNA in whole blood, buffy coat, eschar/skin rash
Leptospirosis	Icterus, myalgia, renal failure	Leptospira PCR in blood Specific IgM in blood
Enteric fever	Protracted illness, hepatosplenomegaly	Blood cultures
Cerebral malaria	Pallor, splenomegaly	Smear or rapid antigen test for malaria
Sepsis associated encephalopathy	Infection at extra CNS site	Blood, urine cultures, CXR, chest and abdominal CT

Step III: Empirical Treatment (must be started immediately after drawing blood cultures)

- Ceftriaxone
- Acyclovir (use in all suspected sporadic viral encephalitis)
- Artesunate (stop if peripheral smear and RDT are negative)
- Doxycyline

Step IV: Imaging (MRI preferred, CT if MRI not available)*

Step V: Tests to establish a diagnosis (Table 8.2)

Table 8.2: Differentiation of cause of AFE based on CSF analysis

Parameter	ABM	Partially treated ABM	Viral	TBM
CSF TLC	1000-5000 (<100-10000)	100-1000	10-1000	50-1000
CSF DLC	80-95% PMN	L > PMN	L> PMN In acute stage PMN may predominate	L > PMN In acute stage PMN may predominate
CSF sugar	<40 in 50-60%	Low	Normal (except mumps)	ratio <0.5 in 95%
CSF protein mg%	100-500, elevated in all	100-500	100-500	50-1000
CSF lactate	Elevated	Elevated	Normal	?

L: Lymphocytes PMN: polymorphonuclear cells

- Two sets of blood cultures, Urine analysis and cultures, CXR.
- CSF examination with cell count, protein, sugar, aerobic cultures and if available, lactate. Ten ml should be saved for further tests.
- PCR/serology/ viral cultures in CSF/ blood/ respiratory secretions/ stool/ rectal swab

Step VI: Supportive care and treatment

- Maintain euglycemia, control fever, and maintain hydration
- Treat raised intracranial pressure, mild head-end elevation–15-30°
- Treat seizures: Give anticonvulsant if history of seizures, if GCS <8, features of raised ICT
- Steroids: Pulse steroids (methylprednisolone or dexamethasone) must be given in children with suspected ADEM.

Step VII: Review of diagnosis based on reports of the microbiologic tests and MRI to see if a definitive diagnosis has been made and targeted therapy

Step VIII: Prevention/treatment of complications and rehabilitation

- Physiotherapy, posture change, prevent bed sores and exposure keratitis
- Complications: aspiration pneumonia, nosocomial infections, coagulation disturbances
- Nutrition: early feeding
- Psychological support to patient and family

** If the diagnosis of HSV is made a treat for 14-21 days. Stop acyclovir if alternative diagnosis made/ if MRI imaging does not suggest HSV/if two PCR 48 hours apart are negative*

**Imaging should be done before a lumbar puncture in patients with those with focal deficit, papilloedema, immune compromised hosts and those with features of raised ICP. Other contraindications for a lumbar puncture include respiratory/ cardiovascular compromise, platelet counts of less than 30,000 or infection at the site of the lumbar puncture.*

8.2 Acute Bacterial Meningitis (ABM)

8.2.1 Signs and symptoms

Acute meningitis is characterized by the classic triad of fever, neck stiffness and alteration of sensorium. Case definitions have varied in various studies but in one pediatric study clinically suspected meningitis was defined as a child presenting with fever (either by history based on parents'/guardian's recall or based on clinical findings

of body temperature) for a duration of less than seven days along with one of the following signs; neck stiffness, bulging fontanelle, altered or reduced level of consciousness, prostration or lethargy, convulsions without documented seizure disorder. Clinically probable meningitis was defined as a child presenting with suspected meningitis and CSF examination showing turbid appearance, leukocytosis >100 cells/mm^3or leukocytosis 10–100 cells/mm^3 with either decreased glucose (<40 mg/dl) or elevated protein (>100 mg/dl) levels. Confirmed meningitis was defined as a patient with a positive CSF latex/ culture/ PCR and or positive blood culture with clinical syndrome consistent with meningitis.

8.2.2 Etiology

The etiology and resistance pattern of ABM is age dependent (Table 8.3). Unlike the western world, Group B *Streptococcus* and *Listeria* are not reported as common causes of neonatal meningitis in India. A significant proportion of late onset neonatal meningitis can also be due to nosocomial pathogens including MRSA and *Candida.*

H. Influenzae and meningococcus are uniformly susceptible to the 3rd generation cephalopsorins. There is a rising incidence of resistance in *S. pneumoniae* to penicillins and 3rd generation cephalosporins. In a study from Vellore, India 167 CSF pneumococcal isolates were evaluated from 2008-2016. The penicillin non susceptibility increased from 9.5% in 2008 to 42.8% in 2016 and cephalosporin resistance increased from 4.7% in 2008 to 28.5% in 2016. Overall resistant rates were 43.7% for penicillin and 14.9% for cephalosporins. Of the 25 isolates that were resistant to cephalosporins, 8 were fully resistant (MIC $\geq$ 2) and 17 were intermediately resistant (MIC 1)

10.2.3 Investigations and Diagnosis

The initial evaluation for a patient with suspected bacterial meningitis should include at least a complete blood count, two sets of blood cultures and if available CRP and PCT. CSF evaluation is a must. When a lumbar puncture cannot be done immediately, blood cultures should be drawn and empiric antibiotics administered.

- The CSF should be sent for cell count, sugar and protein, gram stain and culture. An extra sample should be preserved for later tests that may be required. Samples should ideally be examined within 30- 60 minutes to increase positivity in CSF culture and for accurate assessment of cell counts. If the delay is expected the samples should be kept at room temperature and never refrigerated. The sensitivity of latex agglutination tests is kit dependent and variable.
- Molecular tests have enhanced sensitivity as compared to cultures and can be requested if available. Commercially available multiplex meningitis panels covering common bacterial, viral and fungal pathogens that cause community acquired meningitis (Pneumococcus, Meningococcus, *H. Influenza*, Group B *Streptococcus, Listeria*, *E. coli* K1, Cytomegalovirus, Enterovirus, Herpes simplex virus 1 and 2,

Human herpes virus 6, Human parechovirus, Varicella zoster virus and *Cryptococcus neoformans/gattii*

- The empiric antibiotic regime for suspected/ probable bacterial meningitis is discussed in Table 8.3.

Table 8.3: Etiology and empiric therapy of community acquired acute bacterial meningitis

Age	Likely pathogens	First line	Alternative
Age < 1 month	Gram negative (*Klebsiella*, *E coli*, *Pseudomonas, Acinetobacter*) *Staphylococcus, Enterococcus, Pneumococcus, Candida*	Meropenem (Add vancomycin if risk of MRSA)	Cefotaxime and gentamicin
1month – 50 years	*S. pneumoniae, Haemophilus influenzae, Meningococcus*	Ceftriaxone and vancomycin	Cefotaxime and vancomycin
>50 years, alcoholism or other diseases of impaired CMI	*S. pneumoniae, Meningococcus, Listeria*, gram negative bacilli	Ampicillin and ceftriaxone and vancomycin	Meropenem and vancomycin

- The administration of dexamethasone 15- 20 minutes prior to giving the first dose of antibiotic has been found to be beneficial for pneumococcal meningitis in adults and *Hemophilus influenza* meningitis in children. The benefit of dexamethasone in childhood pneumococcal meningitis is debatable. The dose is 0.15 mg/kg every 6 hours for 48 hours -96 hours (10 mg 6 hourly in adults). A practical issue is that the turnaround time for confirmation of etiology of meningitis is at least 48 hours unless molecular tests are used. Also in most suspected meningitis, the first dose of antibiotic is given soon after drawing blood cultures/ doing the lumbar puncture even before the basic CSF reports come in. Therefore it is acceptable to at least give one dose prior to the antibiotic in suspected meningitis. Further doses can be continued depending on the CSF reports. Steroids are not recommended for meningitis in neonates.
- If an organism is identified, therapy can be modified accordingly. If the organism is cephalosporin susceptible, vancomycin can be stopped. Consider adding rifampicin if cephalosporin MIC ≥4 µg/mL, if the child's condition worsening after 48 hours of vancomycin + ceftriaxone, if dexamethasone has been given or if repeat LP shows the presence of bacteria.
- In patients improving clinically, there is no need to repeat CSF analysis to demonstrate improvement or prior to stopping therapy. Repeat CSF should be done in cases of clinical non response at 48 hours, patients with penicillin/cephalosporin resistant strains who have received adjunctive dexamethasone, and in neonates to document

sterilization of CSF. Causes of clinical non response in a case of bacterial meningitis include complications such as subdural empyema, cerebral abscess, ventriculitis etc or drug resistance.

- The duration of therapy for uncomplicated meningitis is generally 10-14 days. If a specific pathogen is identified then duration is pathogen dependent: 7 days for meningococcus and *H. influenzae*, 10-14 days for pneumococcus, 2-3 weeks for group B *Streptococcus*, 3-6 weeks for *Listeria*, and 3 weeks for gram negative meningitis.

8.3 Health care associated meningitis/ ventriculitis:

- Health care associated meningitis/ ventriculitis is seen in patients undergoing neurosurgeries, head trauma, external ventricular drainage, lumbar punctures etc.
- The etiology depends on local epidemiology but commonly includes multi drug / extremely drug resistant gram negative pathogens including *Acinetobacter, Pseudomonas, Klebsiella* and *Staphylococcus aureus/ epidermidis*.
- Diagnosis is a challenge since sensorial obtundation (a cardinal symptom of meningitis) may be due to the underlying disease/ surgery. The CSF may be abnormal due to pre existing bleed/ surgery induced chemical meningitis. The patients are frequently on antibiotics and hence microbial isolation rates are low.
- CSF should be sampled and sent for cell count, protein, sugar and aerobic cultures. Elevated CSF lactate (> 4 mmol/l) and procalcitonin help in differentiating between infective and chemical meningitis. The results of cultures especially those obtained through EVD should be carefully interpreted since they may grow colonizers/ contaminants. Contrast MRI is recommended to pick up meningitis, ventricular enhancement, abscesses, cerebritis, and empyemas.
- Empirical therapy depends on local flora but usually includes high dose meropenem with vancomycin. Therapy should be modified based on culture reports. Surgical drainage of pus and removal of hardware may be needed. For carbapenem resistant pathogens, intraventricular / intrathecal therapy with colistin/ polymyxin B/ aminoglycosides is indicated. The drugs are best administered through an Omaya reservoir but may sometimes have to be given through EVD/ lumbar punctures. Doses of drugs that can be administered in the CSF are listed in Table (Annexure 2). The duration of therapy varies depending on the causative organism but is generally 2-3 weeks (Table 8.4).

Table 8.4: Treatment of health care associated meningitis and ventriculitis

Organism	Preferred drug	Alternative drug
Methicillin sensitive *Staphylococcus*	Cloxacillin	Ceftriaxone
Methicillin resistant *Staphylococcus*	Vancomycin	Linezolid/Cotrimoxazole if susceptible
Non ESBL gram negative	Ceftriaxone	Cefotaxime/ Ceftazidime
ESBL gram negative	Meropenem	Cotrimoxazole/ Moxifloxacin
Carbapenem resistant gram negative	Systemic Colistin/ Polymyxin B with (depending upon susceptibility) high dose tigecycline/minocycline/ fosfomycin/ co-trimoxazole/ quinolones/chloramphenicol With intraventricular/ intrathecal colistin/ polymyxin / aminoglycosides	

8.4 CSF shunt infections

- The usual symptoms include fever with headache/ nausea/ lethargy, tenderness or erythema over the subcutaneous tunnel and symptoms of peritonitis/pleuritis in patients with ventriculoperitoneal/ ventriculopleural shunts.
- The initial investigation should be a tap of the shunt chamber and sending the CSF for cell count, protein, sugar and aerobic cultures. The lab should be asked to incubate the samples for 10 days to detect organisms such as *Propionibacterium acnes*.
- For confirmed shunt infections the shunt should be removed and a temporary external ventricular drain inserted. The shunt should be sent for cultures.
- Antimicrobial therapy depends on the causative organism. For culture negative shunt infections/ pending culture reports, a combination of ceftriaxone and vancomycin may be used. If the organism is highly drug resistant/ not responding to treatment, antibiotics should be administered through the external ventricular drain.
- The time of shunt re implantation depends on the causative organism and extent of infection. It can be done as soon as after 2 days of negative cultures in patients with CONS and normal CSF sugar, or 7 days of negative cultures in patients with CONS and abnormal CSF findings, 10 days of negative cultures in patients with infection with S. aureus/ gram negative bacilli. The total duration of antimicrobial therapy varies from 7-10 days for CONS to 10-14 days for *S. aureus* and gram negative bacilli.

8.5 Brain abscess:

- The etiology of brain abscess is based on the underlying predisposing factor and is listed in Table 8.5 along with the choice of empiric therapy.
- An attempt should be made to establish the etiology by blood cultures and aspiration of pus. This is especially required if the host is immunocompromised. Imaging of the chest and abdomen should be done to see if an extra-CNS site can be sampled.

- Drainage by aspiration is important for large abscesses/ drug resistant organisms. Primary excision can also be attempted. Treatment should be modified as per cultures and should be given for at least 4-6 weeks and till radiologic stabilization. Medical treatment is significantly shortened if abscess drainage is performed and can be even 3 weeks where excision of the abscess is done.

Table 8.5: Etiology and empiric therapy for brain abscess

Predisposing factor	**Likely etiology**	**Empiric therapy**
Hematogenous spread from cyanotic congenital heart disease/ lung infections/ endocarditis	Aerobic/ microaerophilic *Streptococci, S. aureus*	Cefriaxone and metronidazole with/ without vancomycin
Contiguous spread from otitis media/mastoiditis/sinusitis/ dental infection	Aerobic, microaerophilic, anaerobic streptococci, Anaerobic gram negative bacilli, *S. aureus*, *Pseudomonas*	Ceftriaxone and metronidazole
HIV	*Mycobacterium* tuberculosis, *Nocardia, Toxoplasma, Cryptococcus, Listeria*	No empiric therapy
Immunocompromised	*Nocardia, Mycobacterium, Toxoplasma, Mucorales, Aspergillus, Listeria, Cryptococcus, Candida*	
Neonates	*Citrobacter*/ Enterobacteriaceae, *Candida*	Meropenem

Table 8.6: Doses of drugs used in CNS infections

Drug	**Adult dose**	**Paediatric dose**
Artesunate	2.4 mg/kg 0,12 and 24 hours and then q 24 hourly	< 20 kg 3 mg/kg at 0,12 and 24 hours and then q 24 hourly
Acyclovir	10 mg/kg 8 hourly	10 mg/kg 8 hourly and in children below 12 20 mg/kg 8 hourly
Ceftriaxone	2 gm 12 hourly	50 mg/kg 12 hourly
Ceftazidime	2 gm q 6-8 hourly	50 mg/kg 8 hourly
Cefepime	2 gm 8-12 hourly	50 mg/ kg 12 hourly
Cefotaxime	2 gm 6 hourly	50 mg/kg 6 hourly
Meropenem	2 gm 8 hourly	40 mg/kg 8 hourly
Colistin	9 million unit loading and then 4.5 million units 12 hourly	150,000 units/ kg loading and then 75000 units/kg 12 hourly
Polymyxin B	20000- 25000 units/kg loading and then 12500 to 15000 units/kg 12 hourly, single dose	15-25,000 units/ kg loading and then 5000-7500 units/ kg 8 hourly

	not to exceed 20,00,000 units	
Fosfomycin	4 gm 6 hourly	75-100 mg/kg/dose 6 hourly
Cotrimoxazole	3-6 mg/kg of TMP thrice daily	
Vancomycin	15 mg/kg (max 2 gm)eight hourly	15 mg/kg 6 hourly
Cloxacillin	2 gm 4 hourly	50 mg/kg 6 hourly
Doxycycline	100 mg 12 hourly	1.5-2 mg/kg 12 hourly
Chloramphenicol	1-2 gm 6 hourly	25 mg/kg 6 hourly
Rifampicin	600 mg once daily	10-20 mg/kg once daily
Metronidazole	400 mg 8 hourly	10 mg/kg 8 hourly
Amphotericin B deoxycholate	1 mg/kg/day	
Liposomal amphotericin B	3-5 mg/kg/day	
Fluconazole	800 mg loading and then 400 mg once daily	12 mg/kg loading and then 6 mg/ kg daily 25 mg/kg loading in neonates and then 12 mg/kg daily

Table 8.7: Doses of drugs to be given by the intrathecal/ intraventricular route (CSF shunt infections)

Drug	Dose
Vancomycin	5-20 mg
Teicoplanin	5-40 mg
Amikacin	5-50 mg
Gentamicin	1-8 mg
Colistin	10-20 mg
Polymyxin B	50,000 units
Daptomycin	2-5 mg
Tobramycin	5-20 mg

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CHAPTER: 9

Management of Urinary Tract Infections (UTI)

9.1 UTI syndromes

- **Asymptomatic bacteriuria (ASB):** The presence of microbiologically significant bacteria in a non-contaminated urine specimen in a patient without signs and symptoms of urinary tract infection.
- **Acute Cystitis:** Syndrome involving dysuria, frequency and urgency with or without fever with chills. Similar symptoms can also be seen in urethritis. This is termed simple UTI.
- **Acute Pyelonephritis:** A clinical syndrome characterized by flank pain, tenderness or both and fever associated with dysuria, urgency and frequency. Acute pyelonephritis indicates acute infection in the kidney. In children, this is considered as complicated UTI. In infants, it may present as septicemia without overt clinical source.
- **Complicated UTI:** UTI occurring in a patient with co-morbid medical/ surgical conditions e.g.diabetes mellitus and/or anatomic abnormalities of the urinary tract e.g. stricture urethra. In young children, suspected pyelonephritis is termed complicated UTI, as a significant percentage will have an underlying congenital abnormality of the kidney and urinary tract (CAKUT).

9.1.2 Other commonly used terminologies

- **Relapse**: Recurrence of bacteriuria with the same infecting microorganism that was present before therapy was started.
- **Re-infection**: Recurrence of bacteriuria with microorganism different from the original infecting organism.

9.1.3 When to suspect (risk factors)

• Female sex • Vaginal infection • Prior UTI • Sexual activity • Diabetes mellitus • Urinary catheter • Neurogenic bladder	• Renal calculi • Renal stent • Urethral stricture • Benign prostatic hypertrophy(BPH) • Prostate cancer • Vesicoureteric reflux • Bladder dysfunction

9.1.4 Common organisms causing UTI (As per ICMR - AMRSN data 2017)

- *Enterobacteriaceae* - 73.2 %
  - *E. coli* - 49.24%
  - *Klebsiella spp* -17.44%
  - *Proteus spp* - 1.4%
  - *Citrobacter* - 1.3%

- *Enterococcus species* - 10.9%
- Non-fermenting gram-negative bacilli - 8.2%
- *Staphylococcus aureus* - 0.9%

9.1.5 Management of Urinary tract infection

9.1.5.1 Investigation and diagnosis

a. **Urine microscopy** - the presence of 10 leukocytes/mm^3 of uncentrifuged urine or 10 leukocytes/hpf of the centrifuged sample, in a clinically suspected UTI, is important for diagnosis.
b. **Dipstick leukocyte esterase test** – This is a rapid screening test for UTI; a negative test result does not rule out UTI.
c. **Urine culture** –
   - This is most useful when collected from a patient with clinical features of UTI, and should always be collected before the first dose of antibiotic.
   - Usually, bacteriuria of 10^5cfu/ml is associated with UTI. However, any colony count is significant in symptomatic young women and men with pyuria. Any colony count of bacteria grown from a suprapubic aspirate is significant.
   - The sample is to be collected in a sterile screw-capped container and up to a minimum volume of 10-20 ml.
     - Midstream clean catch
     - Supra-pubic aspiration especially in infants
     - Aseptic single catheterization for sample collection
     - Collection procedure in a catheterized patient: If the catheter is in place <14 days, urine must be collected using a syringe and needle (No. 26) from the Foley's catheter after disinfecting the rubber surface with 70% ethyl alcohol. If the catheter is >14 days, replace the old catheter before collection of urine for culture.
   - Urine samples should not be obtained from catheter bags.
   - Storage & Transport**:** Transport of the specimen and plating should be done within 1 hour. If delay, the urine sample must be refrigerated at 4ºC for a maximum of 6-8 hours.

d. **Blood cultures (two sets)** – Should be sent before the first dose of antibiotics if the patient is febrile, has suspected acute pyelonephritis or complicated UTI.

e. **Radiology** – Radiology should only facilitate diagnosis of UTI

- Ultrasound of kidney, urinary tract and bladder is essential for all complicated and recurrent (more than 2 episodes) UTI.
- CECT of kidney and the urinary system is indicated when pyelonephritis, perinephric abscess or intra-renal abscess are suspected.

Table 9.1: Clinical features and investigations for different UTI syndromes

Condition	Clinical symptoms	Routine urine analysis	Culture	Radiology
Asymptomatic bacteriuria (ASB)	Nil	May or may not have significant pyuria and/or dipstick leukocyte esterase test positive	Positive	Normal
Acute Cystitis	Fever with chills Frequency, urgency, dysuria Suprapubic tenderness	Significant pyuria and/or Dipstick leukocyte esterase test positive	Positive	Bladder wall thickening
Acute Pyelonephritis	In addition to cystitis- •Vomiting, flank pain, renal angle tenderness •Hypotension •Features of septicemia in young infants	Significant pyuria and/or Dipstick leukocyte esterase test positive	Positive	- Ultrasound –renal swelling - CECT if performed - Renomegaly, decreased opacification of affected area, perinephric fat stranding underlying Congenital anomalies of the kidney and urinary tract (CAKUT) - DMSA if performed - Photopenic area
Acute epididymo-orchitis	Acute onset unilateral scrotal pain with / without swelling; Torsion to be ruled out	Significant pyuria and/or dipstick leukocyte esterase test positive	-Urethral swab for *N. gonorrhoeae* culture -MSU for microscopy and culture First pass urine /urethral swab for	- Colour Doppler ultrasound for Testicular vascularity assessment to differentiate between epididymo-orchitis and testicular torsion.

			nucleic acid amplification test (NAAT) for *N. gonorrhoeae*, *C. trachomatis* and *M. genitalium*, if available	

9.1.6 Treatment:

Table 9.2: Empiric treatment regimens for urinary tract infections, (when culture results are awaited)

Urinary syndrome	Drug of choice	Alternative choice	Comments
Acute cystitis	• Nitrofurantoin • Fosfomycin	• Co-trimoxazole • Ertapenem • Amikacin (can be used in children as well)	• Dosage adjustment as per eGFR. • Fosfomycin and nitrofurantoin should be avoided when there is suspicion of pyelonephritis or prostatitis / presence of systemic features of infection. • Fosfomycin susceptibility to being requested for, and used only for Gram-negative MDR organisms.
Acute Pyelo-nephritis	• Piperacillin – tazobactam • Ertapenem	• Imipenem • Meropenem • Amikacin (recommended for children as well)	• Dosage adjustment as per eGFR. • Treatment is for a minimum of 7 days. • The total duration of treatment is 14 days in children. • Same treatment regimen to be used for complicated UTI except the duration is extended (7-14 days).
Acute Prostatitis	• Ertapenem 1 g IV once daily	• Piperacillin-tazobactam • Imipenem • Meropenem • Trimethoprim-Sulfamethoxazole	Urine and prostatic massage specimen for cultures to be collected before antibiotics. Prostatitis requires a minimum of 21 days antibiotics.
Epididymo-orchitis (High risk of sexually transmitted)	Ceftriaxone + Doxycycline	• Ofloxacin • Levofloxacin	Total duration of treatment is 14 days (except for Levofloxacin where it is 10 days)
Epididymo-orchitis (Low	• Ofloxacin • Levofloxacin		

risk of sexually transmitted; likely due to enteric or urinary organisms)			

**ICMR, AMRSN data 2017*

Note: -

1. Local antimicrobial resistance patterns should be the basis for empiric treatment.
2. For acute pyelonephritis, three strategies may be employed: hospital admission, completely outpatient parenteral antibiotic therapy (OPAT) or single dose of parenteral antibiotic and supportive care in emergency room before home discharge with subsequent OPAT.
3. Antibiotics should be changed based on susceptibility results as soon as they are available.
4. Intravenous antibiotics must be reviewed at 48 hours, and stepping down to oral antibiotics should be considered.
5. Post-treatment urine cultures in asymptomatic patients are not indicated routinely.
6. UTIs in males are usually complicated and uncommon in the absence of obstructive pathology.
7. No antibiotic treatment is required when there is the presence of pus cells in urine, along with negative culture results or in those with asymptomatic bacteriuria. If the pyuria persists, causes for sterile pyuria should be investigated.

9.2 UTI in children

- Cystitis can be treated with nitrofurantoin or amoxycillin for duration of 5-7 days.
- Acute pyelonephritis and complicated UTI is best treated with amikacin as a single dose for the first few days till the child is accepting oral feeds. Thereafter the antibiotic may be changed to an oral preparation based on susceptibility pattern. Duration of treatment is 14 days. There is no role for a short-term treatment in children.
- Children with a Vesicoureteric reflux may be treated with antibiotic prophylaxis as a single nighttime dose. Co-trimoxazole or Nitrofurantoin is preferred in children beyond three months of age.

Table 9.3: Standard doses of antimicrobial agents

Antibiotics	Doses, duration and route of administration
Acute cystitis	
1. Nitrofurantoin	100mg BD for 5 days
1. Nitrofurantoin	1.25-1.75 mg/kg oral 6 hourly (Dose in children)
2. Fosfomycin	3.0 gm single dose
3. Co-trimoxazole	ds 1 tab bd for 3 days
4. Ertapenem	1 g IV once daily for 7 days
5. Amikacin	15mg/ kg/day once daily IVor IM for 3 days
Acute Pyelo-nephritis	
6. Piperacillin – tazobactam	4.5 g IV 6 hrs
7. Ertapenem	1 g IV once dailyfor 7 -10 days
8. Imipenem	1 gm 8 hourly IV
9. Meropenem	1 g IV q8h
10. Amikacin	15mg/kg/day once daily IV/IM for 7-14 days
Acute Prostatitis	
11. Ertapenem	1 g IV once dailyfor 7 -10 days
12. Piperacillin-tazobactam	4.5 g IV 6 hrs
13. Imipenem	1 gm 8 hourly
14. Meropenem	1g IV q8h
15. Trimethoprim-Sulfamethoxazole	(160-800mg) BD
Epididymo-orchitis	
16. Ceftriaxone	500 mg IM
17. Doxycycline	100 mg BD
18. Ofloxacin	200 mg BD
19. Levofloxacin	500 mg OD

Table 9.4: Antimicrobial Susceptibility of Enterobacteriaceae isolates from urine*.

	E. coli	**C**	**E**	**K**	**M**	**P**	**Pr**
Amikacin	86	83	61	56	NI[#]	79	NI
Cefazolin	24	-	-	27	-	NI	-
Cefotaxime	26	56	33	28	NI	62	NI
Ciprofloxacin	28	66	47	38	NI	43	NI
Colistin	100	NI	97	91	NI	-	NI
Cotrimoxazole	40	59	37	30	NI	NI	-

Etrapenem	83	88	65	56	NI	88	NI
Fosfomycin	84	-	-	-	-	-	-
Imipenem	91	88	75	78	NI	90	NI
Levoflox	35	77	68	48	NI	63	NI
Meropenem	85	79	62	57	NI	88	NI
NFT	83	85	45	48	NI	34	
Pip-Taz	80	84	60	56	NI	97	NI

*ICMR, AMRSN data 2017 # number less than 30 (number insignificant)

C: Citrobacter, E: Enterobacter, K: Klebsiella, M: Morganella , P: Proteus, Pr: Providencia

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CHAPTER: 10

Management of Hospital Acquired Infection (HAI)

10.1 Problem statement

Hospital acquired infections (HAIs) refer to an infection that was neither present nor incubating at the time of admission to a healthcare facility. It is estimated that worldwide, over 1.4 million patients suffer from HAI at any given point of time. Multidrug resistant organisms are commonly responsible for HAI. The problem is further compounded by the severe paucity of new antimicrobials, making treatment extremely difficult.

10.2 Factors responsible for HAIs

10.2.1 Microbial agent

Patients are constantly exposed to a variety of microorganisms in the hospital. Whether contact results in an infection depends on agent related factors such as inoculum of infection, virulence of the organism and antimicrobial resistance of the prevailing organisms. The source of the organism may be exogenously acquired from another person or indirectly via inanimate objects or hands of healthcare workers. It may also be endogenous (patient's own flora) as is the case in *Clostridium difficile* infections.

Genes coding resistance determinants are often present on mobile genetic elements which spread across hospital environments and species barriers, leading to the emergence of multidrug resistant strains of bacteria under antibiotic selection pressure. The normal microbiota of patients also changes due to these selection pressures, leading to suppression of sensitive organisms to any given drug, while the resistant bugs thrive. An example is *Acinetobacter baumanni* which is intrinsically resistant to a high degree to commonly used antibiotics and is able to especially thrive in hospital environments inspite of the antibiotic selection pressures.

10.2.2 Host factors

Important host related factors include immune status of the individual, co-morbidities and disease processes as well as diagnostic and therapeutic interventions.

10.2.3. Environment

Hospitals provide a unique environment where there is a mix of infectious sources, reservoirs, vehicles of transmission and susceptible hosts interact at close quarters. Patients coming into the hospital with an infection or asymptomatic carriage of pathogenic microorganisms become primary sources of infection for susceptible patients

and staff. Staff in turn may act as vehicles of transmission to other patients who acquire and further the spread of the infection. The busy activity in a crowded hospital with frequent transfers of patients from one unit to another, and specialty specific units where concentration of highly susceptible patients occurs in one area (e.g. NICU, burn units, medical and surgical intensive care units, haemoncology and transplant units), all contribute to the development of nosocomial infections. Microorganisms spread through contaminated objects, devices, and materials which act as fomites, or through health care worker hands, which subsequently come into contact with susceptible body sites of patients.

10.2.4 Infection control and HAIs

The results of the SENIC study carried out almost 33 years ago in the USA, reported that with an effective infection control program, the incidence of HAI can be reduced by as much as 32% along with a substantial reduction in health care costs. Hospitals in the US have been practising infection control and surveillance for over 50 years; have sufficient human and medical resource availability, and a comprehensive legal framework backing infection control programs, including mandatory surveillance and hospital accreditation policies. The situation is far less rosy in developing countries which consequently show manifold higher rates of HAIs. Apart from resource constraints, the primary plausible causes of these higher rates in developing countries include:

- Many hospitals lack a formal infection control policy and procedures.
- There are still no legally enforceable regulations for the implementation of infection control programs (e.g. national infection control guidelines).
- If there is a legal framework, adherence to and compliance with the guidelines is irregular.
- Hospital accreditation is not mandatory in some countries.
- Low nurse-to-patient staffing ratios, which have proved to be highly connected to high HAI rates.
- Hospital overcrowding.
- Lack of medical supplies, and
- Lack of training for nurses and health care workers on infection control.

10.2.5 Impact on patient care and outcomes

Impact of HAI is measurable in terms of the following:

- prolonged hospital stay
- long-term disability
- increased antimicrobial resistance
- additional financial burden for health system
- high costs for patients and their family
- mortality

As an example, the mortality rate directly attributable to bloodstream infection in critically ill patients has been estimated to be 16–40% and the increase in length of stay between 7.5–25 days. Less than 36% of population in India has some form of health insurance coverage and out-of-pocket payments are still among the highest in the world. A study conducted in the cardiothoracic unit of a tertiary care hospital in North India revealed that the costs of hospital treatments in patients with HAIs were six times higher than that of controls without HAIs, in terms of drug costs, hospital stay, consultation fees, cost of antibiotics and investigations. Thus the additional burden of costs attributable to these infections has serious implications on the patients. The emergence of drug resistance in hospitals has the potential of becoming a global phenomenon with medical tourism.

It is therefore imperative that adequate importance be given to prevention of these infections with appropriate infection control policies and procedures as well as antimicrobial stewardship based on local and national antibiotic resistance data.

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10.3 Surgical Site Infections (SSI)

10.3.1 Introduction

Surgical site infections are now the most common and costly of all hospital-acquired infections, accounting for 20% of all HAIs. With an incidence of 2-5% in patients undergoing in-patient surgery, SSIs are associated with increased length of stay on an average 9 days and a 2 to 11- fold higher mortality, of which almost 77% may be attributed to the infections itself. Perioperative antimicrobials are often the most common antimicrobial prescriptions in health care facilities.

According to the CDC's NHSN, SSIs are classified by the depth and tissue involved a superficial SSI that involves only the skin or subcutaneous tissue, a deep incisional SSI involves the fascia and /or muscular layers and an organ space SSI involves any part of the body opened or manipulated during a procedure excluding the previously mentioned layers (CDC).

10.3.2 Criteria for defining a Surgical Site Infection (SSI)

10.3.2.1 Superficial incisional SSI

a. Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:
b. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
c. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
d. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and the superficial incision are deliberately opened by the surgeon unless incision is culture-negative.
e. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

10.3.2.2 Do not report the following conditions as SSI:

a. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
b. Infection of an episiotomy or newborn circumcision site.
c. Infected burn wound.
d. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.

10.3.3 Deep incisional SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if the implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38 ºC), localized pain or tenderness unless the site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.
   Notes:
   - *Report infection that involves both superficial and deep incision sites as deep incisional SSI.*

- *Report an organ/space SSI that drains through the incision as a deep incisional SSI.*

10.3.4 Organ/space SSI:

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Table 10.1: Classification of surgical wound and their antimicrobial prophylaxis

Surgical Wound Classification	Antimicrobial prophylaxis
Class I/Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet the criteria.	None or single perioperative dose of cefuroxime/ cefazolin
Class II/ Clean-Contaminated: An operative wound in which the respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category,	**Cefazolin or Ampicillin-sulbactam or Ceftriaxone or** (Limited to patients requiring antimicrobial treatment for acute cholecystitis or acute biliary tract infections which may not be determined prior to incision. Factors that indicate a high risk of infectious complications in laparoscopic

provided no evidence of infection or major break in technique is encountered.	cholecystectomy include emergency procedures, diabetes, long procedure duration, intraoperative gallbladder rupture, age of >70 years, conversion from laparoscopic to open cholecystectomy, American Society of Anesthesiologists classification of 3 or greater, episode of colic within 30 days before the procedure, re-intervention in less than one month for noninfectious complication, acute cholecystitis, bile spillage, jaundice, pregnancy, nonfunctioning gallbladder, immunosuppression) **Clindamycin or** **Vancomycin** For procedures in which pathogens other than staphylococci and streptococci are likely, an additional agent with activity against those pathogens could be considered. For example, if there is surveillance data showing that gram-negative organisms are a cause of surgical-site infections (SSIs) for the procedure, practitioners may consider combining clindamycin or vancomycin with another agent like cefazolin, aztreonam, gentamicin, or single-dose fluoroquinolone if the patient is β-lactam allergic).
Class III/Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.	Cefuroxime + Metronidazole Metronidazole+Aminoglycoside/ Fluoroquinolone
Class IV/Dirty-Infected: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.	Cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin–sulbactam, ceftriaxone + metronidazole, ertapenem Clindamycin + aminoglycoside or aztreonam or fluoroquinolone + metronidazole

10.3.5 Common pathogens

a. *Staphylococcus aureus*
b. *E. coli*
c. *Pseudomonas aeruginosa*
d. *Klebsiella pneumonia*
e. *Proteus sp.*
f. Coagulase negative *Staphylococcus*
g. *Enterococcus sp.*

10.3.6 Investigations

a. Samples: From pus or wound swab
b. Transport: Immediate transport to the lab
c. Culture:
   - Aerobic: Blood agar, Mac Conkey agar, 37 ^{0}C in air
   - Anaerobic: Brain Heart Infusion agar with hemin and vitamin K (anaerobic incubation): 37 ^{0}C, under anaerobic conditions
   - Fungal culture (if needed): SDA with appropriate antibiotics/ BHI-BA with appropriate antibiotics and incubation temperatures (25 ^{0}C and/or 37 ^{0}C)

In culture confirmed cases of SSI/ soft tissue infections, antimicrobials should be based on lab AST reports

10.3.7 Choosing an appropriate prophylactic antibiotic for surgical procedures

- Antibiotics should be chosen on the basis of their effectiveness against the pathogens most likely to be encountered rather than against every possible pathogen. Skin flora (eg, *Staphylococcus*) are the usual target, so the first-generation cephalosporins are recommended (cefazolin) in most studies. Some studies also recommend cefuroxime.
- Patients with a history of anaphylaxis or urticaria or rash occurring immediately after penicillin therapy are at increased risk of immediate hypersensitivity to penicillins and should not receive prophylaxis with a beta-lactam antibiotic.

10.3.8 Timing of prophylactic antibiotics

- Give the first dose within one hour before incision.
- Antibiotics should be administered before an incision is made to ensure that antimicrobial levels in the tissue are adequate and maintained for the duration of the procedure.

10.3.9 Route of administration and dose selection:

Prophylactic antibiotics for surgical procedures should be administered intravenously. The dose of an antibiotic required for prophylaxis is the same as that for therapy of infection. The full therapeutic dose of an antibiotic should always be given. The upper range of the dose should be considered for large patients or those undergoing long operations.

10.3.10 Continue no longer than 24 hours postoperatively

- Most studies have demonstrated efficacy of peri-operative antibiotic prophylaxis for only 12 hours or less. Whenever short and long courses are compared, the shorter course has proven equally effective. A single dose is as effective as multiple doses, and antimicrobial prophylaxis after wound closure is unnecessary.

- Prolonged antibiotic prophylaxis beyond 48 hours is not only ineffective in reducing infections but increases antimicrobial resistance and the risk of infection with *Clostridium difficile*.

10.3.11 Re-dose for long surgeries

- Patients undergoing surgery that extends beyond two half-lives of an antibiotic should be re-dosed intra-operatively.
- An additional dose of prophylactic agent is not indicated in adults unless there is blood loss of up to 1500 ml during surgery or haemodilution of up to 15 ml/kg.

Table 10.2: Operations and likely Surgical Site Infection (SSI) pathogens

Operations	**Likely Pathogens**	**Prophylactic antibiotic before surgery**
Placement of all grafts, prostheses, or implants	*Staphylococcus aureus*; CoNS	Cefazolin OR Cefuroxime
Cardiac	*Staphylococcus aureus; CoNS*	Cefazolin OR Cefuroxime
Neurosurgery	*Staphylococcus aureus; CoNS*	Cefazolin OR Cefuroxime
Breast	*Staphylococcus aureus; CoNS*	Cefazolin OR Cefuroxime
Ophthalmic	*S. aureus*; CoNS; streptococci; Gram negative bacilli	Topical moxifloxacin given as 1 drop every 5–15 min for 5 doses
Orthopedic Total joint replacement, closed fractures/use of nails, bone plates, other internal fixation devices, functional repair without implant/device,	*Staphylococcus aureus*; CoNS; Gram-negative bacilli	Cefazolin For 'below-the-belt' surgeries, Piperacillin-Tazobactam +

trauma		Clindamycin
Non-cardiac thoracic Thoracic (lobectomy, pneumonectomy wedge resection, other non-cardiac mediastinal procedures), closed tube thoracostomy	*Staphylococcus aureus*; CoNS; Streptococcus pneumonia; gram-negative bacilli	Cefazolin OR Cefuroxime OR Ampicillin-sulbactam
Vascular	*Staphylococcus aureus*; CoNS	Cefazolin OR Cefuroxime
Appendectomy	Gram-negative bacilli; anaerobes	Piperacillin-Tazobactam OR Cefoperazone-sulbactam
Biliary tract	Gram-negative bacilli; anaerobes	Piperacillin-Tazobactam OR Cefoperazone-sulbactam
Colorectal	Gram-negative bacilli; anaerobes	Piperacillin-Tazobactam OR Cefoperazone-sulbactam
Gastroduodenal	Gram-negative bacilli; Streptococci; oropharyngeal anaerobes (e.g., peptostreptococci)	Piperacillin-Tazobactam OR Cefoperazone-sulbactam
Head and neck (major procedures with an incision through oropharyngeal mucosa)	*Staphylococcus aureus*; streptococci; oropharyngeal anaerobes (e.g., peptostreptococci)	Amoxicillin-clavulanate OR Ampicillin-sulbactum OR Cefazolin+metronidazole
Obstetric and gynecologic	Gram-negative bacilli; enterococci; group B streptococci; anaerobes	Cefazolin OR Ampicillin-sulbactam
Urologic	Gram-negative bacilli	Prophylaxis based on pre-operative urine culture susceptibility pattern OR Cefazolin, Cotrimoxazole

Table 10.3: Antibiotics for treatment of incisional surgical site infections

Surgery of Intestinal or Genitourinary Tract
Single-drug regimens
Piperacillin-tazobactam 3.375 g every 6 h or 4.5 g every 8 h IV
Imipenem- 500 mg every 6 h IV/ Meropenem1 g every 8 h IV
Combination regimens
Ceftriaxone 1 g every 24 h + metronidazole 500 mg every 8 h IV
Ciprofloxacin 400 mg IV every 12 h or 750 mg po x 12 h + metronidazole 500 mg every 8 h IV

Surgery of trunk or extremity away from axilla or perineum
Cloxacillin or flucloxacillin
Cefazolin 0.5–1 g every 8 h IV
Surgery of axilla or perineum
Metronidazole 500 mg every 8 h IV Plus Ciprofloxacin 400 mg IV every 12 h or 750 mg po x 12 h

In the ICMR's surveillance data, 39% of the 12,336 isolates from out-patients and 32% of the isolates from ward were from pus samples. Gram negative pathogens accounted for 76% isolates from the surgical site and 62% from pus, which should have an important bearing which framing treatment guidelines, especially, since most guidelines target *S. aureus.*The overall rate of MRSA was 32% for the year 2017. The commonest species of CONS were S. *haemolyticus* and *S. epidermidis*, the former had MR rate of 86.6% & the latter 61%.

The profile of surgical site isolates in the ICMR surveillance data is as under:
OPD - 11.6 %
IPD - 68.6 %
ICU - 19.8 %

Organisms
Enterobacteriaceae – 46.20%
Salmonella – 0.3%
NFGNB – 27.4%
Staphylococcus – 7%
Enterococcus – 16.8%
Fungi – 0.8%
Faceal pathogens– 1.5%

Pus samples
OPD – 33.2%
Wards – 57.4%
ICU – 9.3%

Organisms
Enterobacteriaceae– 38.3%
Salmonella – 0.1%
NFGNB – 23.7%
Staphylococcus – 33.3%
Enterococcus – 44%

Fungi – 0.2%
Faecal pathogens – 0%

Considering the AST profile of *S. aureus*, clindamycin, tetracycline and trimethoprim-sulphamethoxazole appear to be a reasonable choice for treating suspected *S. aureu*s infections.

The highest susceptibility in *Acinetobacter baumannii* recovered from pus samples was against levofloxacin and minocycline. If we exclude colistin and carbapenems, the same for *Pseudomonas aeruginosa* was seen with amikacin, piperacillin/tazobactam and tobramycin and for Enterobactericeae, it was amikacin, levofloxacin and piperacillin-tazobactam.

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10.4 Central Line-associated Blood Stream Infection (CLABSI)

10.4.1 Definitions

Central line (CL): A central line is an intravascular access device or catheter that terminates at or close to the heart, or in one of the great vessels. The line may be used for infusion of intravenous fluids and drugs, or for haemodynamic monitoring. Central line (CL) infection can be local (e.g. phlebitis) or systemic.

Catheter-related bloodstream infection (CRBSI) is bloodstream infection (BSI) attributed to an intravascular catheter by quantitative culture of the catheter tip or by differences in growth between catheter and peripheral venipuncture blood culture specimens. This definition is primarily used in research. The BSI should not be related to an infection at another site.

Central Line-Associated Bloodstream Infections (CLABSI) is defined as a laboratory-confirmed BSI where an eligible BSI organism (see case definition of BSI) is identified, and an eligible central line is present on the day/ day before the event.

Eligible Central Line: A CL that has been in place for more than two consecutive calendar days, following the first access of the central line, in an inpatient location, during the current admission. Such lines are eligible for CLABSI events and remain eligible for CLABSI events until the day after removal from the body or patient discharge, whichever comes first.

10.4.2 When to suspect

CLABSI should be suspected in patients with:

- Fever in a patient with a central venous catheter with no other apparent source
- Erythema, induration or tenderness within 2 cm of the catheter exit site
- Catheter dysfunction (intraluminal clot)
- Clinical signs of sepsis that start abruptly after catheter infusion

10.4.3 Diagnosis

Confirmation of CLABSI requires both a positive blood culture and a collaborative clinical and microbiological review of the patient.

Blood culture should be obtained prior to initiation of antibiotic therapy. Paired blood samples, drawn from the catheter and a peripheral vein, should be sent for culture, and the bottles should be appropriately marked to reflect the site from which the samples were obtained. If a blood sample cannot be drawn from a peripheral vein, it is recommended that 2 blood samples should be drawn through different catheter lumens.

The case definition for BSI (must meet one of two criteria):

Criterion 1:

- Patient has a recognized pathogen cultured from one or more blood cultures AND
- Organism cultured from blood is not related to an infection at another site

Criterion 2:

- Patient has at least one of the following signs or symptoms: fever (>38°C) or hypotension AND
- Organism cultured from blood is not related to an infection at another site
- Common skin contaminant is cultured from two or more blood cultures drawn on separate occasions

Establishing diagnosis of CRBSI requires the presence of BSI and demonstrating that the infection is related to the catheter. The catheter tip should be cultured and growth of >15 colony-forming units (CFU) from a 5-cm segment tip by semiquantitative (roll-plate) culture, or growth of > 10^2cfu by quantitative (sonication) broth culture of the same pathogen as in peripheral blood culture supports the diagnosis of CRBSI.

10.4.4 Treatment:

Empiric antibiotic therapy must be started in sick patients (hypotension, organ dysfunction) in suspected CLABSI before culture and susceptibility reports are available. The choice of the empiric antibiotics is given in the table. Treatment should be appropriately modified after the culture and susceptibility report.

Systemic antibiotic therapy is usually NOT required if:

1. Positive catheter tip culture in absence of clinical signs of infection.
2. Positive blood cultures from the catheter with negative cultures through the peripheral vein, in absence of clinical signs of infection.
3. Phlebitis in absence of signs of infection.

Table 10.4: Antibiotics for treatment of CLABSI

Aetiology	Suggested regimens		Remarks
EMPIRIC THERAPY Gram-negative (*Klebsiella pneumoniae*> *Acinetobacter* spp.) more common than Gram positive (*Staphylococcus* spp., *Enterococcus* spp.)	Preferred	Alternative	
	Imipenem-Cilastatin 500 mg IV q6h ***plus*** Gentamicin (80 mg IV q8h) ***plus*** Inj. Vancomycin (15 mg/kg IV q8–12h) Or Inj. Teicoplanin (400mg IV every 12h for 3 doses followed by 400mg IV q24h)	Cefoperazone – Sulbactam (3g IV BD) ***plus*** Gentamicin (80 mg IV q8h) ***plus*** Inj.Vancomycin (15 mg/kg IV q8–12h) Or Inj.Teicoplanin (400mg IV every 12h for 3 doses followed by 400mg IV q24h)	Catheter removal is warranted in the following circumstances a) Septic shock b) Hemodynamic instability c) Suppurative thrombophlebitis d) Endocarditis or evidence of metastatic infection e) Persistent bacteraemia after 72 hours of appropriate therapy f) CLABSI caused by *Staphylococcus aureus*, enterococci, GNB, fungi, mycobacteria (for short-term catheters) • Duration of therapy for uncomplicated bacteraemia- *10 to 14 days from the day the culture was negative* • Persistent bacteraemia after 72 hours of catheter removal- treat for 4- 6 weeks

Table 10.5: CLABSI due to Gram positive cocci and suggested antibiotics

Etiology	Suggested regimens		Remarks
	Preferred	Alternative	
Methicillin-resistant*S. aureus*	Inj. Vancomycin (15 mg/kg IV q8–12h) Or Inj. Teicoplanin (400mg IV every 12h for 3 doses followed by 400mg IV q24h)	Inj Daptomycin 6 mg/kg IV q24h	• Catheter removal essential. • Following catheter removal, a new catheter may be placed if additional blood cultures demonstrate no growth at 72 hours • Duration of treatment at least 2 weeks in absence of hematogenous

Methicillin sensitive*S. aureus*	Cefazolin 2gm iv q8h or Cloxacillin 2gm IV q4h	Inj. Vancomycin (15 mg/kg IV q8–12h)	complications. • Patients with hematogenous complications- treat for 4-6 weeks. • Echo to rule out infective endocarditis is desirable • A beta-lactam is a preferred agent for treatment of MSSA. Vancomycin is less effective and should be reserved for patients unable to tolerate a beta-lactam due to allergy/ adverse effects
Methicillin resistant Coagulase negative *Staphylococcus* (CONS)	Inj. Vancomycin (15 mg/kg IV q8–12h) Or Inj. Teicoplanin (400mg IV every 12h for 3 doses followed by 400mg IV q24h)	Inj Daptomycin (6 mg/kg IV q24h)	• Catheter salvage may be attempted • Duration of therapy for uncomplicated bacteraemia- *10 to 14 days from the day the culture was negative*
Methicillin sensitive Coagulase negative *Staphylococcus* (CONS)	Cefazolin 2gm iv q8h or Cloxacillin 2gm IV q4h	Inj. Vancomycin (15 mg/kg IV q8–12h)	
Enterococcus			
Ampicillin susceptible	Ampicillin +/- gentamicin (80 mg IV q8h)	Vancomycin (15 mg/kg IV q8–12h) +/- gentamicin (80 mg IV q8h)	• Catheter removal is encouraged if feasible • Duration of therapy for uncomplicated bacteraemia- *10 to 14 days from the day the culture was negative*
Ampicillin resistant Vancomycin susceptible	Vancomycin (15 mg/kg IV q8–12h) +/- gentamicin (80 mg IV q8h)	Linezolid (600 mg q 12h) or Daptomycin (6 mg/kg IV q24h)	
Ampicillin resistant Vancomycin resistant	Linezolid (600 mg q 12h) or Daptomycin (6 mg/kg IV q24h)		

N.B.
1. For patients with CRBSI for whom catheter salvage is attempted, additional blood cultures should be obtained after 72 hours of appropriate antimicrobial therapy. If blood culture results remain positive, the catheter should be removed.
2. Benefit of the antimicrobial impregnated catheter is uncertain.

10.4.5 CLABSI due to Gram negative bacilli

- For all gram negative infection in patients on short-term catheters, catheter removal is essential.
- When CLABSI due to gram negative bacilli is suspected, initial empiric coverage with antibiotics belonging to two different classes is recommended when MDR organisms are prevalent, which may be de-escalated to a single appropriate antibiotic, once culture and susceptibility results are available.
- Antibiotic lock therapy may be used if catheter salvage is essential, but only in combination with systemic antimicrobial therapy. Response to therapy should be closely monitored and line removal considered if there is persistent bacteraemia.
- Duration of antimicrobial therapy is usually 7-14 days. In patients with gram-negative bacillary CLABSI involving a long-term catheter and persistent bacteraemia or severesepsis despite systemic and antibiotic lock therapy, the deviceshould be removed, an evaluation for endovascular infectionand metastatic infection should be pursued, and the durationof antibiotic therapy should be extended beyond 7–14 days.

Table 10.6: CLABSI due to Gram negative bacilli and suggested antibiotics

Etiology	Suggested regimens		Remarks
	Preferred	Alternative	
E. coli Carbapenem sensitive	Imipenem/cilastatin IV 500 mg q6h ***Or*** Meropenem IV 1g q8h	Cefoperazone Sulbactam(2:l) IV 3 g q12 h ***Or*** Piperacillin-tazobactam IV 4.5g q6h	Third generation cephalosporins may be used in *E. coli/Klebsiella* infections if the organism is susceptible When using fosfomycin for patients with estimated creatinine clearances of 40, 30, 20, and 10 ml/min, a reduction to 70%, 60%, 40%, and 20% of the daily recommended dose, respectively, is proposed. In patients undergoing intermittent dialysis (every 48 h), 2 g after
E. coli Carbapenem-resistant	Colistin IV 9MU loading dose and 4.5MU q8h	Fosfomycin IV 4-8g q12h	

			each session is recommended (Falagas CMR 2016)
Klebsiella spp Carbapenem resistant	Colistin IV 9MU loading dose and 4.5MU q8h ***plus*** imipenem/cilastatin IV1g q6h	Fosfomycin IV 8g q12h	High dose imipenem may be combined with colistin when imipenem MICs are favourable. Meropenem is superior to Piperacillin- tazobactam while treating ceftriaxone resistant, carbapenemsensitive*E.coli/ Klebsiella* infections.
Klebsiella spp Carbapenem sensitive	Imipenem/cilastatin IV 500 mg q6h ***Or*** Meropenem IV 1g q8h	Cefoperazone Sulbactam(2:l) IV 3 g q12 h ***Or*** Piperacillin-tazobactam IV 4.5g q6h	
Klebsiella spp Colistin resistant	Fosfomycin IV 8g q12h ***plus*** Imipenem/cilastatin IV 1g q6h	Chloramphenicol 500mg IV q6h **Or** Doxycycline 50mg IV q12h	Combinations of susceptible agents should be used with carbapenem, colistin resistant *Enterobacteriaceae*
Acinetobacter spp Carbapenem resistant	Colistin IV 9MU loading dose and 4.5MU q8h	Cefoperazone Sulbactam(2:l) IV 3 g q12 h ***Or*** Ampicillin –sulbactam IV 3g q6h	
Acinetobacter spp Carbapenem sensitive	Meropenem IV 1g q8h	Piperacillin-tazobactam IV 4.5g q6h	
Pseudomonas spp Carbapenem resistant	Colistin IV 9MU loading dose and 4.5MU q8h	Piperacillin-tazobactam IV 4.5g q6h	
Pseudomonas spp Carbapenem sensitive	Meropenem IV 1g q8h **Or** Piperacillin-tazobactam IV 4.5g q6h	Ceftazidime 2 g IV q8h **Or** Cefepime 2 g IV q8h	
Enterobacter/ Citrobacter/ Proteus/ Serratia	Imipenem/cilastatin IV 500 mg q6h **Or** Meropenem IV 1g q8h	-	
Burkholderia cepacia complex	Meropenem IV 1g q8h	Ceftazidime 2 g IV q8h or	

		Minocycline 200 mg loading dose and 100mg q12h	
Stenotrophomonas maltophilia	Minocycline 200 mg stat and 100mg q12h	Trimethoprim-sulfamethoxazole 3–5 mg/kg IV q8h	

10.4.6 CLABSI due to pathogenic yeasts

- Catheter removal is essential.
- Antifungal therapy is recommended for all cases of CLABSI due to *Candida* species.
- Treat 14 days after first negative blood culture result or resolution of signs and symptoms associated with candidemia, whichever is longer.
- The ophthalmological examination is recommended for all patients.

Table 10.7: CLABSI due to to pathogenic yeasts and suggested antibiotics

Etiology	Suggested regimens		Remarks
	Preferred	Alternative	
Candida species (unspeciated)/ *C. albicans, C. tropicalis/ C. parapsilosis*	Micafungin 100 mg IV daily **Or** Anidulafungin loading dose 200 mg, then 100 mg daily **Or** Caspofungin loading dose 70 mg, then 50 mg daily **Or** Fluconazole 800-mg loading dose, then 400 mg daily	Amphotericin B (lipid) 3−5 mg/kg daily **Or** Amphotericin B deoxycholate- 0.5−1 mg/kg daily **Or** Voriconazole 400 mg (6 mg/kg) q12h for 2 doses then 200 mg (3 mg/kg) q12h	Fluconazole may be used as a preferred agent/ step down agent after 5-7 days of initial echinocandin therapy if the isolate is susceptible; the patient has no previous azole exposure and is not critically ill.
C. auris/ C. haemulonii/ C. krusei	Micafungin 100 mg daily; **Or** Anidulafungin loading dose 200 mg, then 100 mg daily	Voriconazole 400 mg (6 mg/kg) bid for 2 doses then 200 mg (3 mg/kg) bid	

C. glabrata	Voriconazole 400 mg (6 mg/kg) bid for 2 doses then 200 mg (3 mg/kg) bid **Or** Micafungin 100 mg daily; **Or** Anidulafungin loading dose 200 mg, then 100 mg daily	Fluconazole (step down) 800 mg daily **Or** Amphotericin B (lipid)	Fluconazole may be given as step down therapy in high dose if MIC favourable.

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10.5 Pneumonia

10.5.1 Definitions

- **Hospital Acquired Pneumonia (HAP)** is pneumonia that develops 48 hours or more after admission and did not appear to be incubating at the time of admission.
- **Ventilator Associated Pneumonia (VAP)** is pneumonia that develops after more than 48 hours of mechanical ventilation.

10.5.2 When to suspect

When a patient who is hospitalized/on mechanical ventilation for > 48 hourrs develops new or progressive infiltrates on chest radiography and has at least 2 of the following features:

1. Fever> 100.4^{o} F.
2. Leucocytosis (>12000/µl) or leucopenia (<4000/ µl).
3. Altered mental status with no other recognizable cause in the elderly.
4. New onset purulent sputum or change in sputum character.
5. Worsening gas exchange (i.e. increased FiO_2 requirement).
6. New onset or worsening cough or dyspnea.
7. Rales or bronchial breathing.

10.5.3 Diagnosis

HAP: Respiratory samples should be obtained by spontaneous expectoration, sputum induction or nasotracheal suctioning and subjected to semi-quantitative cultures.

VAP: The preferred method for lower respiratory tract sample collection (blind or targeted, bronchoscopic or non-bronchoscopic) depends upon centre expertise, available facilities and cost issues; however, blind endotracheal aspirate is the easiest and associated with similar patient outcomes.

10.5.4 Treatment

Empiric antibiotic therapy should be initiated in VAP/HAP based on clinical criteria after sending blood and respiratory tract cultures. The best guide to the empiric regimen is data on local microbiological flora and resistance profiles. In absence of such data, the empiric choice can be made as mentioned in the table below:

Table 10.8: Antimicrobials guidelines for HAP/VAP

Etiology	Treatment		Special Remarks
	Preferred/early onset/minimum prior antibiotic exposure	**Alternative/late onset/prior antibiotic exposure**	
Empiric	Cefoperazone –	Meropenem	1. Levofloxacin (750 mg IV

(VAP/HAP)	Sulbactam or Piperacillin-tazobactam **Either alone or with** Amikacin	Or Imipenem-Cilastatin **Plus either** Amikacin **Or** Colistin/polymyxin B* *In settings where carbapenem resistance is >20%	q24h) may be used as an alternative to amikacin as a second anti-pseudomonal agent. 2. Consider adding nebulized colistin for carbapenem resistant organisms along with IV colistin 3. Empirical therapy for MRSA recommended if prevalence >10-20% in the setting
Culture proved VAP/HAP Most commonly (*Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa*)	Choose any one according to culture sensitivity from: Piperacillin-Tazobactam Cefoperazone – Sulbactam, Imipenem-Cilastatin, Meropenem, Colistin Polymyxin B	-	1. Colistin and Polymixin B should be used only when there is resistance to all the other tested antibiotics. 2. For HAP/VAP due to *CRE* who remain in septic shock/ at high risk for the poor outcome, combination therapy using 2 antibiotics to which the isolate is susceptible rather than monotherapy is preferred
MRSA	Inj. Linezolid	Inj. Vancomycin or Inj. Teicoplanin	The choice between vancomycin and linezolid to be guided by patient-specific factors (renal functions, concomitant bacteraemia)

Table 10.9: Standard doses of antimicrobial agents

Antibiotics	**Doses, duration and route of administration**
Cefoperazone –Sulbactam	(3g IV q12h)
Inj. Linezolid	(600 mg IV q12h)
Inj. Vancomycin	(15 mg/kg IV q8–12h)
Inj. Teicoplanin	400mg IV every 12h for 3 doses followed by 10 mg/kg q24h)
Colistin	(9MU IV stat followed by 4.5 MU IV q12h or 3MU q8h)
Polymyxin B	(15000-25,000 U/kg/day in two divided doses)
Sulbactam	(3g IV q12h
Imipenem-Cilastatin	(500 mg IV q6h),
Meropenem	(1 g IV q8h),

Amikacin	(15–20 mg/kg IV q24h)
Imipenem-Cilastatin	(0.5- mg IV q6h or 1g q8h)
Meropenem	(1 g IV q8h)
Piperacillin-tazobactam	(4.5 g IV q6h),
Amikacin	(15–20 mg/kg IV q24h)
Levofloxacin	(750 mg IV q24h)

- In susceptible cases, Levofloxacin may be used as an oral step-down therapy.
- Faropenem should not be used as a step-down therapy in VAP/HAP susceptible to Carbapenems.
- Tigecycline is not recommended routinely in the treatment of VAP.
- If a patient with suspected VAP has septic shock and rapidly deteriorating status, empiric coverage for MRSA and carbapenem resistant GNB can be added along with antipseudomonal beta-lactam.

- Antibiotic doses should be adjusted according to GFR and ideal body weight except in those with morbid obesity where the dose is calculated using this formula

$$= \frac{(\text{actual body weight} + \text{ideal body weight})}{2}$$

General comments

1. De-escalation should be done once the culture reports are available.
2. Recommended duration of therapy: 7 days if there is a good clinical response or longer if clinically indicated (immunodeficiency, empyema, lung abscess, cavitations, necrotising pneumonia, etc)
3. Clinical picture and procalcitonin levels may be used to guide discontinuation of antibiotics.

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10.6 *Clostridium difficile* infection (CDI)

Clostridium difficle infection (CDI) in adults is associated with increased morbidity, additional length of hospital stay and an increase in healthcare costs. The available literature suggests that the prevalence of CDI is ranging between 4%- 34% across various centers in India. In a recent study from a tertiary care centre in Mumbai, the mean incidence of CDI was estimated to be 0.2/1000 patient days. The increasing prevalence is related to the increasing use of antibiotics across specialities. Management and prevention of CDI require an early suspicion, rapid and accurate diagnosis and measures for appropriate use of antibiotics. Antimicrobial stewardship programmes need to be emphasized for reducing incidence and morbidity associated with CDI.

10.6.1 Which tests should be recommended for rapid diagnosis of *C. difficle* ?

Tests should not be performed for asymptomatic patients & do not perform repeat testing (within 7 days) during the same episode of diarrhoea (Table 10.10).

Table 10.10: Sensitivity and specificity of the diagnostic methods for CDI

	Sensitivity	**Specificity**	**Turnaround Time**
Glutamate dehydrogenase [GDH] plus C. difficile toxic A & B assays	60-90%	76-98%	6 hours
Xpert C. difficile assay (Xpert CD assay; Cepheid)	90-100%	94.6-100%	45 mins (Less than 1 hour)

10.6.2 Treatment:

The treatment strategies for CDI include discontinuing antibiotics as soon as possible, as this may influence the risk of CDI recurrence. Therapy for CDI should be started empirically only in for fulminant CDI or in situations where a substantial delay in laboratory confirmation is expected.

Vancomycin or metronidazole (much less expensive) are both appropriate for an initial episode of mild CDI. Vancomycin is the drug of choice for modetate to severe CDI. For fulminant CDI, vancomycin administered orally is the regimen of choice. If ileus is present, vancomycin can also be administered (as per the vancomycin dosage is 500 mg orally 4 times per day) and 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema. Intravenously administered metronidazole should be administered together with oral or rectal vancomycin, particularly if ileus is present. The metronidazole dosage is 500 mg intravenously every 8 hours (Table 10.11).

If surgical management is necessary for severely ill patients, perform subtotal colectomy with preservation of the rectum. Diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach that may lead to improved outcomes. For children with an initial episode of severe CDI, oral Vancomycin is recommended over metronidazole. There are insufficient data at this time to recommend the administration of probiotics for primary prevention of CDI outside of clinical trials

Table 10.11: Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Etology	Primary Regimen	Alternate Regimen
Initial episode, non-severe : Leukocytosis with a white blood cell (WBC) count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	VAN 125 mg given 4 times daily for 10 days	Oral Vancomycin is not available - metronidazole, 400 mg 3 times per day by mouth for 10 days
Initial episode, severe : Leukocytosis with a WBC of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	VAN, 125 mg 4 times per day by mouth for 10 days	
Initial episode, fulminant : Hypotension or shock, ileus, megacolon	VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present	
First recurrence	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode.	Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks).
Second or subsequent recurrence	VAN in a tapered and pulsed regimen • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days.	• Faecal microbiota transplantation

Abbreviations: VAN =Vancomycin

a. All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

b. The opinion of the panel is that appropriate antibiotic treatment for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering faecal microbiota transplantation.

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10.7 Catheter associated urinary tract infections

10.7.1 Introduction

Catheter-associated urinary tract infection (CA-UTI) is the leading cause ofsecondary health care-associated bacteraemia. CA-UTI are the fourth commonest health care associated infection (HAI) reported to the National Healthcare Safety Network, making up two-thirds of hospital-acquired UTIs (CDC 2019).

In India, exact data for prevalence of CA-UTI are limited. Pooled Indian data for catheter-associated urinary tract infection rates for adult and paediatric ICUs were 2.1 catheter-associated urinary tract infections/1,000 urinary catheter days. Subsequently extra length of stay in adult and pediatric ICUs was 10 days and estimated crude extra mortality was 6.6% for catheter-associated urinary tract infections in adult and pediatric ICUs.

Approximately 40% of nosocomial infections originate in the urinary tract. Most patients with nosocomial urinary tract infections (UTIs) either had genitourinary or urological manipulation or permanent urethral catheterization or both. The daily risk of acquisition of bacteriuria varies from 3% to 7% when an indwelling urethral catheter remains in-situ. While the proportion of bacteriuric subjects who develop symptomatic infection is low, the high frequency of use of indwelling urinary catheters resulting in substantial increase in CA-UTI burden.

10.7.2 Case definition

CA-UTI in patients with indwelling urethral, indwelling suprapubic, or intermittent

a. Patient has at least one of the following signs or symptoms compatible with UTI with no other identified source of infection
   i. New onset fever
   ii. Supra-pubic tenderness
   iii. Costo-vetebral angle pain or tenderness, acute haematuria
   iv. Urinary urgency, urinary frequency, dysuria and

b. Patient has a urine culture with 1000 colony forming units (cfu)/mL of ≥1 bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hrs.

Note: In patients with spinal cord injury, increased spasticity, autonomic dysreflexia, or sense of unease are also compatible with CA-UTI.
Indwelling urinary catheters are generally considered

a. Short term if they are in-situ for <30 days
b. Chronic or long term when in-situ for ≥ 30 days

10.7.3 Common pathogens associated with CA UTI

Approximately two-thirds of the uropathogens that cause CA-bacteriuria in patients with indwelling urethral catheters are extraluminally acquired (by ascension along the catheter urethral mucosa interface), and one-third are intraluminally acquired.

Gram positive cocci	Gram negative bacilli	Fungi
Staphylococcus aureus *Coagulase negative Staphylococcus* *Enterococcus faecalis/ E. faecium*	*Escherichia coli* *Klebsiella species* *Pseudomonas species* *Proteus mirabilis* *Morganella morganii* *Enterobacter species* *Aceinatobacter species*	*Candida species*

The most important predisposing factor for nosocomial UTI is urinary catheterization, which perturb host defense mechanisms and provides easy access of uropathogens to the bladder. Once attached to the catheter surface, bacteria change phenotypically and produce exopolysaccharides that entrap and protect replicating bacteria, forming microcolonies and eventually, mature biofilms and they migrate to the bladder within 1–3 days. Biofilms are usually initially caused by single species but may become polymicrobial, especially with long-term catheters. These organisms are often highly antimicrobial resistant.

10.7.4 Risk factors for development of CA-UTI

- The duration of catheterization is the most important risk factor for developing infection. Reducing unnecessary catheter placement and minimizing the duration the catheter in- situ are the primary strategies for CA-UTI prevention.
- Additional risk factors include female sex, older age, and not maintaining a closed drainage system.
- Risk factors for developing hospital onset urinary tract–related blood stream infection include neutropenia, renal disease.

10.7.5 Acceptable Indications for Indwelling Urinary Catheter Use

- Management of acute urinary retention and urinary obstruction
- Peri-operative use for selected surgical procedures
- Accurate measurement of urine output in critically ill patients
- Assistance in wound healing for incontinent patients
- Required immobilization for trauma or surgery
- End-of-Life care

10.7.6 Diagnostic evaluation

10.7.6.1 Clinical diagnosis

Signs and symptoms compatible with CA-UTI include new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified

cause, flank pain, costo-vertebral angle tenderness, acute haematuria, pelvic discomfort and in those whose catheters have been removed- dysuria, urgent or frequent urination and supra-pubic pain or tenderness.

10.7.6.2 Collection of urine specimen

- Short term catheterization - specimens to be obtained by sampling through the catheter port using aseptic technique or, if a port is not present, puncturing the catheter tubing with a needle and syringe
- Long term indwelling catheters - preferred method of obtaining a urine specimen for culture is to replace the catheter and collect a specimen from the freshly placed catheter
- Symptomatic patient- urine culture should be done immediately prior to initiating antimicrobial therapy

10.7.6.3 Laboratory diagnosis

- Semi-quantitative urine culture -Urine cultures are recommended prior to treatment to confirm that an empirical regimen provides appropriate coverage and to allow tailoring of the regimen on the basis of antimicrobial susceptibility data.
- Blood culture for patients with suspected bacteremia – hypotension, fevers with chills and features of sepsis with organ dysfunction.

Note:

- Culture specimens should not be obtained from the drainage bag
- Do not send urine culture from an asymptomatic patient with indwelling urinary catheter
- Pyuria in urinalysis is not useful in diagnosing CA-UTI
- Presence or absence of odorous or cloudy urine alone should not be used as an indication for urine culture
- CA-ASB (asymptomatic bacteruria) is diagnosed when one or more organisms are present at quantitative counts ≥1,00,000 cfu/ml from an appropriately collected urine specimen in a patient with no symptoms attributable to urinary infection
- CA-UTI - Presence of symptoms or signs compatible with UTI with no other identified source along with 1000 cfu/mL of ≥1 bacterial species in a single catheter urine specimen or in a midstream voided urine specimen

10.7.7 Treatment of CA-UTI

The two important considerations in the management of CA-UTI

- Removal of the indwelling catheter (7 days or longer)
- Antimicrobial chemotherapy (type and duration of therapy)

Because of the possibility of biofilm formation on the catheter surface, it may be reasonable to replace the catheter before the therapy if it has been in place for >7 days

10.7.8 Antimicrobial Therapy

- Routine use of prophylactic antimicrobials at the time of catheter removal or replacement has not been shown to be beneficial.
- Empirical treatment should be started with broad-spectrum antibiotics according to local susceptibility patterns.

Table 10.12: Antimicrobials guidelines for CA-UTI

Category	Treatment	Comments
Asymptomatic CA-ASB	Not recommended	Only recommended in the following circumstances -Before urologic surgery or implantation of prosthesis in the urinary tract -In pregnancy
Symptomatic CA-UTI	Patients with CA-UTI -not severely ill/without upper UTI symptoms Nitrofurantoin 100 mg PO BID Fosfomycin 3 g PO once stat Levofloxacin 750 mg PO daily Ciprofloxacin 500 mg PO BID Amikacin 15 mg/kg single dose	Patients with CA-UTI who are severely ill -Piperacillin/tazobactam 4.5 g IV q6hr -Ertapenem 1 g IV q24hr -Meropenem 1 g IV q8hr* * preferably used in patients with sepsis and septic shock
Candiduria – Indication Symptomatic Neutropenia (rule out candidemia) urological surgery	Flucanazole- Susceptible strains Flucytosine – *Candida glabrata* and *Candida krusei*	-Isolation of *Candida* in urine usually suggest a colonization -Always rule out obstructive uropathy with imaging if symptomatic candidal urinary infection is suspected
Post-op infections following solid organ transplant with CA-UTI (kidney, liver, heart, lung)	Piperacillin-tazobactam 4.5 g IV q6h or cefoperazone-sulbactam 3 g IVq12h Imipenem- cilastatin 1g IV q8h or Ertapenam 1 g IV q24hr /Meropenem 1g IV q8h	-Obtain blood and urine cultures before starting antibiotics -De-escalate to narrow spectrum agent on receipt of sensitivities

Targeted therapy should be initiated according to urine culture result and tailored according to the susceptibility report. For multidrug resistant organisms, colistin may be necessary; its empiric use is preferably avoided.

10.7.9 Duration of therapy

- The optimal treatment duration for CA-UTI has not been well defined. However, the IDSA and the European Association of Urology recommend treating CA-UTI associated pyelonephritis for 7 days in patients who have timely resolution of symptoms and for 10–14 days in those with a delayed clinical response, persistent fever, hypotension, or signs of severe sepsis.
- In the absence of symptoms indicative of pyelonephritis, women younger than 65yrs with CA-UTI may be treated for 3 days after the indwelling catheter is removed

10.7.10 Recommended strategies for CA-UTI prevention

- Limiting unnecessary catheterization
- Indwelling catheters should be removed as soon as they are no longer required to reduce the risk of CA-UTI
- Infection prevention -
  a. Hospitals should develop, maintain, and promulgate policies and procedures for recommended catheter insertion indications, insertion and maintenance techniques, discontinuation strategies, and replacement indications
  b. Strategies should include education and training of staff relevant to these policies and procedure
- Alternatives to indwelling urethral catheterization

Alternative	**Indication**
Intermittent catheterization	Neurogenic bladder, spinal cord injury, Prostate enlargement
External catheters	Condom catheters in male patient with no urinary obstruction and retention

- Prevention of CA-UTI through a bundled 6-C Approaching ICU consisting of six easy-to-remember elements, this includes “6 Cs” of CA-UTI reduction
  1. Consider alternatives
  2. Connect with a securement device
  3. Keep it Clean
  4. Call for bladder scan before irrigating
  5. Keep it Closed
  6. Culture urine only when indication is clear

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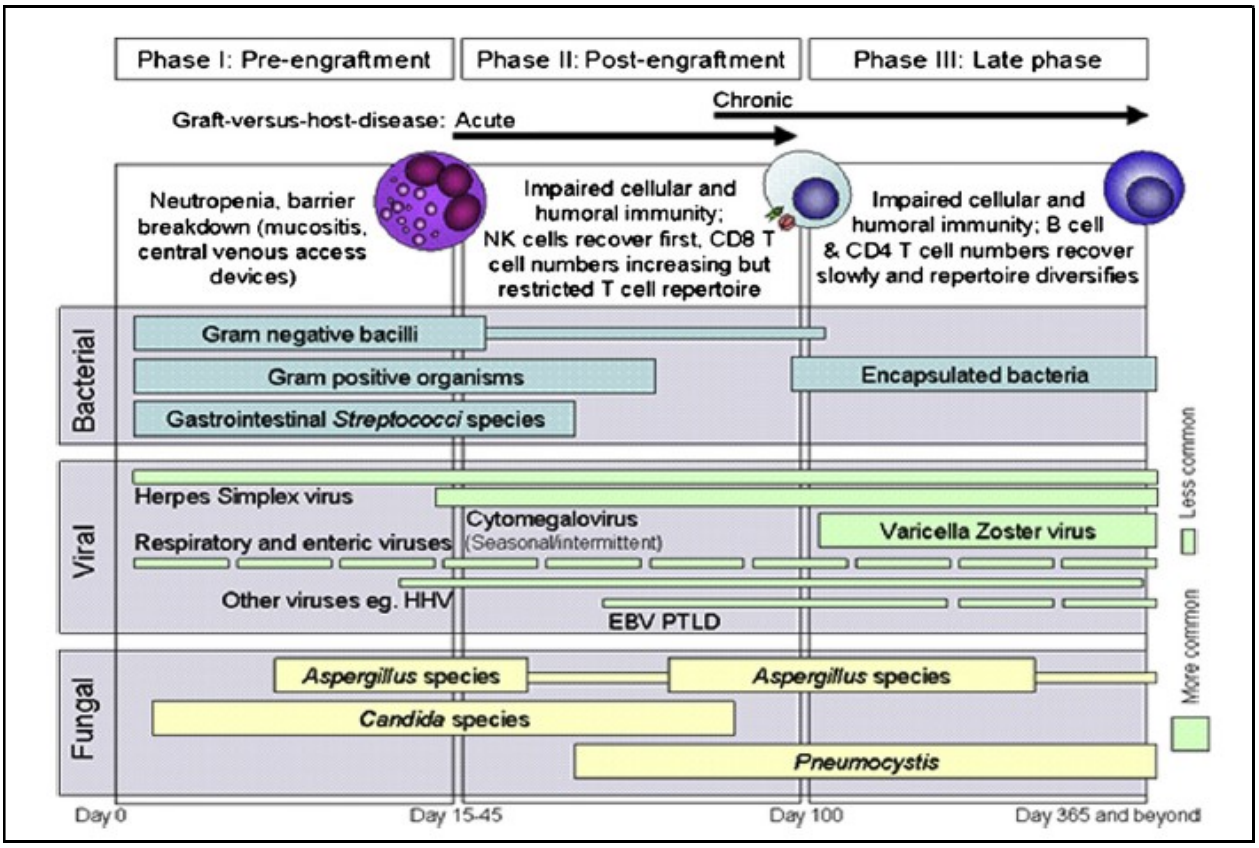
CHAPTER: 11

Infections in Immunocompromised Host

11.1 Prophylaxis and treatment in Hematopoietic Stem Cell Transplantation (HSCT)

Infections are an important cause of morbidity, mortality, hospital stay, intensive care unit admissions and healthcare cost, besides, healthcare resource utilization in the setting of hematopoietic stem cell transplantation (HSCT). Infections can occur at different stages of hematopoietic stem cell transplantation starting from pre-transplant conditioning phase, post-transplant pre-engraftment, post-transplant post-engraftment, early post-transplant phase (within 100 days) and late post-transplant phase (after 100 days). The characteristics of infections (bacterial, viral, fungal, and parasitic) and the subsequent consequences are dependent on the immunity of host, prophylaxis provided and other clinical, microbiological, immunological factors.

HSCT is potentially a life-saving procedure in patients with haematological malignancies (leukaemia, lymphoma), myelodysplastic syndrome (MDS), thalassemia and certain congenital immuno-deficiency disorders. However, infection remains the principal cause of morbidity, mortality, hospital stay and healthcare costs. Prevention of infection and its appropriate management in HSCT requires a multidisciplinary approach, which needs to include not only BMT physicians but also skilled nursing, high-quality housekeeping and adequate Heating Ventilation Air Conditioning (HVAC) system, good water quality, quality assured Central Sterile Supply Department (CSSD) products, timely and appropriately investigation along with necessary antimicrobial treatment. Infection control and management in HSCT is a coordination of all those diverse activities to ensure better patient outcome. In this brief guideline a summary of the prophylactic and therapeutic strategies in HSCT with regard to antimicrobial agents has been provided.



Source: *Tomblyn M et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009 Oct;15(10):1143-238.*

Table 11.1: Antimicrobial prophylaxis and surveillance in HSCT patients

Policy	Details	Comments
BMT pre-engraftment		
Antibiotic prophylaxis	No antibiotic prophylaxis is given	
Surveillance culture	Stool surveillance culture for multidrug resistant bacteria in stool and throat swab samples may be done to detect colonization with MDR bacteria. Note this should not be used to initiate prophylaxis	This detects ESBL, AmpC, carbapenemase producers, MRSA and VRE. However patients colonized with resistant pathogens should not be presumed to be the only cause of fever without microbiological confirmation
Surveillance PCR for MDRO colonization	Stool and throat swab samples from patients may be screened for the presence of genes indicating colonization with MDR bacteria	These real-time PCR or end point multiplex PCR based tests can detect NDM, OXA-48, KPC, IMP-1 and VIM genes associated with carbapenem resistance and mecA genes and VanA or vanB genes encoding for MRSA and VRE respectively.
Antifungal prophylaxis	Posaconazole	This may be administered IV/oral. Blood levels may be monitored if TDM (Therapeutic Drug Level) monitoring

		facilities are present. If posaconazole is contraindicated then alternative agents include liposomal Amphotericin or an echinocandin (e.g. Micafungin/Anidulafungin)
Antiviral prophylaxis	Acyclovir Influenza vaccination	Continued in the post transplant period for 6 months for autologous and 1 year for allogeneic BMT. Yearly vaccination preferably at the beginning of flu season (April-September) and at least 2 weeks before starting chemotherapy
CMV surveillance	**Haplo and MUD (Matched Unrelated Donor) transplant:** First CMV viral load at D+14, then every 7-14 days depending on risk. **Matched sibling transplant:** First CMV viral load at D+28. If CMV viral load is negative then repeat viral loads are sent based on risk stratification of the underlying disease and previous treatment received. **For patients on GVHD treatment:** CMV viral load once every 2 weeks.	Consider pre-emptive therapy if 2 consecutive viral loads (CMV viral load 1000-10,000 copies/mL) are showing an upward trend suggesting possibility of progression to CMV disease. Start pre-emptive anti-CMV therapy if CMV viral load is high (>10,000 copies/mL). Start definitive therapy of CMV disease (any viral load) with ganciclovir or valganciclovir. Note: CMV disease may occur without detectable CMV viremia. Treatment response assessment once every 2 weeks: clinically as well as based on CMV PCR. Autologous transplant: no CMV surveillance
BMT post engraftment		
Antibiotic prophylaxis	**Stable and engrafted patient:** • Cotrimoxazole double strength (960 mg) Q12H for twice weekly for 1 year, and • Penicillin 400 mg orally Q12H for 1 year.	• Penicillin prophylaxis in those with splenectomy or those with sickle cell anemia to be continued till 14 years. • Penicillin prophylaxis in those patients who have not taken Pneumococcus, Haemophilus and Meningococcal vaccination
Vaccination following splenectomy or functional asplenia	PNEUMOCOCCAL CONJUGATE VACCINE (13-valent) followed by (at least 8 weeks later by PNEMOCOCCAL POLYSACCHARIDE VACCINE (23 valent) 0.5ML VACCINE) (0.5 ML intra-muscular upper arm) X 1 stat. *Haemophilus influenzae* vaccine 0.5ML INJ. (0.5 ML intra-muscular upper arm) X 1 stat: to be given intramuscularly into the	VACCINES should be taken (Pneumococcal + Hib+Influenza+meningococcus) at least 14 days prior to the splenectomy or 14 days after splenectomy. All could be administered simultaneously into different limbs. Individuals with a bleeding disorder should be given vaccine by deep

	upper arm or antero-lateral thigh. A reinforcing (booster) dose of Hib vaccine is recommended at 12 months. Influenza vaccine 0.5ML vaccine: (0.5 mL) X 1 stat. To be administered yearly at the beginning of the Influenza season every year; given by intramuscular injection should be given preferably into the upper arm. Meningococcal vaccine ACWY 0.5mL vaccine (0.5 mL) X 1 stat; All meningococcal-containing vaccines are given intramuscularly into the upper arm or anterolateral thigh.	subcutaneous injection to reduce the risk of bleeding. Re-vaccination with pneumonococcal vaccine may be considered 5 years after primary vaccination.
Antifungal prophylaxis	Posaconazole oral syrup: 600-800 mg/ day (200 mg Q8H or Q6H); Posaconazole IV: Loading dose of 300 mg twice a day on the first day, then 300 mg once a day thereafter. Liposomal amphotericin B 1 mg/kg/day or 3mg/kg twice weekly.	Posaconazole/ liposomal amphotericin B or echnocandin (Micafungin/Anidulafungin) based on oral medication tolerability, requirement of mold active prophylaxis, intolerance to azoles (liver function derangement, hallucination, drug interaction, etc), and presence of GVHD.
Antiviral prophylaxis	Yearly Influenza vaccination	Yearly vaccination preferably at the beginning of flu season (April-September) and at least 2 weeks before starting chemotherapy. Please note the recommended vaccine composition (northern/southern hemispheric vaccine) from the WHO website updated twice yearly

Table 11.2: Antimicrobial therapy in the bone marrow transplant setting

Clinical Condition	Common Pathogens	Empirical Antimicrobial Agents	Alternate Antimicrobial Agents	Comments
Febrile Neutropenia (FN)/ sepsis	*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter species, Staphylococcus aureus,* Coagulase	Piperacillin-tazobactam + amikacin	**First line:** Piperacillin-tazobactam + amikacin **Second line:** Meropenem± Teicoplanin/Vancomycin **Third line or patient in septic shock:** Meropenem+ Colistin/Polymyxin B± Teicoplanin/Vancomycin	Continue broad-spectrum antibiotics until the patient is afebrile for at least 2 days and the neutrophil count is >500 cells/mm3 on at least one occasion. If blood cultures are negative at 3 days following initiation of antibiotic the Teicoplanin/Vancomycin

	Negative *Staphylococci, Enterococcus species, Candida species*		+ caspofungin± Fosfomycin/Tigecycline	may be discontinued. Note: Fosfomycin should be considered only in patients where Colistin Resistant Klebsiella/E. coli/Enterobacter are suspected.
Community acquired pneumonia (CAP)	*Streptococcus pneumoniae, Haemophilus influenzae, atypical agents (Mycoplasma, Chlamydia, Legionella),* respiratory viruses *(influenza A, influenza B, RSV, parainfluenza, rhinovirus, Enterovirus,* human *Metapneumovirus, Adenovirus, Coronavirus)*	Piperacillin-tazobactam+ clarithromycin/ azithromycin	Meropenem+ clarithromycin or azithromycin+ Teicoplanin/Vancomycin	If viral infection is suspected consider sending respiratory sample (nose and throat swab in viral transport media/ BAL/ endotracheal secretion) for respiratory viral PCR and consider early empirical use of oseltamivir. Oseltamivir may be discontinued once influenza PCR is negative
Health Care Associated Pneumonia (HAP)	*E. coli, Klebsiella, Pseudomonas, Acinetobacter, Staphylococcus aureus (methicillin resistant and methicillin sensitive)*	Meropenem+ Polymyxin B+ Teicoplanin/Vancomycin		Consider use of colistin with meropenem and Teicoplanin/Vancomycin in case of severe infection requiring respiratory support (ventilation) and this may be discontinued once cultures are negative and patient is stable. Also consider use of aerosolized colistin as an adjunct to intravenous antibiotics in the treatment of multi-drug resistant pathogens
Blood stream infection	*E. coli, Klebsiella, Pseudomonas, Acinetobacter, Staphylococcus aureus (methicillin resistant and methicillin sensitive), Staphylococcus epidermidis, Enterococcus species, Candida (albicans and non-albicans species of Candida)*	Stable patient: meropenem + amikacin	Second line/Unstable patient: Meropenem± Colistin ± Teicoplanin/Vancomycin ± caspofungin	Duration of treatment depends on the source of blood stream infection

Intravenous catheter associated infection	*Staphylococcus aureus, Staph. epidermidis, Coliforms (Enterobacteriaceae) and non-fermentative Gram negative bacilli*	Meropenem+ Vancomycin	Meropenem+ Teicoplanin/Vancomycin +colistin	Consider the use colistin/Polymyxin B or anti-fungal agents based on specific clinical/laboratory diagnosis
Skin and soft tissue infection	*Staphylococcus aureus, Streptococcus species, coliforms* and non-fermentative *Gram Negative Bacilli* (in compromised host), *Candida, Zygomycetes, Aspergillus, Fusarium*	Piperacillin-Tazobactam + Teicoplanin/ Vancomycin	Necrotizing fasciitis: Meropenem+ Teicoplanin/Vancomycin + Clindamycin	Consider the use of anti-fungal agents based on specific clinical/laboratory diagnosis. For MRSA coverage consider use of Teicoplanin/Vancomycin. Consider the use of clindamycin where anti-toxin activity is desired (e.g. necrotizing fasciitis).
Intra-abdominal infection	*Coliforms* and non-fermentative Gram Negative *Bacilli, Anaerobes, Enterococcus species, Candida*	Piperacillin-Tazobactam+ Amikacin ± metronidazole	Meropenem+ Teicoplanin/Vancomycin ± metronidazole	Consider the use of anti-fungal agents based on specific clinical/laboratory diagnosis Note: Piperacillin-tazobactam/meropenem provides good anaerobic cover. Addition of metronidazole to be considered only if enhanced anaerobic coverage is considered essential.
Urinary Tract infection	*Coliforms and non-fermentative Gram Negative Bacilli, Enterococcus species, Coagulase negative Staphylococci, Candida*	Piperacillin-Tazobactam+ Amikacin	Meropenem+ Teicoplanin/Vancomycin	Consider the use of anti-fungal agents based on specific clinical/laboratory diagnosis
Antibiotic associated diarrhoea	*Clostridium difficile*	Oral metronidazole	Oral vancomycin	Oral vancomycin may be used as first line in severe infections
Invasive pulmonary aspergillosis	*Aspergillus flavus, Aspergillus fumigatus, Aspergillus nidulans, Aspergillus niger, Aspergillus terreus*	Voriconazole	Amphotericin B (preferably liposomal, otherwise conventional)	Duration of therapy: ~ 6 weeks. Treatment should be continued until lesions have resolved or clinically stable. Consider doing voriconazole therapeutic drug level monitoring (TDM) wherever feasible.
Mucormycosis	*Apophysomyces, Basidiobolus, Conidiobolus,*	Liposomal Amphotericin B with Surgical	Caspofungin may be considered along with liposomal amphotericin B	Surgical debridement as far as possible. Antifungal therapy for mucormycosis

	Cunninghamella, Mortierella, Mucor, Lichtheimia (Absidia), Rhizomucor, Rhizopus, Saksenaea, Syncephalestrum	debridement (wherever feasible)		should be continued until: there is resolution of clinical signs and symptoms of infection, there is resolution or stabilization of residual radiographic signs, there is resolution of underlying immunosuppression. Adjunctive therapies may be tried in case of non response.
Herpes simplex	Herpes Simplex Virus Type 1 and Type 2 (HSV1, HSV2)	Acyclovir or Valacyclovir	Foscarnet	Dose and Duration of therapy depends on organ involvement.
Varicella or disseminated zoster or localized zoster	Varicella Zoster Virus	Acyclovir or Valacyclovir	Foscarnet	Intravenous therapy is recommended in all severe and complicated cases.
CMV reactivation or disease (colitis, pneumonitis, hepatitis, retinitis, encephalitis)	Cytomegalovirus	Ganciclovir or Valgancyclovir	Foscarnet or Cidofovir	Treat till resolution of clinical symptoms and signs or resolution of viremia (2 negative viral load reports). In case of treatment failure with Ganciclovir, foscarnet is the drug of choice.
***Pneumocystis jirovecii* pneumonia**	*Pneumocystis jirovecii*	Co-trimoxazole (10-15 mg/kg of TMP component in divided doses	Clindamycin+ Primaquine	Duration of therapy: 21 days Corticosteroids to be considered as an adjunctive therapy along with antimicrobial therapy against PCP.

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11.2 Solid organ transplant

11.2.1 Introduction

For the last three decades, solid organ transplantation (SOT) has been an accepted mode of therapy for the terminal disease of organs including the kidneys, liver, heart and lungs and less frequently intestine and pancreas. Immunosuppressive therapy is an essential component deciding the acceptability of the transplanted organ and it predisposes recipients of SOT to infectious sequelae. Optimal management of infectious complications in SOT recipients is an important deciding factor of care for this immunocompromised and highly susceptible population.

11.2.2 Common pathogens

Immunocompromised hosts remain exposed to normal community acquired pathogens and are at risk of developing opportunistic infections. The pathogens involved are by and large the same as those affecting immune competent hosts. Some specific pathogens unique to patients with compromised cell mediated immunity include *Listeria monocytogenes, Nocardia* spp, *Pneumocystis jirovecii*, cytomegalovirus (CMV), *Cryptococcus neoformans*, *Aspergillus* spp, *Strongyloides stercoralis*, etc.

SOT recipients are at risk of acquiring infections from donors with active or latent infections at the time of harvesting the organ. The organ being transplanted is a critical determinant of the location of infection in the immediate post-operative period. The chest, abdomen and urinary tract are the most common sites of infection in recipients of thoracic, liver and kidney transplantation, respectively. Intra-operative factors including events during surgery also contribute to infectious complications. Four weeks after transplant, immunosuppression is the major risk factor predisposing to infection.

The time of infectious event relative to the time of surgery may have an important bearing on the type of infection. Early infections (0–30 days after transplant) are usually associated with preexisting conditions or complications of surgery. Bacteria and yeast are the most frequent pathogens. Donor-derived infections usually present during this period. The intermediate period (31–180 days after transplant) is usually complicated by infections due to latent pathogens from donor organs, blood products, those re-activated in the recipient and the classical opportunistic agents. In the later period (beyond 180 days after transplantation), infection risks depend on immunosuppression and exposures.

Table 11.3: Central nervous system infections

Clinical condition	Common pathogens	Empirical antimicrobial agents	Alternative antimicrobial agents	Comments
Acute bacterial meningitis	*S. pneumoniae*, *Listeria monocytogenes*, *Haemophilus influenzae*, *Neisseria meningitidis*	Ceftriaxone or cefotaxime plus ampicillin (for listeria) Plus vancomycin	Moxifloxacin or meropenem	Exclude TB, *Cryptococcus* If penicillin allergic, use cotrimoxazole (TMP component) or meropenem to cover for *Listeria* Duration: 10-14 days, 21 days for *Listeria* or gram-negative infections
Brain abscess, subdural empyema	Streptococci, *Bacteroides* spp, Enterobacteriaceae, *S. aureus,* TB, *Nocardia*, Aspergillus	Ceftriaxone or cefotaxime plus Metronidazole Duration based on clinical and radiological response, minimum 8 weeks	Meropenem	Aspiration / surgical drainage required unless abscess <2.5cm and patient neurologically stable
	Nocardia spp	Co-trimoxazole (TMP component) IV/PO plus imipenem/ceftriaxone	Linezolid	Duration: 3-6 weeks of IV therapy followed by 12 months PO

Table 11.4: Respiratory tract infections

Clinical condition	Common pathogens	Empirical antimicrobial agents	Alternative antimicrobial agents	Comments
Pneumonia	*S. pneumoniae, H. influenzae, Legionella* spp, *K. pneumoniae, P. aeruginosa, Acinetobacter* spp	Piperacillin-tazobactam plus azithromycin or doxycycline Duration 5-7 days	Imipenem-cilastatin	If MRSA is a concern, add linezolid. Avoid fluoroquinolones unless TB excluded. Consider TB, influenza, Nocardia, fungi.

	Pneumocystis jirovecii	Co-trimoxazole	Clindamycin plus primaquine (if sulpha allergy)	
Lung abscess, empyema	*S. pneumoniae,* viridans streptococci, *K. pneumoniae, P. aeruginosa, S. aureus*	Piperacillin-tazobactam	Cefoperazone-sulbactam + clindamycin	Drainage of pleural space essential for empyema. Duration: 3-4 weeks
Acute bacterial pharyngitis	*Streptococcus pyogenes*	Benzathine penicillin or amoxycillin		Most cases viral. Confirm bacterial etiology before antibiotic *Rx*
Head & neck space infections	Polymicrobial, *S. pyogenes, S. aureus,* viridans streptococci, oral anaerobes	Clindamycin or amoxy-clav	Piperacillin-tazobactam	
Acute sinusitis	Viral, *S. pneumoniae, H. influenzae, M. catarrhalis*	Amoxy-clav	Piperacillin-tazobactam	Exclude fungal etiology
Acute bronchitis	Mostly viral			Antibiotics not needed

Table 11.5: Gastrointestinal and intra-abdominal infections

Clinical condition	**Common pathogens**	**Empirical antimicrobial agents**	**Alternative antimicrobial agents**	**Comments**
Acute gastroenteritis	Viral, enterotoxigenic & enteropathogenic *E. coli*	None	None	Rehydration (oral/IV) essential
Food poisoning	*S. aureus, B. cereus*	None	None	Rehydration (oral/IV) essential
Cholera	*V. cholera*	Doxycycline	Azithromycin or ciprofloxacin	Rehydration (oral/IV) essential
Bacterial dysentery	*Shigella, Campylobacter, Salmonella, E. coli*	Ceftriaxone	Azithromycin	
Amoebic dysentery	*E. histolytica*	Metronidazole	Tinidazole	Add diloxanide furoate 500mg q 8h for 7-10 days
Biliary tract infections	Enterobacteriaceae	Piperacillin-tazobactam or Cefoperazone-	Imipenem-cilastatin 500mg q 6h	Surgical or endoscopic intervention may

		sulbactam or ertapenem	or meropenem 1g IV q 8h	be considered for biliary obstruction
Spontaneous bacterial peritonitis	Enterobacteriaceae	Piperacillin-tazobactam or Cefoperazone-sulbactam or ertapenem	Imipenem-cilastatin or meropenem	
Secondary peritonitis, intra-abdominal abscess	Enterobacteriaceae	Piperacillin-tazobactam or Cefoperazone-sulbactam or ertapenem	Imipenem-cilastatin or meropenem	Source control is important

Table 11.6: Skin and soft tissue infections

Clinical condition	**Common pathogens**	**Empirical antimicrobial agents**	**Alternative antimicrobial agents**	**Comments**
Cellulitis	*S. pyogenes, S. aureus* (MSSA)	Cefazolin	Clindamycin	Shift to oral when improving
Abscess, carbuncle	*S. aureus*	Clindamycin	Linezolid	Cover for MRSA till sensitivities back
	MSSA	Cefazolin		
	MRSA	Vancomycin	Clindamycin	
Necrotizing fascitis	*S. pyogenes, S. aureus*, anaerobes, Enterobacteriaceae	Piperacillin-tazobactam or Cefoperazone-sulbactam plus Clindamycin	Imipenem-cilastatin or meropenem plus Clindamycin	Early surgical debridement essential

Table 11.7: Urinary tract infections

Clinical condition	**Common pathogens**	**Empirical antimicrobial agents**	**Alternative antimicrobial agents**	**Comments**
Cystitis	Enterobacteriaceae	Nitrofurantoin	Co-trimoxazole or ciprofloxacin	Collect urine for culture before antibiotics
Acute pyelonephritis	Enterobacteriaceae	Piperacillin-tazobactam or Cefoperazone-sulbactam or ertapenem	Imipenem-cilastatin or meropenem	Collect urine for culture before antibiotics. Duration 10-14 days

Acute prostatitis	Enterobacteriaceae	Piperacillin-tazobactam or Cefoperazone-sulbactam or ertapenem	Co-trimoxazole	Collect urine or preferably prostatic fluid for culture before antibiotics. Duration 3-4 weeks
Chronic prostatitis	Enterobacteriaceae	Ciprofloxacin	Co-trimoxazole	Collect urine or preferably prostatic fluid for culture before antibiotics

Table 11.8: Bone and joint infections

Clinical condition	Common pathogens	Empirical antimicrobial agents	Alternative antimicrobial agents	Comments
Acute osteomyelitis, septic arthritis	*S. aureus,* *S. pyogenes,* Enterobacteriaceae	Inj Vancomycin plus Inj Cefoperazone-sulbactam	Piperacillin-tazobactam or plus Clindamycin	Treatment based on culture results. Surgical debridement essential
Chronic osteomyelitis				Definitive therapy based on culture result

Table 11.9: Severe sepsis and septic shock of unknown source

Clinical condition	**Common pathogens**	**Empirical antimicrobial agents**	**Comments**
Community acquired	Enterobacteriaceae, *P. aeruginosa,* *S. aureus*	Imipenem-cilastatin **or** meropenem	Add vancomycin if *S. aureus* is a concern. Add colistin or polymyxin B if risk factors
Hospital acquired	Enterobacteriaceae, *P. aeruginosa,* *Acinetobacter* spp, *S. aureus*	Imipenem **or** meropenem plus polymyxin B or colistin plus vancomycin	

Table 11.10: Post-operative infections following solid organ transplant

Clinical condition	**Common pathogens**	**Empirical antimicrobial agents**	**Alternative antimicrobial agents**	**Comments**
Post-	Usually of non-	None		Rule out non-

operative fever without hemodynamic instability	infectious etiology			infectious causes, hematoma, DVT, transfusion fever, etc.
Surgical site infection	*S. aureus,* Enterobacteriaceae, *P. aeruginosa*			Treatment based on culture results
VAP/HAP	*P. aeruginosa, Acinetobacter* spp, Enterobacteriaceae	Piperacillin-tazobactam **or** Cefoperazone-sulbactam		Colistin may be considered based on local epidemiology or culture results
CLABSI	*S. aureus,* Enterobacteriaceae, *P. aeruginosa, Acinetobacter* spp	Imipenem-cilastatin or meropenem **or** Cefoperazone-sulbactam **plus** Vancomycin	Cefoperazone-sulbactam **plus** Vancomycin	Colistin may be considered based on local epidemiology
CAUTI	Enterobacteriaceae, *P. aeruginosa,* enterococci	Piperacillin-tazobactam or Cefoperazone-sulbactam	Imipenem-cilastatin or meropenem	Collect urine for culture before antibiotics

Table 11.11. Standard doses of antimicrobial agents for central nervous system infections

Antibiotics	**Doses and duration**
Ceftriaxone	2 g IV q 12h
Cefotaxime	2 g IV q 4-6h
Ampicillin	2 g IV q 4h
Vancomycin	1g IV q8-12h
Moxifloxacin	400 mg IV q 24h
Meropenem	2 g IV q 8h
cotrimoxazole	15 mg/kg/day
Ceftriaxone	2 g IV q 12h
Metronidazole	1 g IV q 12h
Co-trimoxazole	15 mg/kg
Linezolid	600 mg IV or PO q 12h

Table 11.12. Standard doses of antimicrobial agents for respiratory tract infections

Antibiotics	Doses and duration
Piperacillin-tazobactam	4.5 g IV q 6h
Azithromycin	500 mg PO/IV OD
Doxycycline	100 mg PO q 12h
Imipenem-cilastatin	500 mg q 6h
Linezolid	600 mg IV/PO BD
Co-trimoxazole	(TMP 15 mg/kg/day) for 14 days (21 days if HIV positive)
Clindamycin	600 mg IV q 8h
Primaquine	15 mg q 12h
Cefoperazone-sulbactam + clindamycin	3 g IV q 12h + 600-900 mg IV q 8h
Benzathine penicillin	1.2 MU IM
Amoxycillin	500 mg PO q 8h for 7 days
Amoxy-clav	1.2g IV/PO q 8h for 1 week

Table 11.13. Standard doses of antimicrobial agents for gastrointestinal and intra-abdominal infections

Antibiotics	Doses and duration
Doxycycline	300 mg PO stat
Azithromycin	1 g PO stat (Cholera)
Ciprofloxacin	500 mg q 12h for 3 days
Ceftriaxone	2 g IV OD for 5 days
Azithromycin	1 g OD for 3 days (Bacterial dysentery)
Metronidazole	500-750 mg IV/PO q 8h for 7-10 days
Tinidazole	2 g PO OD for 3 days
Piperacillin-tazobactam	4.5 g IV q 6h
Cefoperazone-sulbactam	3 g IV q 12h
Ertapenem	1 g IV OD
Imipenem-cilastatin	500 mg q 6h
Meropenem	1g IV q 8h

Table 11.14. Standard doses of antimicrobial agents for skin and soft tissue infections

Antibiotics	Doses and duration
Cefazolin	2 g IV q 8h for 5-7 days
Clindamycin	600-900 mg IV q 8h
Linezolid	600 mg iv q12h
Cefazolin	2 g IV q 8h for 5-7 days
Vancomycin	1 g IV q 12h
Piperacillin-tazobactam	4.5 g IV q 6h
Cefoperazone-sulbactam	3 g IV q 12h
Imipenem-cilastatin	500 mg q 6h
Meropenem	1 g IV q 8h

Table 11.15. Standard doses of antimicrobial agents for urinary tract infections

Antibiotics	Doses and duration
Nitrofurantoin	100 mg q 12h for 5 days
Co-trimoxazole	DS BD
Ciprofloxacin	500 mg BD for 3 days (Cystitis)
Piperacillin-tazobactam	4.5 g IV q 6h
Cefoperazone-sulbactam	3 g IV q 12h
Ertapenem	1 g IV OD
Imipenem-cilastatin	500 mg q 6h
Ciprofloxacin	750 mg PO BD (Chronic prostatitis)

Table 11.16. Standard doses of antimicrobial agents for urinary tract infections

Antibiotics	Doses and duration
Piperacillin-tazobactam	4.5 g IV q 6h
Clindamycin	600-900 mg IV q 8h

Table 11.17. Standard doses of antimicrobial agents for severe sepsis and septic shock of unknown source

Antibiotics	Doses and duration
Imipenem-cilastatin	500 mg q 6h
Meropenem	1 g IV q 8h
Imipenem	1 g q 8h

Table 11.18. Standard doses of antimicrobial agents for Post-operative infections following solid organ transplant

Antibiotics	Doses and duration
Piperacillin-tazobactam	4.5 g IV q 6h
Cefoperazone-sulbactam	3 g IV q 12h
Imipenem-cilastatin	500 mg q 6h
Meropenem	1 g IV q 8h
Vancomycin	1 g IV q 12h

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CHAPTER: 12

Management of Pelvic infections

12.1 Introduction

Common gynaecological conditions which need treatment with antibiotics are pelvic inflammatory disease, bacterial vaginosis, vaginal candidiasis and vaginal trichomoniasis. Serious conditions include surgical site infections (SSI), puerperal sepsis and septic abortion. Antibiotic prophylaxis in surgical procedures reduces colonization by microorganisms introduced at surgery to a level which the patient's immune system can overcome.

12.2 Case definition

a. **Surgical Site Infection (SSI)**: These are defined by the Centre for Disease Control, USA (CDC) and may be superficial, deep or involving organ/space. SSI section is given in detail in chapter 10.

b. **Puerperal sepsis**: Defined as "Infection of the genital tract occurring between rupture of membranes or labour and the 42nd day postpartum with 2 or more of the following":
   - Pelvic pain
   - Pyrexia *i.e.* oral temperature 38.5°C or higher on any occasion
   - Abnormal vaginal discharge, *e.g.* presence of pus or discharge with a foul odour
   - Delay in the rate of reduction of the size of the uterus (<2cm/day during the first 8 days)

c. **Pelvic inflammatory disease (PID)**: Comprises inflammatory disorders of the upper genital tract, including endometritis, salpingitis, tubo-ovarian abscess, or pelvic peritonitis. The symptoms include fever, pelvic pain, dyspareunia and abnormal vaginal discharge. The diagnosis of PID would be likely in the presence of features listed below:
   1. Sexually active young women
   2. Symptoms of pelvic or lower abdominal pain
   3. Presence of cervical motion tenderness or uterine tenderness or adnexal tenderness on clinical examination
   4. No other cause identified for the above symptoms and signs

d. **Vaginitis & cervicitis:** It comprises a spectrum of inflammatory disorders of the lower female genital tract characterized by vaginal discharge, odour, pruritus, and dyspareunia.

12.3 Common pathogens

The common organisms causing sepsis in the **puerperium** are mostly from endogenous microbiota of vagina and includestreptococci (Group B), enterococci, lactobacilli, diphtheroids, *Escherichia coli,* genital mycoplasma*, Bacteroides* spp andotheranaerobes.

Following caesarean section – Organisms to cover would include Staphylococci, Streptococci, Enterococci, Lactobacilli, Diptheroids, *E. coli*, anaerobic streptococci, *Bacteroides*and *Fusobacterium*spp. A meta-analysis showed that prophylaxis is definitely recommended and reduces fever, endometritis, SSI, UTI etc.The common organisms causing sepsis in **gynaecologic surgery** are polymicrobial and includeenterococci, aerobic gram-negative bacilli*,* gram-positive cocci, *Bacteroides* spp and other anaerobes. For the majority of SSI, the endogenous flora of the vagina or the skin is responsible. Aerobic gram-positive cocci, like staphylococci, are causative agents in the majority of the cases but faecal flora (*Enterobacter* spp and *E. coli*) may also contribute when the incision is near the perineum or groin.

The multicenter, randomized, double-blind, active and placebo-controlled study compared single doses of ampicillin, cefazolin, and placebo administered to women undergoing elective total abdominal hysterectomy at two centres in Thailand. The study found a significantly lower rate of infection, including superficial and deep SSIs, urinary tract infections, vaginal cuff infection, and pneumonia, with cefazolin (10.3%) compared with placebo (26.9%) and ampicillin (22.6%).

The staphylococci may be MSSA (methicillin-sensitive *Staphylococcus aureus*) or MRSA, the latter more likely when the patient is referred after treatment at some other healthcare facility. During procedures like hysterectomy, which involve opening of the vaginal cuff, the surgical site may be exposed to a variety of anaerobes and aerobes from the vaginal microflora. There is evidence that the cervical region and surrounding uppermost part of the vaginahavefewer anaerobes and aerobes of the proteobacteria class, which are responsible for the majority of infections.

- Common pathogens causing pelvic inflammatory disease (PID) are *C. trachomatis, N. gonorrhoea, Bacteroides*, peptostreptococci, mycoplasma, *Gardnerella vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, *Streptococcus agalactiae* and anaerobes.
- Common pathogens causing vaginitis are Candida species, *Trichomonas vaginalis* and organisms causing bacterial vaginosis like *Gardnerella*, peptostreptococci, *Bacteroides*, other anaerobes, ureaplasma and mycoplasma.
- Common pathogens causing cervicitis are chlamydia and *N. gonorrhoea.*

Puerperal endometritis is polymicrobial, (aerobic–anaerobic). These organisms are part of the vaginal flora and are introduced into the upper genital tract coincident with vaginal examinations during labour and/or instrumentation during surgery

12.4 Investigations

Blood cultures and other samples such as mid-stream urine, vaginal swab, cervical swab, throat swab, placental swabs, sputum, cerebrospinal fluid, epidural site swab, caesarean section or episiotomy site wound swabs should be obtained prior to starting antibiotics.Antibiotics should be given as soon as possible. Results of laboratory tests should be checked and the microbiologist consulted to ensure optimum antimicrobial therapy.

12.5 Antibiotic prophylaxis regimens

12.5.1 Obstetrics

a. Vaginal Delivery: Antibiotics are not routinely recommended. Women who do not know their Group B streptococcus (GBS) status are given antibiotics in situations mentioned in table II.

Antibiotic regimens:

- Ampicillin 2 gm IV initial dose followed by 1gm IV 4-6 hourly till delivery for GBS prophylaxis. If allergic, vancomycin 1 gm IV 12 hourly till delivery.
- Third/fourth-degree perineal tear: Single dose IV cefuroxime 1.5 gm plus metronidazole 500 mg or IV amoxicillin-clavulanic acid 1.2 gm or clindamycin 600 mg IV if penicillin allergic).

b. Preterm prelabour rupture of membranes: Ampicillin 2 gm followed by 1 gm IV 4-6 hourly for 48 hours followed by oral amoxicillin for 5 days PLUS oral erythromycin stearate 250-500 mg 6^{th} hourly for 7 days.

c. Caesarean Delivery: Antibiotic prophylaxis is recommended for all caesarean sections

- A single dose of first-generation cephalosporin, IV cefazolin, 2gm, within 60 minutes before incision. Minimum interval before incision should be 15 minutes, preferably 30 minutes.
- If allergic to cefazolin, give a single dose of IV clindamycin 600-900mg + gentamicin 80 mg.

After a single dose, therapeutic drug level is maintained for 3-4 hours; repeat dose if the duration of surgery is >3 hours or blood loss is >1500 ml. Cefazolin prophylaxis is recommended even for those receiving ampicillin during labour for GBS prophylaxis. This is because ampicillin is less effective against MSSA, the chief cause of SSI, due to beta-lactamase production. If the patient is already receiving appropriate antibiotics (*e.g.*,

for chorioamnionitis), then cefazolin prophylaxis may be omitted. Tita et al showed the addition of 500 mg azithromycin to cefazolin for caesareans (in labour or with membranes ruptured) reduced endometritis & wound infection significantly (6.1% vs. 12.0%, P<0.001), endometritis (3.8% vs. 6.1%, P=0.02) wound infection (2.4% vs. 6.6%, P<0.001).

d. Rescue cervical encerclage: Ampicillin 2 g IV single dose to reduce the risk of infection due to exposed membranes in the vagina.

12.5.2 Gynaecological surgery

a. Hysterectomy and surgeries for pelvic organ prolapse and/or stress urinary incontinence: All women undergoing laparoscopic/ vaginal/abdominal hysterectomy (VH, AH), or surgery for stress urinary incontinence should receive prophylactic antibiotics.

- A single dose of cefazolin 2 g IV. The dose is 3 gm if weight is >100 kg. The alternative is a second-generation cephalosporin like cefuroxime.
- If allergic to cephalosporins, use clindamycin 600 mg IV.
- Administer 15 to 60 minutes prior to incision. An additional dose is given 3 hours after the initial dose if a surgical procedure is lengthy (*e.g.*>3 hours), or blood loss is >1500 mL.
- Give oral metrogyl 500mg BD x 7 days, starting at least 4 days before surgery, to prevent post-operative vaginal cuff infection if there is evidence of bacterial vaginosis.

b. Other gynaecological procedures

- Laparoscopy (uterus and/or vagina not entered) / hysteroscopy / ectopic pregnancy: Single dose of cefazolin 1gm IV (if allergic, use clindamycin 600 mg). The alternative is a second-generation cephalosporin like cefuroxime. Give oral doxycycline 100 mg twice daily for 5 days post-operatively if there is a history of PID or if fallopian tubes are dilated at the procedure.
- Abortions: Women undergoing an induced abortion (surgical or medical) must receive antibiotics effective against *Chlamydia trachomatis* and anaerobes. There is no need of antibiotics following curettage for a missed or incomplete abortion. Regimens: doxycycline 100 mg oral twice daily for 7 days, starting on the day of abortion, plus metronidazole 800 mg oral at time of abortion OR azithromycin 1 g oral plus metronidazole 800 mg oral at time of the abortion.
- HSG: Oral doxycycline 100 mg prior to the procedure, to be continued twice daily for 5 days if there is a history of PID or fallopian tubes are found dilated at the procedure.

c. Gynaecological cancer surgery: Although current guidelines do not recommend any different antibiotics for gynaecological cancer surgery, the wound infection rate may be

higher, especially if bowel surgery is performed during surgery for ovarian cancer. Here, the infection may be reduced by instituting all measures for surgical prophylaxis, pre-operative use of oral antibiotics and mechanical bowel preparation, and newer measures being added like a change of gloves and instrument tray prior to skin closure. The SSI rate in vulvectomy for carcinoma vulva is high (58% among 149 patients by Leminen et al) and use of second generation cephalosporins with nitroimidazoles is suggested.

12.5.3 Emergency area (septic cases)

a. Puerperal sepsis / septic induced abortion / chorioamnionitis: Inj. Piperacillin-tazobactam 4.5 gm IV 6 hourly x 7-14 days.If patients have received antibiotics elsewhere OR have septic shock OR are intubated, consider optimum and appropriate antibiotics like imipenem and vancomycin, or teicoplanin to cover MRSA. It is important to consider and cover *C. sordelli* and *C. perfringens.*Amikacin may be included among the initial antibiotics to treat puerperal sepsis in India.

Table 12.1: Summarizing use of antimicrobial agents (AMA) in Obstetrics & Gynaecology

S. no.	Clinical condition / procedure	Common pathogens	Preferred AMA	Alternate AMA	Comments
1.	Vaginal delivery: For GBS (Group B *Streptococcus*) prophylaxis in women who do not know their GBS status in the following situations: • Preterm labour (< 37 wks) • Prolonged rupture of membranes (>18 hrs) • Fever during labour or chorioamnionitis • History of the previous baby with GBS infection • Bladder or kidney infection due to GBS	Group B Streptococci	Ampicillin	Cefazolin ; If allergic, vancomycin	Not recommended routinely for normal vaginal delivery Delivery is considered akin to drainage of an abscess as the fetus and placenta is removed which are the nidus of infection
2.	3rd or 4th degree Perineal tear	**Gram positive** *S. aureus,* **Gram negative** *Enterobacteriaceae*	Cefoxitin or cefotetan	Cefazolin plus metronidazole OR cefuroxime plus	Prophylaxis is considered to prevent adverse outcomes arising from infection *e.g.* fistulas

		Anaerobes		metronidazole OR amoxicillin-clavulanic acid if allergic, clindamycin	
3.	Preterm pre-labour rupture of membranes	**Gram positive** GBS **Gram negative:** Enteric gram-negative bacilli, Ureaplasma, mycoplasma **Anaerobes** (including *G. vaginalis*)	Ampicillin followed by oral amoxycillin PLUS oral erythromycin	If erythromycin 333 mg is not available, use erythromycin stearate	
4.	Caesarean delivery	**Gram positiveaerobes:**GBS, Staphylococci, Enterococci	Cefazolin + azithromycin	If allergic, clindamycin + gentamicin	
5.	Rescue cervical encerclage	Vaginal flora	Inj ampicillin		To prevent ascending infection from vaginal flora to exposed membranes
6.	Puerperal sepsis / Septic abortion / chorioamnionitis	**Gram positive***:* Streptococci (A, B, D), *S.aureus* **Gram negative***: E.coli, Enterobacteriaceae including Klebsiella, Enterobacter, Citrobacter, Pseudomonas aeruginosa, Proteus mirabilis, Gardnerella vaginalis,*	Inj. piperacillin-tazobactam	Clindamycin + gentamicin If the patient is in septic shock, consider imipenem/meropenem with or without amikacin plus vancomycin, or to cover MRSA	Usually polymicrobial

		Bacteroides Clostridium perfringens, **Anaerobes**			
7.	Hysterectomy (AH, VH, laparoscopic) and surgeries for pelvic organ prolapse and/or stress urinary incontinence	Polymicrobial: **Gram-positive:** Staphylococci, **Gram Negative**: Enterococci, aerobic gram-negative, **Anaerobes** *Bacteroides* spp,	Cefazolin	Cefuroxime +/- metronidazole OR If allergic to cephalosporin, use clindamycin + gentamycin	In AH & LH, the vagina is opened at end of procedure & exposure to vaginal flora is brief. In VH, there is greatercolonisation of the surgical site. In AH for cancer with resection of upper vagina, there may be colonization with anaerobes. In such cases, metronidazole 500 mg IV may be added. If BV is suspected, oral metronidazole 500mg BD for 7 days is given, beginning at least 4 days pre-op
8.	Laparoscopy (uterus and/or vagina not entered) / Hysteroscopy / Ectopic pregnancy	Skin commensals: *S. aureus*	Cefazolin	Cefuroxime If allergic, use clindamycin	
9.	Abortions (medical and surgical)	*Chlamydia, Neisseria gonorrhoeae*	Azithromycin plus metronidazole	Doxycycline plus metronidazole	No prophylaxis for missed / incomplete abortion
10.	HSG	*Chlamydia, Neisseria gonorrhoeae*	Doxycycline		Doxycycline continued twice daily for 5 days if there is a history of PID or fallopian tubes are dilated at the procedure
11.	Pelvic Inflammatory disease (mild to moderate)	*N. gonorrhoeae*, *C. trachomatis* and anaerobes. *E. coli, Bacteroides* GBS, GAS, *S.*	NACO based: Tab. Cefixime **PLUS** Tab. Metronidazole	CDC based: Levofloxacin with Metronidazole OR Ceftriaxone	

		aureus	**PLUS** Cap. Doxycycline	plus Doxycycline with or without Metronidazole	
12.	Pelvic Inflammatory disease (severe) eg turbo-ovarian abscess, pelvic abscess		Cefotetan PLUS doxycycline	Cefoxitin PLUS Doxycycline OR Clindamycin PLUS gentamicin loading dose Or Piperacillin-tazobactam/imipenem (for severely ill patients)	An attempt should be made to obtain cultures and de-escalate based on that. Duration is two weeks but can be extended depending upon the clinical situation. Antibiotics may be altered after obtaining culture reports of pus/or blood
13.	Vaginal candidiasis	*C. albicans, C. glabrata, C. tropicalis*	Tab Fluconazole **OR** local Clotrimazole	Miconazole, nystatin vaginal tablets/creams	Treat for 7 days in pregnancy, diabetes Recurrent infections: 150 mg Fluconazole on day 1,4,7 then weekly for 6 months
14.	Vaginal trichomoniasis	*T. vaginalis*	Tab.Secnidazole **OR** Tab. Tinidazole **OR** Tab. Metronidazole		Alcohol avoided during treatment and 24 hours after metronidazole or 72 hours after completion of tinidazole to reduce the possibility of a disulfiram-like reaction. Partner treatment essential
15.	Bacterial vaginosis	Overgrowth of anaerobes *(Gardnerella vaginalis)*	Metronidazole OR Metronidazole gel OR clindamycin Cream	Secnidazole OR Tinidazole OR Tinidazole OR clindamycin OR clindamycin ovules	Refrain from sexual activity or use condoms during the treatment. Clindamycin cream is oil-based and might weaken latex condoms

Table 12.2: Standard doses of antimicrobial agents

Antibiotics	Doses, duration and route of administration
Vaginal delivery	
Ampicillin	2 gm IV followed by 1g IV 4-6 hourly till delivery
Cefazolin	2 g IV followed by 1 g 8 hourly till delivery
Vancomycin	1 gm IV 12 hourly till delivery
3rd or 4th degree Perineal tear	
Cefoxitin or Cefotetan	Single dose 1gm IV
Cefazolin + Metronidazole	Single dose Cefa (1 g IV) + Met (500 mg IV)
Cefuroxime + Metronidazole	single dose Cefu (1.5 g IV) + Met (500 mg IV)
Amoxicillin-Clavulanic acid	1.2 gm IVsingle dose
Clindamycin	600-900 mg IV single dose
Preterm pre-labour rupture of membranes	
Ampicillin-Amoxycillin + Erythromycin	Amp (2 g IV followed by 1 gm 4-6 hourly for 48 hours) – oral Amoxy (500mg 8 hourly for 5 days) + Eryth (333 mg 8 hourly for 7 days)
Erythromycin Stearate	250 mg 6 hourly for 7 days
Caesarean delivery	
Cefazolin + Azithromycin	Single dose Cef (2gm IV) +Azi (500 mg) The dose is 3gm if the patient is >100kg
Clindamycin + Gentamicin	single dose clinda (600-900mg IV)+ Genta (1.5mg/kg IV)
Rescue cervical encerclage	
Ampicillin	Inj. 2gms single dose
Puerperal sepsis / Septic abortion / chorioamnionitis	
Piperacillin-Tazobactam	Inj. 4.5 gm IV 6 hourly X 7-14 days
Clindamycin + Gentamicin	Clinda (600-900mg IV 8 hourly) + Genta (60mg IV 8 hourly (if penicillin allergic)
Hysterectomy and surgeries	
Cefazolin	2 gm IV single dose (The dose is 3gm if the patient is >100kg)
Cefuroxime +/- Metronidazole	Cef (1.5 g IV single dose) +/- met (500 mg)
Clindamycin + Gentamicin	Clinda (600 -900 mg IV) + 1.5mg/kg IV
Laparoscopy/ Hysteroscopy / Ectopic pregnancy	
Cefazolin	2gm IV single dose.
Cefuroxime	1.5 g IV sinlge dose
Clindamycin	600 mg IV

Abortions	
Azithromycin + Metronidazole	Azi (1 g orally) + Met (800 mg orally at the time of abortion)
Doxycycline + Metronidazole	Doxy (100 mg orally twice daily for 7 days, starting on the day of abortion) +Metro (800 mg orally at the time of abortion)
HSG	
Doxycycline	100 mg orally before the procedure
Pelvic Inflammatory disease (mild to moderate)	
Cefixime + Metronidazole + Doxycycline	Cef (400 mg orally STAT) + Metro (400 mg tds X 14D) + Doxy (100 mg bd X 14 D)
Levofloxacin with Metronidazole	Levo (500 mg OD X 14 days) with Metro (400 mg tds X 14 days)
Ceftriaxone + Doxycycline with /without Metronidazole	Ceftr (250 mg IM single dose) +Doxy (orally 100 mg BD X 14 days) with Metro (500 mg BD X 14 days)
Pelvic Inflammatory disease (severe)	
Cefotetan + Doxycycline	Cefot (2 g IV BD) + Doxy (100 mg orally or IV BD)
Cefoxitin +Doxycycline	Cefotx (2 g IV every 6 hours) + Doxy (100 mg orally or IV every 12 hours)
Clindamycin + Gentamicin loading dose	Clinda (900 mg IV every 8 hours) + Genta IV or IM (2 mg/kg), followed by amaintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted
Vaginal candidiasis	
Fluconazole	150 mg orally single dose
Clotrimazole	500 mg vaginal tablet once only
Secnidazole	2 gm oral, single dose
Tinidazole	500 mg orally, twice daily for 5 days
Metronidazole	400 mg, twice daily for 7 days
Bacterial vaginosis	
Metronidazole	400 mg BD, orally X 7 days
Metronidazole gel	0.75%, one applicator (5 g) intravaginal x 5 days
Clindamycin Cream	2%, one applicator (5 g) intravaginal x 7 days
Secnidazole	2 g orally OD X one day
Tinidazole	2 g orally OD X 2 days/ 1 g orally OD X 5 days
Clindamycin	orally 300 mg BD X 7 days
Clindamycin ovules	100 mg intravaginally OD HS for 3 days*

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CHAPTER: 13

Management of Infective Endocarditis

13.1 Infective Endocarditis

13.1 Introduction:

Infective endocarditis (IE) is one of the most challenging syndromes in the landscape of infectious diseases. It is infection of the endothelial surfaces of the heart or iatrogenic foreign bodies like prosthetic valves and other intracardiac devices.

Management of IE with surgery and appropriate antibiotics has implications on patient outcome, healthcare costs, length of hospital stay, and antimicrobial resistance. Appropriate use of antibiotics in IE can be a "low-hanging fruit" from antimicrobial stewardship perspective as well.

13.2 Epidemiology:

Recently there have been substantial changes in epidemiology of IE. In India, IE is increasingly becoming common in older age group (> 40 years) with no previously known valve disease as compared to younger patients (with mean age-25 years) with underlying valvular heart disease. This is comparable to the data reported by developed countries. In children, the common risk factors include ventricular septal defect (VSD) and rheumatic heart disease (RHD).

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Microbiological profile of IE is illustrated in is Table 13.1

Table 13.1: Microbiology profile of Infective endocarditis

Study	Culture Positive Cases (%)	Etiologies
Soman et al, 2018[1]		VGS (31.8%), Enterococci (20.4%), Aspergillus (2.27%), NTM (15.9%), MSSA (6.8%), Candida (4.54%)
Gupta et al, 2015[2]	69% (22/32)	VGS (15.6%), Enterococci (15.6%), MSSA (9.3%), MRSA (6.25%), Pseudomonas (3.1%), Klebsiella Pneumoniae (3.1%), Scaedosporium (3.1%), Candida (6.25%), Brucella (3.1%)
Soman et al, 2013[4]	74.2 % (26/35)	VGS (34.5%), Enterococci (23%), Aspergillus (3.8%), NTM (19.2%), MSSA (3.8%), Candida (3.8%)
Subhramanian et al, 2010	22.3% (27/121)	VGS - (55.5%), *Staphylococcus* species - 4 (14.8%) cases.

Streptococci (VGS) and enterococci are the most common organisms isolated. Enterococcal IE appears to be becoming more common especially in elderly patients, patients with chronic liver disease or in patients with urinary tract infection. Overall, prevalence of MRSA is less than 10% in the various studies reported.

13.3 Diagnosis

Clinical suspicion, blood culture and echocardiography remain the cornerstone of diagnosis of IE. Modified Duke's Criteria which includes major and minor criteria is useful in the diagnosis of IE (Table 13.2). Presence of 2 major criteria or 1 major and 3 minor criteria or 5 minor criteria is suggestive of **definite IE** while presence of 1 major and 1 minor or 3 minor criteria is suggestive of **possible IE**. **Rejected IE** is firm alternative diagnosis explaining evidence of IE; or resolution of IE syndrome with antibiotic therapy for ≤4 days; or no pathological evidence of IE at surgery or autopsy with antibiotic therapy for ≤4 days; or does not meet criteria for possible IE as above.

Table 13.2: Modified Duke's Criteria for the Diagnosis of IE[9]

Criteria	Features
Major criteria	1. Blood culture positive for IE Typical microorganisms consistent with IE from 2 separate blood cultures: Viridans streptococci, Streptococcus bovis, HACEK group, ***Staphylococcus aureus***; or community-acquired enterococci in the absence of a primary focus, or microorganisms consistent with IE from persistently positive blood cultures defined as follows: at least 2 positive cultures of blood samples drawn >12 h apart or all 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart) **Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titer ≥1:800** 2. Evidence of endocardial involvement Echocardiogram positive for IE **(TEE recommended for patients with prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients)** defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; abscess; or new partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)
Minor criteria	1. Predisposition, predisposing heart condition, or IDU 2. Fever, temperature >38°C 3. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions 4. Immunological phenomena glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor 5. Microbiological evidence: positive blood culture but does not meet a

	major criterion as noted above (excludes single positive cultures for coagulase negative staphylococci and organisms that do not cause endocarditis) or serological evidence of active infection with organism consistent with IE

HACEK indicates Haemophilus species, Aggregatibacter species, cardiobacterium hominis, Eikenella corrodens, and Kingella species; IDU, injection drug use; IE, infective endocarditis; IgG, immunoglobulin G; TEE transesophageal echocardiography; and TTE, transthoracic echocardiography

13.4 St Thomas modification of Dukes criteria:

Inclusion of elevated ESR or CRP, the presence of newly diagnosed clubbing, splenomegaly and microscopic hematuria as minor criteria (St. Thomas modifications) have been shown to increase the sensitivity by 10%, without significant loss of specificity of the western setting.

13.5 Antimicrobial therapy for IE

13.5.1 Empirical therapy

Treatment of IE should be started promptly only in patients who are in frank sepsis or who are hemodynamically unstable. As blood culture data is crucial in antibiotic selection, in stable patients with recent antibiotic exposure it is reasonable to stop all antibiotics and draw blood cultures after an antibiotic free interval. Three sets of blood cultures should be drawn at 30 minutes interval before the initiation of antibiotics. Empirical treatment for IE is described in Table 13.3.

Table 13.3: Empirical antibiotic therapy for IE (pending blood culture results)

Native Valve IE	Etiologies (usual)	Suggested Regimens (Primary)	Adjunct Diagnostic or Therapeutic Measures or comments
Empirical Treatment-awaiting cultures (No h/o skin/soft tissue infection or abscesses, no h/o IV drug abuse, no h/o CVC line or recent cardiac/prosthetic valve replacement)	VGS, Enterococci, NVS, Streptococcus gallolyticus,	**Ampicillin-sulbactam 3g q6h** (Ampicillin- 150mg/kg/day or Sulbactam 50 mg/kg/day) in 4 divided doses or Ampicillin 2 g IV in q4h Or 200 mg/kg/day in six divided doses plus Ceftriaxone 2 g IV q24h Paed Dose: 50-100 (60 mg/kg/day) in two divided doses ***Plus*** Gentamicin 1 mg/kg q8h	Gentamicin used for synergy, peak levels need not exceed 4 mcg/ml. • Advantage of Ampicillin-sulbactam (AS) over CP/Ampicillin: AS Covers β-lactamase producing Enterococci & HACEK Group of organisms • **Combination of ceftriaxone with Gentamicin does not cover Enterococcus, Nutritionally variant Streptococci**

			(Abiotrophica & Granulicatella)
Native Valve IE (Risk factors for S. aureus)	MSSA, CA-MRSA, HA-MRSA***	Vancomycin 25 mg/kg loading dose followed by 30per/kg per 24 h IV in 2-3 equally divided doses Alternative Therapy: Daptomycin 6 mg/kg q24h (for Right-sided IE) Or 8-10 mg/kg q24h (For left- sided IE) For Possible MSSA: Flucloxacillin or Cefazolin	Vancomycin trough levels -1 hour before the 4rth dose of vancomycin Recommended Vancomycin. trough levels in serious MRSA infections- 15-20 µg/ml. **Nephrotoxicity** (0-12%) which is associated with vancomycin trough levels greater than or equal to 15 µg/mL, in those receiving high dose vancomycin (greater or equal to 4 g/day), **concomitant use of nephrotoxic agents**, and duration of vancomycin therapy
PVE pending blood cultures or with negative blood cultures		Ceftriaxone 2 g IV q24h Paed Dose: 50-100 (60 mg/kg/day) in two divided doses AND Vancomycin (25 mg/kg loading dose followed by 30-60 mg/kg per 24 h IV) AND Gentamicin 1mg/kg q12h AND Rifampicin 300-600 mg q12H po/IV	Use lower dose of rifampicin in severe renal impairment.

- *NVS – Nutrionally variant streptococci
- **CP- crystalline penicillin
- ***MSSA- methicillin sensitive Staphylococcus aureus, CA-MRSA- community- acquired methicillin resistant Staphylococcus aurueus, HA-MRSA- hospital acquired methicillin resistant staphylococcus aureus

13.6 Definitive antimicrobial treatment for IE[9-14]

IE is most commonly caused by viridans group of streptococci (VGS) in the indian subcontinent. The taxonomy of VGS is evolving. The species that most commonly cause IE are *S. sanguis, S. oralis (mitis), S. salivarius, S. mutans,* and *Gemella morbillorum* (formerly called S. morbillorum). Members of the S. anginosus group (S. intermedius, anginosus, and constellatus) also have been referred to as the S milleri group, and this has caused some confusion. In contrast to other α-hemolytic streptococcal species, the S. anginosus group tends to form abscesses and to cause hematogenously disseminated infection (eg, myocardial and visceral abscesses, septic arthritis, and vertebral osteomyelitis). The recommendations are intended to assist clinicians in selecting appropriate antimicrobial therapy for patients with IE caused by VGS and S. gallolyticus (bovis, a nonenterococcal penicillin-susceptible group D Streptococcus) (Table 4). S. gallolyticus (bovis) expresses the group D antigen, but it can be distinguished from group D Enterococcus by appropriate biochemical tests. Patients with either S gallolyticus (bovis) bacteremia or IE should undergo a colonoscopy to determine whether malignancy or other mucosal lesions are present.

Table 13.4: Antibiotic therapy for native valve IE due to VGS and group D streptococci, *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis*), *Abiotrophia defectiva*, and Granulicatella Species

Etiologies (usual)	**Suggested Regimens (Primary)**	**Adjunct Diagnostic or Therapeutic Measures or comments**	**Duration of antibiotic therapy**
Highly Penicillin-Susceptible VGS and *S gallolyticus (bovis)* (MIC ≤0.12 μg/mL)	**Aqueous crystalline penicillin G (CP) sodium** 20 -40 lac Units/kg/day IV 4 hrly Or 12–18 million U/24 h IV in 4-6 divided doses or continuously if possible	Ampicillin 200 mg/kg/day in six divided doses (Max dose - 2 g IV in q4h Or Ceftriaxone 50-100 (60 mg/kg/day) in two divided doses (Max dose- 2 g IV q24h) For penicillin Allergy- Vancomycin is an alternative	If only β-lactam is used – then, 4 weeks But if the combination of β-lactam with Gentamicin (3mg/kg/day) is used – then, 2 weeks is sufficient except in with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired eighth cranial nerve function, or Abiotrophia, Granulicatella, or Gemella spp infection.
Relatively resistant VGS **(MIC >0.12 -0.5 μg/mL)**	Aqueous crystalline penicillin G (CP) sodium Plus Gentamicin	Ampicillin Or ceftriaxone Plus Gentamicin For penicillin	β-lactam for 4 weeks and Gentamicin for 2 weeks

		allergy- Vancomycin is an alternative	
VGS isolates with a penicillin MIC ≥0.5 µg/mL & *Abiotrophia* and *Granulicatella spp.* (nutritionally variant streptococci)	Aqueous crystalline penicillin G (CP) sodium Plus Gentamicin	Ampicillin Or ceftriaxone Plus Gentamicin For penicillin allergy- Vancomycin is an alternative	β-lactam and Gentamicin for 6 weeks

Staphylococcus aureus

Table 13.5: Antibiotic therapy for due to *Staphylococcus aureus* *

Etiologies (usual)	Suggested Regimens (Primary)	Adjunct Diagnostic or Therapeutic Measures or comments
Native valve MSSA IE	Cloxacillin 12gm/day in three divided doses for 6 weeks	Flucloxacillin (200 -300 mg/kg/day in 4-6 equally divided doses)or Cefazolin Paediatric dose is 30-100 (60 mg/kg/day) in three divided doses for 6 weeks
Prosthetic valve MSSA IE	Cloxacillin 12gm/day in three divided doses, With Rifampicin max dose 900 mg for 6 weeks with Gentamicin 1mg/kg TDS for 2 weeks	Flucloxacillin (200 -300 mg/kg/day in 4-6 equally divided doses) with Rifampicin Paediatric 15 mg/kg/day in three divided doses, max dose 900 mg for 6 weeks with Gentamicin 1mg/kg TDS for 2 weeks
Native valve MRSA IE	Vancomycin for 6 weeks	Daptomycin * for 6 weeks
Prosthetic valve MRSA IE-	Vancomycin with Rifampicin in three divided doses, max dose 900 mg for 6 weeks with gentamicin 1mg/kg TDS for 2 weeks	Daptomycin for 6 weeks with rifampicin Paediatric 15 mg/kg/day in three divided doses, max dose 900 mg for 6 weeks with gentamicin 1mg/kg TDS for 2 weeks

*Vancomycin Doses mentioned in Table 13.3

** Daptomycin dose for right sided IE is 6 mg/kg/dose and for left-sided IE or complicated IE is 8-10 mg/kg/dose

13.7 IE Caused by *Coagulase-Negative Staphylococci*

Coagulase-Negative Staphylococci (CoNS) in the presence of prosthetic valves or other prosthetic material can cause infective endocarditis. It can be the etiological agent for IE even in native valve if it's isolated in multiple blood cultures like in patients on hemodialysis (HD) with an HD catheter or central venous catheter (CVC). CoNS that cause PVE usually are methicillin resistant, particularly when IE develops within 1 year after surgery. Treatment recommendations for IE caused by MR CoNS is illustrated in Table 13.6.

Table 13.6: IE caused by *Coagulase-Negative Staphylococci*

Etiologies (usual)	Suggested Regimens (Primary)
Native valve MR CoNS IE	Vancomycin (30mg/kg/day in two divided doses) for 6 weeks
Prosthetic valve MR CoNS IE-	Vancomycin (30mg/kg/day in two divided doses) with rifampicin in three divided doses, max dose 900 mg for 6 weeks with gentamicin 1mg/kg TDS for 2 weeks

IE caused by **Enterococci** is increasingly becoming common. Antibiotic therapy is ummarized in Table 13.7.

Table 13.7: Antibiotic therapy for due to Enterococcus spp

Etiologies (usual)	Suggested Regimens (Primary)
Ampicillin sensitive (MIC ≤4 mg/L) and non-HLAR (MIC ≤128 mg/L)	Ampicillin with Gentamicin for 4-6 weeks
Ampicillin Resistant (β-lactamase producing) and non-HLAR	Ampicillin-sulbactam with Gentamicin for 4-6 weeks
Ampicillin Resistant (β-lactamase producing) and HLAR/Risk of nephrotoxicity	Ampicillin-sulbactam with Ceftriaxone for 6 weeks[14]
Ampicillin Resistant (aPBP) and HLAR/Risk of nephrotoxicity	Vancomycin with gentamicin or daptomycin for 6 weeks

Ampicillin 200 mg/kg/day in six divided doses (Max dose - 2 g IV in q4h). Native valve: 4-wk therapy recommended for patients with symptoms of illness <3 mo; 6-wk therapy recommended for native valve symptoms >3 mo and for patients with prosthetic valve or prosthetic material. Recommended for patients with creatinine clearance >50 mL/min.
Ampicillin-sulbactam with Gentamicin : (Ampicillin- 150mg/kg/day and Sulbactam 50 mg/kg/day) in 4 divided doses and Gentamicin 3 mg/kg per 24 h IV or IM in 3 equally divided doses
Ampicillin-sulbactum with ceftriaxone: (Ampicillin- 150mg/kg/day with Sulbactam 50 mg/kg/day)
Vancomycin with gentamicin: Vancomycin 30 mg/kg per 24 h IV in 2 equally divided doses and Gentamicin 3 mg/kg per 24 h IV or IM in 3 equally divided doses
Daptomycin 8-10mg per kg per day

Appropriate antibiotic therapy in IE can have immense impact from stewardship perspective. In a recent study[2], following ID consultation, a change to optimal antibiotics was done in 25 of the 32 patients. Of these, de-escalation from meropenem or β-lactam- β-lactamase inhibitor (βL-βLI) combination to ampicillin or ampicillin-sulbactam was done in 12 patients. Vancomycin/teicoplanin was discontinued in 8 patients. Linezolid discontinued in 3 patients.

Escalation to meropenem, vancomycin, gentamicin and rifamipicin combination was done in 2 patients with early onset-PVE. No change of antibiotics was done in 4 patients with IE. Following the ID consultation with de-escalation of carbapenem and vancomycin/teicoplanin, the healthcare costs was reduced significantly.

13.8 Treatment of fastidious & atypical pathogens

13.8.1 HACEK endocarditis - Treatment should be with a β-lactamase-stable cephalosporins or amoxicillin if the isolate is susceptible. Gentamicin should only be added for the first 2 weeks of therapy. Ciprofloxacin can be considered an alternative agent.
NVE should receive 4 weeks and PVE 6 weeks of treatment.

13.8.2 Antibiotic prophylaxis prior to invasive procedures:

Prophylaxis should be considered for patients at highest risk for IE:
(1) Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair.
(2) Patients with a previous episode of IE.

(3) Patients with congenital heart disease (CHD):
(a) Any type of cyanotic CHD.
(b)Any type of CHD repaired with a prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains.

Antibiotic prophylaxis is not recommended in other forms of valvular or CHD.
Recommended prophylaxis for high-risk dental procedures in high-risk patients includes amoxicillin or ampicillin 50 mg/kg orally or i.v. or clindamycin 20 mg/kg orally 30-60 minutes before the procedure.

Table 13.8: Indication for surgery in patient with associated condition[9-13, 15]

Indication for surgery	Timing
Heart failure	
Aortic/mitral IE with severe regurgitation/valve obstruction causing pulmonary oedema or cardiogenic shock	Emergency
Aortic/mitral IE with fistula into cardiac chamber or pericardium causing refractory pulmonary oedema or shock	Emergency
Aortic/mitral IE with severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor hemodynamic tolerance	Urgent
Aortic /mitral IE with severe regurgitation and no HF	Elective
Uncontrolled Infection	
Locally uncontrolled infection (abscess/aneurysm/fistula/enlarging vegetation)	Urgent
Persisting fever and positive blood culture >7-10 days	Urgent
Infection caused by fungi or multiresistant organism	Urgent

Prevention of Embolism	
Aortic/mitral IE with large vegetation(>10mm) following episode of embolism despite appropriate antibiotic therapy	Urgent
Aortic/mitral IE with large vegetation(>10mm) and predictor of a complicated course	Urgent
Isolated very large vegetation(>15mm)	Urgent

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CHAPTER: 14

Tables on Duration, Drug Interaction, Dosage and Administration

Table 14.1: Duration, Drug Interaction, Dosage and Administration

Sr. No.	Name	Daily Dose	Maximum daily dose	Dose modification with CrCl (ml/min)	Available	Re-constitute	Further Dilution	Incompatibility	Infusion time (mins)	Additional comments
1	Benzylpenicillin Inj.	Low Dose: 0.6 to 1.2 MU q 4 hrs IM per day High Dose: 20 - 40 lac Units IV q 4 hourly (For meningococcal meningitis, the administration should be done q 2h	24 million Units	10-50 , decrease dose by 25%, <10%, decrease dose by 50% , post HD	5 lacs / 10 lacs	3 ml of WFI	100 ml of N.S.	IV incompatibilities include dobutamine, dopamine, norepinephrine, gentamicin, vancomycin, cefazolin, erythromycin, lidocaine, morphine, -	30 min	Cross sensitivity to most cephalosporins, β lactams. No cross sensitivity to aztreonam. Probenecid, indomethacin, sulfonamides, thiazides, salicylates may increase its level due to inhibition of tubular secretion potassium chloride 1MU of penicillin G potassium contains 0.3 mEq of Na and 1.68 mEq of K. Caution should be exercised when given in high doses
2	Cloxacillin Inj	Most infections: 1 g 4 hourly (6 g) Serious infections: 2 g 4 hourly (12 g)	12 g	NC	250/500mg	.	500 mg in 10 ml of NS or 5% dextrose	Blood products or with lipid emulsions. A list of 19 drugs have been shown to be incompatible with	Inject slowly over 3-4 minutes	bactericidal for methicillin sensitive *S. aureus* (MSSA): Potential to interact with probenecid, methotrexate and

								cloxacillin in some studies although these are not listed in prescribing information		warfarin
3	Ampicillin Inj.	2 g 4 hourly (total 12 g/day)	12 g	**< 10-20**: 0.5-1 g 8 hourly **HD**: 1 g 12 hourly; 1 g post HD	500 mg	5 ml of WFI	100 ml of N.S.		30-60 min	Prolonged infusion* Increased incidence of rashes with allopurinol
4	Amoxicillin sodium & clavulanate potassium (each 30 mg contains 25 mg Amoxicillin & 5 mg clavulanate	Usual dose: 1.2 g 8 hourly Severe infections: 1.2 g 6 hourly		**10-30:** 1.2 g IV stat followed by 600 mg 12 hourly **<10**: 1.2 g IV stat followed by 600 mg OD	300 mg / 600 mg / 1.2 g 300 mg / 600 mg / 1.2 g	5 ml of WFI per 300 mg 5 ml of WFI per 300 mg	None 50 – 100 ml of NS (50 ml of NS per 600 mg Augmentin)	Aminoglycosides, blood products, glucose, dextran, bicarbonate iv lipid emulsions	4 min (BOLUS) 30 – 40 min (INFUSION)	Prolonged infusion* Potential to interact with acenocoumarol, warfarin and probenecid
5	Ampicillin & Sulbactam Inj	1.5- 3 g 6 hourly; for Acinetobacter 3g iv q 4hourly	Ampicillin: 12 g Sulbactam : 4 g	**< 30** : 1.5-3 g 12 hourly **< 15**: 1.5- 3 g OD	1.5 g/ 0.75 g 1.5 g / 0.75 g	5 ml WFI 2 ml of WFI per 0.75 g	None 25 ml of N.S. / 0.75 g	Aminoglycosides	5 min (BOLUS) 15-30 min (INFUSION)	Prolonged infusion* Probenecid may impair its excretion
6	Piperacillin sodium & Tazobactam Inj.	4.5 g 8 hourly Severe infections and anti-Pseudomonal coverage: 4.5 g 6 hourly	Piperacillin 16 g / tazobactam 2 g	20-40:3.375g, q6h;<20-2.25gq 6h, HD, 2.25g, q 8h. Loading dose must always be given irrespective of status of clearance	2.25 g/ 4.5 g	5 ml of WFI per gm of Piperacillin (20 ml for 4.5	100 ml of N.S.	RL, blood products, albumin, hydrolysates, aminoglycosides	30 min	1 vial (4.5 g of piperacillin-tazobactam) has 12 meq of sodium . Prolonged infusion* Potential for interaction

				An additional dose of 0.75g piperacillin-tazobactam should be administered following each hemodialysis session		gm of piperacillin-tazobactam)				with warfarin, heparin and methotrexate. May prolong neuromuscular blockade of vecuronium Increased nephrotoxicity if combined with vancomycin
7	Ticarcillin & Clavulanic acid	50 mg/kg/day Usual dose: 3.1 g 6 hourly Severe infections: 3.1 g 4 hourly		30- 60: 2 g 4 hourly 10 – 30: 2 g 8 hourly < 10: 2 g 12 hourly < 10 with hepatic dysfunction: 2 g OD **Patients on peritoneal dialysis**: 3.1 g 12 hourly **Patients on HD**: 2 g 12 hourly,with 3.1 g post HD	3.1 g	13 ml of WFI	50 ml of N.S.	Sodium bicarbonate, aminoglycoside	30 min	Prolonged infusion* Probenecid may decrease its elimination
8	Cefazolin Sodium Inj.	50 mg/kg/day in three divided doses Usual dose: 1 g 8 hourly For severe infections: 2 g 6-8 hourly	8 g	35-54 : Full doses at 8 hourly interval, 11-34-half the usual dose every 12 h, less than 10- half the usual dose every 24h: 0	500 mg / 1 g	10 ml of WFI	30 ml of NS	-	10 min	Do not give as prolonged infusion for preoperative prophylaxi Probenecid may decrease renal tubular secretion

9	Cefuroxime Sodium Inj.	30-100 (60 mg/kg/day) in three divided doses Adults:750 mg 8 hourly Serious infections : 1.5 g 8 hourly	-	**10-20**: 750 mg 12 hourly **< 10** : 750 mg OD	250 mg / 750 mg / 1.5 g 250 mg / 750 mg / 1.5 g	2/6/15 ml of WFI 2/6/15 ml of WFI	None 50-100 ml of NS	- Aminoglycosides sodium bicarbonate	5 min (BOLUS) 15-30 min (INFUSION)	Do not give as prolonged infusion for preoperative prophylaxis
10	Cefotaxime Sodium Inj.	100 mg/kg/day in 3-4 divided doses Usual dose: 1 g 8 hourly Severe infections: 2 g 4-8 hourly	12 g	**< 50-10**: 2g 12 hourly **<10:**:: 2 g OD	250 mg / 1 g	5 ml of WFI	20 ml of NS	Aminoglycosides	10 min	Prolonged infusion*
11	Ceftriaxone Inj.	50-100 (60 mg/kg/day) in two divided doses Usual dose2 gm OD Meningitis, synergistic treatment for enterococcal endocarditis: 2 g 12 hourly	4 g	NC	250 mg / 1 g	10 ml of WFI	50 ml of NS	Aminoglycosides, Vancomycin, fluconazole **calcium-containing IV solutions like RL, TPN**	30 min	CI in hyperbilirubinemia

12	Ceftazidime Inj. BOLUS Ceftazidime Inj. INFUSION	Usual dose : 2 g 8 hourly Severe infections : 2 g 6-8 hourly	8 g	**< 50 -30** 1g iv bd 30-10: 1g iv OD **<10**: 500 mg OD	250 / 500 / 1 g / 2 g 250 mg / 500 mg / 1 g / 2 g	2.5 ml of WFI / 250 mg 2.5 ml of WFI / 250 mg	None 50 ml of N.S.	- Sodium bicarbonate aminoglycosides, vancomycin	5 min 15 – 30 min	Nephrotoxicity with concomitantly administered nephrotoxic agents such as aminoglycosides..or potent diuretic such as furosemide Contains 2.3mEq of Na per gram of ceftazidime
13	Cefoperazone (CPZ) sodium Inj. BOLUS Cefoperazone sodium Inj. INFUSION	40-80 mg/kg/day Usual dose: 2 g 12 hourly (4 g /day) Severe infections : 2-4 g 8 hourly	8 g	NC	1 g / 2 g 1 g / 2 g	1 ml WFI / 100 mg 5 ml of WFI / g	None 20 – 100 ml of N.S. / g	Sodium bicarbonate aminoglycosides	5 min 15 – 60 min	Concomitant severe hepatic & renal dysfunction : Not more than 2 g/day Prolonged infusion*
14	Sulbactam (SBT) & Cefoperazone (CPZ) sodium Inj.(1:1) Sulbactam (SBT)& Cefoperazone (CPZ) sodium Inj. (1:2)	Usual dose: SBT/CPZ (1:1) : 40-80 mg/kg/day SBT/CPZ (1:2) : 60-120 mg/kg/day SBT/CPZ (1:2) Usual dose : 3 g 12 hourly Serious	SBT/CPZ (1:1) : 8 g (i.e. SBT 4 g/CPZ 4g) SBT/CPZ (1:2) : 12 g (i.e. SBT 4 g/CPZ 8g) Max dose of	**Sulbactam requires renal dose modification** **< 30-15**: 1 g 12 hourly **(max 2 g/day)** **< 15** : 500 mg 12 hourly **(max 1 g/day)** **<30-15**:Inj cefoperazone/sulbactam (1:2) 1.5 g 8	1 g: (cefoperazone 0.5 g + sulbactam 0.5 g) 1.5 g: (cefoperazone 1 g + sulbactam 0.5 g) 3 g:	3.4 ml of WFI per 1 g vial 3.2 ml of WFI per 1 g vial	100 ml of RL	Sodium bicarbonate aminoglycosides	15 – 20 min	RL should not be used for the initial reconstitution as the mixture is incompatible Prolonged infusion*

		infections: 6 g 12 hourly	sulbactam: 4 g/day	hourly or 3 g 12 hourly **< 15**: Inj **cefoperazone/sulbactam (1:1) 1 g 12 hourly** **plus** **Inj cefoperazone 1 g 12 hourly** (**At least total daily dose of cefoperazone - 3 g/ day)**	(cefoperazone 2 g + sulbactam 1 g					
15	Cefepime Inj.	150 mg/kg/day in three divided doses Usual dose: 2 g 12 hourly Severe infections: 2 g 8 -12 hourly	6 g	**< 50-10**: 1 g OD **< 10**: 0.5-1 g OD Hemodialysis patients: 1 g on day 1 then 500 mg everyday	250 / 500 / 1 g	2.5 ml of WFI / 250 mg	50 – 100 ml of N.S.	-	30 min	Prolonged infusion* **High doses may cause encephalopathy if creatinine clearance reduced**
16	Cefpirome sulphate Inj.	50 mg/kg/day in two divided doses Usual dose: 1 g 12 hourly Severe infections: 2 g 12 hourly	4 g	2 g loading dose followed by **< 50-20** : 1 gm 12 hourly **20-5** : 1 gm OD	1 g 1 g	10 ml of WFI 10 ml of WFI	None 100 ml of NS per g	Sodium bicarbonate	4 min (BOLUS) 20 – 30 min (INFUSION)	Avoid with nephrotoxic agents (aminoglycosides, loop diuretics) Not recommended in children
	Cefepime-tazobactam inj	50/12.5 mg/kg/day in	2g per dose	Loading dose followed by	1000/125 mg	10 ml of WFI per	500 ml of NS	RL	30 min	**Interactions with** aminoglycosides-

17		two divided doses Usual dose: 1.125gm IV 12hourly Severe infections: 2.25g IV 8-12hourly	Max: 6 g	**< 60-30**: 500/62.5 mg OD **<10**: 250/31.25 mg OD **HD**: 1000/125 mg on day 1, then 500/62.5 mg OD Should be given Post HD		vial				nephrotoxicity & ototoxicity Heparin- coagulopathy
18	Imipenem & Cilastatin Sodium Inj.	For most infections : 500 mg 6 hourly Severe infections : 1 g q 8 hourly	4 g	If initial dose is 500 mg 6 hourly, then Loading dose of 500 mg IV stat followed by **< 70-41**: 500 mg 8 hourly **<40-21**: 500 mg 12 hourly **< 20 or HD** : 250 mg OD **<5**: do not give until HD is initiated within 48 hrs Patients on hemodialysis should receive imipenem after dialysis	500 mg	20 ml of WFI	100 ml of N.S. per 500 mg	Lactate and diluents containing lactates	30 min	Risk of seizures if renal dysfunction, CNS infection (meningitis, SOL) and Gancyclovi Patients receiving valproic acid concomitantly may require measurement of valproic acid levels Prolonged infusion*
19	Meropenem Inj.	Usual dose: 1 g 8 hourly Meningitis or treatment of	6 g	**<50**: Loading dose of 1 gm IV stat followed by maintenance dose	500 mg / 1 g	5 ml of WFI per 250 mg	50 ml of N.S.	Should not be added to or mixed with other drugs	15 – 30 min	Prolonged infusion*

		resistant gram negatives : 120 mg/kg/day in three divided doses (2 g 8 hourly)		as follows 26-50, 12 hourly 10-25, half of the dose at 12 hourly interval <10, half dose at 24 hr interval						
20	Vancomycin hydrochloride Inj.	Loading dose 25-30 mg/kg of actual body wt followed by maintenance dose of Usual dose: 15 mg/kg Q8-2 hourly Meningitis: 15 mg/kg 8-12 hourly Adults (60 kgs with normal CrCL): 1.5 g (loading dose) followed by 1 g 12 hourly	Not to exceed 2 g/dose	Dose mg /day: **15.4 mg X CrCL** HD: 1 g q48h (after HD	500 mg / 1 g	10 ml of WFI per 500 mg	100 ml of 0.9 % N.S. or 5% dextrose per 500 mg Concentrations **of no more than 5 mg/mL is recommended** in adults In selected patients in need **of fluid restriction, a concentration up to 10**	Alkaline solutions, β - lactam antibiotics	**Infusion rate not exceeding 15 mg/min** Usual infusion rate: **1 g in 200 ml 0.9% NS over 60 min & 500 mg in 100 ml 0.9% NS over 30 min** 0 to 500 mg in 100 ml (30 minutes) 501-1250 mg in 250 ml (60 minutes) 1251-	Vancomycin trough levels to be drawn1 hour before the 5th dose of vancomycin Recommended trough levels is 10-15 µg/ml in mild-moderate and 15-20 µg/ml in serious infections-. **Nephrotoxicity** (0-12%) is associated with vancomycin trough levels greater than or equal to 15 µg/mL, high dose vancomycin (greater or equal to 4 g/day), **concomitant use of nephrotoxic agents and piperacillin-tazobactam**, and duration of vancomycin therapy Concomitant use of opioids may increase the potential for redman syndrome

							mg/mL may be used		1750mg in 500ml (90 minutes) 1751-2250mg in 500 ml (120 minutes) If red-man syndrome- Infusion can be increased over 3 hours	
21	Teicoplanin Inj. BOLUS Teicoplanin Inj. INFUSION	Loading dose of 6 mg/kg 12 hourly for first 3 doses followed by 6 mg/kg OD Usual dose : 400 mg IV 12 hourly for 3 doses followed by 400 mg OD For more serious infections 12 mg/kg BD for 3 doses followed by 12 mg/kg OD	-	**< 60-40** or on HD, the chosen dose (6 or 12 mg/kg) should be administered every 48 hours and 72 hours, respectively. Maximum dose in patients on HD: 10 mg/kg every 48 to 72 hours.	200 mg / 400 mg 200 mg / 400 mg	1.5 ml of WFI per 200 mg 1.5 ml of WFI per 200 mg	none 100 ml of NS	Aminoglycosides Aminoglycosides	1 min 30 min	Bone marrow suppression- Monitor with CBC weekly

22	Daptomycin Inj	6 mg/kg/day for SSTI, 10-12 mg/kg/day for severe infections and endocarditis		< 30: every 48 hours	350mg		350 mg in 100 ml of NS	Dextrose solution	30 min	Check CPK on day 7, Avoid statins
23	Tigecycline Inj	100 mg IV stat followed by 50 mg 12 hourly Child Pugh Class C- 100 mg IV loading dose followed by 25 mg 12 hourly For hospital acquired infections or Acinetobacter, 200 mg IV stat, followed by 100 mg IV q12h	200 mg (maximum tolerated dose)	NC	50 mg	5 ml of NS	50 mg in 100 ml of NS	Should not be administered through the same line -AmB-d, ABLC, diazepam, esmoprazole, omeprazole	60 min	Give IV Tigecycline with food to decrease nausea and vomiting Carries a black-box warning for VAP/HAP, potential to cause pancreatitis, risk of increased mortality. Potential to interact with warfarin. It can cause fetal harm if given to pregnant woman
24	Clindamycin Inj.	Usual dose: 600-900 mg every 8 hourly Oral dose: 300 mg three-four times a day	2700 mg (900 mg 8 hourly)	NC	300 / 600 mg	20 ml of WFI	20 ml of NS	It is incompatible with ampicillin, phenytoin, barbiturates, aminophylline, calcium gluconate and magnesium sulphate	20 min	Diarrhoea (20%) C. difficile colitis (0.01-10%), minor reversible transaminases alterations. The neuromuscular blockade action may be potentiated. Rifampicin a strong inducer of CYP3A4 may reduce its level. It should not be

										coadministered with erythromycin as invitro antagonism has been demonstrated
25	Amikacin Sulphate Inj.	15 mg/kg IV OD. Dosing beyond 48 hours should be accompanied by determination of peak levels done after 1 hr of dosing (56-64mcg/ml), and trough concentration (<1mcg/ml) Ideal body weight (IBW) should be used for dose calculation	1 g	**40-59, :15 mg/kgq36h** 30-39-15mg/kgq48h <30- Not recommended Patient on intermittent dialysis, the dose should be given after dialysis	500 / 100 mg	1 ml of WFI / 500 mg	100 ml of N.S.	all antibiotics	60 min	Administration with agents causing the following side effects should be avoided Nephrotoxicity (polymyxins, cisplatin, vancomycin, amphotericin), ototoxicity (ethacrynic acid, furosemide), neuromuscular blockade (suxamethonium, halogenated hydrocarbon inhalation, opioids, citrated anticoagulated blood)
26	Gentamicin Inj.	4-5 mg/kg/day - 7mg/kg may be necessary in critically ill patients) Split dose may be preferable in infective	1 g	Cr CL 40-60, -5mg/kg q36hr <40_4 mg/kg, next dose should prefereably be on the basis of concentration and if definitely needed	60 / 80 mg	2 ml of WFI	50 ml	all antibiotics	20 min	Administration with agents carusing the following side effects should be avoided Nephrotoxicity(polymyxins, cisplatin, vancomycin, amphotericin), ototoxicity (ethacrynic acid, furosemide),

		endocarditis, Peak (3-5mg/L) and trough: <1mg/l levels should be targeted Ideal body weight (IBW) should be used for dose calculation								neuromuscular blockade (suxamethonium, halogenated hydrocarbon inhalation, opioids, citrated anticoagulated blood)
27	Tobramycin Inj.	4-5mg/kg q 24h 7mg/kg may be necessary in critically ill patients) Peak and (3-5mg/L), trough: <1mg/l tobramycin levels should be targeted Ideal body weight (IBW) should be used for dose calculation	1 g	Cr CL 40-60, -5mg/kg q36hr <40_4 mg/kg, next dose should preferably be on the basis of concentration and if definitely needed	60 / 80 mg	2 ml of WFI	50 ml	all antibiotics	20 min	Administration with agents causing the following side effects should be avoided Nephrotoxicity(polymyxins, cisplatin, vancomycin, amphotericin), ototoxicity (ethacrynic acid, furosemide), neuromuscular blockade (suxamethonium, halogenated hydrocarbon inhalation, opioids, citrated anticoagulated blood)
28	Azithromycin Inj.	For most infections: 500 mg OD Enteric fever: (20 mg/kg/day)	1 g	NC	500 mg	4.8 ml of WFI	250-500 ml of NS	-	20 min	Empty stomach ECG: QTc prolongation. Potential for drug interactions with the following agents needs

										to be watched for – carbamazepine, digoxin, fluconazole, nelfinavir, efavirenz, indinavir, zidovudine, warfarin
29	Ciprofloxacin Inj	400 mg 8-12 hourly	800 mg	**< 50** : 50% of dose OD	200 mg	-	100 ml of N.S.	Solutions containing multivalent cations such as magnesium	60 min	Use of tizanidine is contraindicated with ciprofloxacin. Clinically significant interactions may occur when it is given with phenytoin, theophylline, cyclosporine, drugs known to cause prolongation of QT interval, methotrexate, NSAIDs, duloxetine, warfarin
30	Levofloxacin Inj.	500-750 mg OD	750 mg	**50-10** : 50% of dose OD **< 10** : 25 % of dose OD or 50% dose every 48 hrs	500 mg	-	100 ml of N.S.	Solutions containing multivalent cations such as magnesium	60 – 90 min	Caution should be exercised ehen administered with NSAIDs and
31	Ofloxacin Inj	400 mg 12 hourly	800 mg	**< 10** :50 % of dose OD	200 mg	-	100 ml of N.S.	Heparin solutions	60 min (Slow infusion)	Maximum dose is 400 mg in patients with cirrhosis Maintain adequate hydration
32	Metronidazole Inj.	Loading dose of 15 mg/kg, then 7.5 mg/kg 8 hourly or 15 mg/kg q12h Adults: usual	4 g	**< 10**: 50% of usual dose 12 hourly	500 mg	-	100 ml of N.S.	-	30 min	**End stage liver disease: 50% of usual dose 12 hourly**

		dose 500 mg 8 hourly or 1g q12h								
33	Colistimethate Inj	Loading dose of 9-12 million unit (MU) followed by 4.5mu q12h Nebulized Colistin: 4.5 million units, q12 hourly Intrathecal/ventricular dose of colistin: 125,000 IU/day	9 million units	Cr CL 50-79: 2.5-3.8 mg CBA/kg/day in 2 divided doses CrCL 30-49: 2.5 mg/kg/da o.d Cr Cl:10-29:1.5 mg CBA /kg every 36 hours	CBA 1 mg=30,000 U of CMS (It is advisable to read the manufacturer's instruction since it may vary	10 ml of 0.9 % NS	40 ml of 0.9 % NS	Mixing drugs in infusion, injections, nebulizer solutions. Erythromycin, tetracycline, cephalothin may lead to precipitation	30 min for each 1 million unit	Neurotoxicity, nephrotoxicity, transient sensory disturbances, facial paraesthesias, confusion, psychosis, nephrotoxicity
34	Polymyxin B	15,000 to 25,000 U/kg/day iv divided every 12 horus Intrathercal/Intraventricular-50,000 U once daily for 3 to 4 days, then every alternate day	25,000 U/kg/day	NA	5L IU	5% dexrose	300-500ml of 5% Dextrose for continuous drip, For intrathecal administration dissolve in NS	Unstable in alkaline solutions	30-60 mins	May enhance the neuromuscular blocking effect of neuromuscular blockers. Concomitant administration with nephrotoxic and neurotoxic drugs should be avaoided

Table 14.2: Duration, Drug Interaction, Dosage and Administration for Antifungal Agents

S.No	Name	Dose	Maximum daily dose	Dose modification With CrCl (ml/min)	Available	Reconstitute	Further Dilution	Incompatibility	Infusion time (mins)	Additional comments
1.	Amphotericin B – deoxycholate (AmB-d)	0.5-1.5 mg/kg/day in D-5% over 24 hours	1.5 mg /kg	Not required	50 mg	5 ml of WFI	500 ml of 5% Dextrose	**NS - precipitates with 0.9% NS**	4 hours	Test doses are unnecessary 24h infusion and saline loading, with 1 L of saline before AmB associated with less nephrotoxicity. Avoid nephrotoxic agents-NSAIDS, aminoglycosides. Good hydration with K rich diet
2.	Amphotericin B- liposomal	**3-5mg/kg/day, once a day**	5mg/kg	Not required	50mg	12 ml of sterile WFI	5%Dextrose to give a final concentration of 1-2 mg/ml	**NS - precipitates with 0.9% NS. Any other drug**	120 minutes	Use of corticosteroids may potentiate hypokalemia. Concomitant administration with other nephrotoxic drugs should be avoided
3.	Fluconazole	For candidemia: loading dose of 12 mg/kg IV stat followed by maintenance dose of 6 mg/kg/day Usual dose:	1200 mg	**< 50** : 50 % of dose **HD**: 100 % dose post HD	100ml contains 200 mg	-	-	-	20 min	**Interactions**: **Prolonged QTc** with hypokalemia, hypomagnesimia, cardiomyopathy, Ivabradine, cisapride, astemizole, terfenadine Fluconazole significantly **increase levels of** cyclosporine, **tacrolimus**, rifabutin (uveitis), phenytoin, theophylline

		loading dose of 800 mg followed by maintenance dose of 200 mg o.d								**Rifampicin decreases** levels of fluconazole. Hypoglycemia with oral hypoglycemic, PT prolongation with coumarin-type anticoagulation
4.	Voriconazole	Loading dose of 6 mg/kg 12 hourly followed by 4 mg/kg 12 hourly Target trough concentration of 1-5 mg/l		NC IV preparation containing cyclodextrin should not be administered in Patients with CrCL < 50	200 mg	19 ml of WFI for each 20 mg of voriconazole	180 ml of 0.9% NS for each each 20 mg of voriconazole	Must not be mixed or co-administered with medical products or electrolytes Blood products must not be administered with voriconazole TPN infusion can be administered	60 min	Dose reduction : 50 % of dose in Child-pugh Class A/B Watch for Visual hallucinations, LFT alterations Contraindicated with rifampicin, carbamazepine, long acting barbiturates, phenytoin, Ivabradine. Interactions with warfarin, Tacrolimus and cyclosporine
5	Caspofungin	Loading dose of 70 mg followed by 50 mg OD	70 mg	NC	70 mg/50 mg	10.5 ml of 0.9 % NS or WFI	0.9% NS (250 ml for 70 mg) & 100 ml for 50 mg	Not compatible with dextrose containing solutions Must not be mixed or co-administered with medical products or electrolytes	60 min	Watch for: Allergic reactions, nausea, vomiting, diarrhea, LFT alterations, anemia Interactions: Cyclosporine increases Caspofungin AUC by 35%. Cyclosporine levels are unchanged Caspofungin decreases Tacrolimua 12 hour blood concentrations Caspofungin levels are

										reduced by phenytoin, rifampicin, dexamethasone, Efavirenz, nevirapine, & carbamazepine
6.	Anidulafungin	Loading dose of 200 mg followed by 100 mg OD	200 mg	NC	100 mg	10.5 ml of 0.9 % NS or WFI	0.9% NS (250 ml for 70 mg) & 100 ml for 50 mg	Not compatible with dextrose containing solutions Must not be mixed or co-administered with medical products or electrolytes	60 min	Watch for: Allergic reactions, nausea, vomiting, diarrhea, LFT alterations, anemia
7.	Micafungin	100 mg OD (No loading dose)	100 mg	NC	100 mg	Package insert	Package insert	Must not be mixed or co-administered with medical products or electrolytes	60 min	Few cases of immune-mediated hemolysis have been reported

WFI, Water for Injection; **NC,** No Change

***Prolonged infusions for β-lactams (penicillins, cephalosporins, and carbapenems):** There is evidence that prolonged infusions will benefit the following patients:

2) Critically ill patients
3) Patients with infections with organisms which have MICs close to breakpoints.
4) Patients who have large apparent volume of distribution (AVD)
5) Patients with normal or increased GFR.

This benefit is more likely with *Pseudomonas* and *Acinetobacter* rather than *Enterobacteriaceae*.

There is an issue of stability of the carbapenems in the infusion at the ambient temperature.

*Prolonged infusion**- Piperacillin-tazobactam- 4 hrs**
Doripenem – 4 hrs
Meropenem- 3 hrs
Imipenem- 2 hrs

- Single daily dose of aminoglycosides is encouraged as it improves efficacy and decreases nephrotoxicity
- Drugs which are incompatible with aminoglycosides should be reconstituted and administered separately
- In case of drugs requiring loading dose, the loading dose should be given to all patients regardless of the patient's creatinine clearance. Maintenance dose is based on the creatinine clearance
- Doxycycline P should be given with half a glass of water and patients advised to avoid recumbent postures for an hour afterwards to avoid esophagitis
- Oral fluoroquinolones and doxycycline should not be given with milk or milk products/calcium supplements as food decreases the absorption

Moellering and associates formula for vancomycin dosing in patients with decreased creatinine clearance: **Dose (mg/day) = 15.4 × creatinine clearance (mL/min).** This formula is not to be used in anephric patients; instead, a dose of 1.9 mg/kg/day should be given after a loading dose of 15 mg/kg.

Renal clearance of cefoperazone -25 % and sulbactam -84 %

Penicillins, Cephalosporins, FQ, Azoles are given post HD

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APPENDIX I
ICMR data 2018

Isolation rates of key pathogens, 2018:

Table 1: Isolation rates of major groups of organisms in different specimen

	Total n=60497 (%)	Blood n=11783 (%)	Urine n=13658 (%)	LRT n =10058 (%)	SI n=15208 (%)	DI n=3511 (%)	SS n =1409 (%)	CSF n=390 (%)	Faeces n=536 (%)	Others n=3944 (%)
Enterobacteriaceae	29666 (49)	4430 (37.6)	11180 (81.9)	3522 (35)	6243 (41.1)	1607 (45.8)	746 (52.9)	112 (28.7)	156 (29.1)	1670 (42.3)
Enteric *Salmonella*	764 (1.3)	620 (5.3)	4 (0)	0 (0)	13 (0.1)	2 (0.1)	3 (0.2)	0 (0)	120 (22.4)	2 (0.1)
NFGNB	13802 (22.8)	1862 (15.8)	919 (6.7)	5392 (53.6)	3325 (21.9)	883 (25.1)	296 (21)	158 (40.5)	5 (0.9)	962 (24.4)
Staphylococci	10499 (17.4)	3153 (26.8)	144 (1.1)	617 (6.1)	4855 (31.9)	701 (20)	144 (10.2)	80 (20.5)	2 (0.4)	803 (20.4)
Enterococci	3442 (5.7)	677 (5.7)	1259 (9.2)	21 (0.2)	727 (4.8)	304 (8.7)	162 (11.5)	28 (7.2)	10 (1.9)	254 (6.4)
Fungi	1191 (2)	713 (6.1)	146 (1.1)	24 (0.2)	28 (0.2)	9 (0.3)	20 (1.4)	9 (2.3)	0 (0)	242 (6.1)

Notes:

1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
5. **DI** (Deep Infection) includes: Abscess aspirate, Pus aspirate, Deep Biopsy and Deep Tissue.
6. **CSF** (Cerebrospinal fluid)

Table 2: Isolation rates of major species of organisms in different specimen

	Total n=60497 (%)	Blood n=11783 (%)	Urine n=13658 (%)	LRT n=10058 (%)	SI n=15208 (%)	DI n=3511 (%)	CSF n=390 (%)	SS n=1409 (%)	Others n=3944 (%)
Escherichia coli	15582 (26)	2134 (18)	7853 (58)	755 (8)	2899 (19)	572 (16)	40 (10)	432 (31)	784 (20)
Klebsiella pneumoniae	8783 (15)	1785 (15)	2065 (15)	2054 (21)	1653 (11)	456 (13)	42 (11)	185 (13)	514 (13)
P. aeruginosa	7273 (12)	650 (5.5)	723 (5.3)	2632 (26.2)	1951 (12.8)	472 (13.4)	43 (11)	144 (10.2)	655 (16.6)
A. baumannii	3869 (6.4)	535 (4.5)	96 (0.7)	1539 (15.3)	980 (6.4)	369 (10.5)	30 (7.7)	51 (3.6)	268 (6.8)
S. aureus	7282 (12)	1046 (8.9)	98 (0.7)	597 (5.9)	4214 (27.7)	572 (16.3)	25 (6.4)	94 (6.7)	635 (16.1)
MRSA	2844 (4.7)	423 (3.6)	38 (0.3)	228 (2.3)	1716 (11.3)	191 (5.4)	16 (4.1)	37 (2.6)	195 (4.9)
E. faecalis	1781 (2.9)	217 (1.8)	676 (4.9)	4 (0)	459 (3)	235 (6.7)	8 (2.1)	42 (3)	138 (3.5)
E. faecium	1216 (2)	415 (3.5)	399 (2.9)	5 (0)	201 (1.3)	62 (1.8)	16 (4.1)	52 (3.7)	61 (1.5)
Enterobacter cloacae	920 (1.5)	203 (1.7)	142 (1)	96 (1)	277 (1.8)	103 (2.9)	6 (1.5)	21 (1.5)	67 (1.7)
Staphylococcus haemolyticus	798 (1.3)	444 (3.8)	7 (0.1)	9 (0.1)	214 (1.4)	68 (1.9)	9 (2.3)	11 (0.8)	36 (0.9)
Staphylococcus epidermidis	760 (1.3)	465 (3.9)	8 (0.1)	3 (0)	182 (1.2)	26 (0.7)	26 (6.7)	14 (1)	36 (0.9)
S.hominis	402 (0.66)	329 (2.8)	1 (0)	2 (0.02)	38 (0.25)	10 (0.28)	7 (1.8)	7 (0.5)	8 (0.2)

Notes:

1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
5. **DI** (Deep Infection) includes: Abscess aspirate, Pus aspirate, Deep Biopsy and Deep Tissue.
6. **CSF** (Cerebrospinal fluid)

Table 3: Isolation of Salmonella from different sample types

Isolate	Culture positive		
	Blood n=13344 (%)	Faeces n=585 (%)	Others n=57437 (%)
Salmonella Typhi	**576 (4.3)**	**98 (16.8)**	**15 (0)**
Salmonella Paratyphi A	**124 (0.9)**	**0 (0)**	**5 (0)**
Total Salmonella	**741 (5.6)**	**465 (79.5)**	**57407 (99.9)**

Table 4: Isolation rates of different fungi from different specimens

Isolate	Total n=71366	Blood n=13344	Urine n=16576	LRT n=11361	SI n=18492	DI n=3963	Genital n=187
Fungal isolates	1428 (2)	932 (6.98)	146 (0.88)	28 (0.2)	30 (0.16)	9 (0.22)	186 (99.46)
Yeasts	1272 (1.78)	809 (6.06)	146 (0.88)	7 (0.1)	29 (0.15)	8 (0.20)	186 (99.46)
-Candida	1253 (1.75)	793 (5.94)	146 (0.88)	6 (0.1)	28 (0.15)	8 (0.20)	186 (99.46)
Candida albicans	395 (0.55)	149 (1.11)	57 (0.34)	3 (0)	13 (0.07)	3 (0.07)	140 (74.86)
Candida tropicalis	384 (0.53)	261 (1.95)	68 (0.41)	1 (0)	7 (0)	2 (0.05)	17 (9.09)
Candida glabrata	143 (0.2)	83 (0.62)	12 (0.07)	0 (0)	5 (0)	2 (0.05)	22 (11.76)
Candida utilis	151 (0.21)	150 (1.12)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Candida parapsilosis	102 (0.14)	94 (0.70)	3 (0)	0 (0)	1 (0)	0 (0)	1 (0.53)
Candida krusei	35 (0.04)	22 (0.16)	2 (0)	1 (0)	1 (0)	0 (0)	6 (3.21)
Candida auris	25 (0.03)	20 (0.15)	3 (0)	1 (0)	1 (0)	0 (0)	0 (0)

Notes:

1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
4. **DI** (Deep Infection) includes: Abscess aspirate, Pus aspirate, Deep Biopsy and Deep Tissue.

Susceptibility patterns of key pathogens, 2018

Table 5: Susceptible percentages of Salmonella isolates (If number of isolates of particular species ≥ 20).

AMA	Blood	
	Salmonella Typhi n=689	*Salmonella Paratyphi A* n=129
Ampicillin	92.7	96.9
Azithromycin	97.2	-
Cefixime	98.6	100
Ceftriaxone	98.1	97.7
Chloramphenicol	95.8	99.2
Ciprofloxacin	12.9	0.9
Levofloxacin	31.8	-
Pefloxacin	28.6	-
Trimethoprim-sulfamethoxazole	94.6	100

Table 6: Susceptible percentages of *Acinetobacter baumannii* isolated from different specimen (except faeces).

AMA	All Specimens	Blood	LRT	SI	DI	CSF	Urine
	n=4526	n=694	n=1778	n=1105	n=385	n=49	n=125
Amikacin	23.1	28.2	17.5	23.4	21.6	30	49.6
Cefepime	13.2	18.1	8.7	13.2	12.4	20.4	40.8
Ceftazidime	13.9	17.6	10.1	14.2	11.7	9.8	42.2
Imipenem	18.2	24.9	10.8	21.6	16.2	24.5	52.1
Levofloxacin	23.8	28.9	14.1	31.7	28.6	26.7	48.2
Meropenem	22.9	29.7	14.7	28.9	17.9	26.7	57
Minocycline	64.3	60.9	56.8	74.9	77.1	60.9	69.7
Piperacillin-tazobactam	17	23.6	10.5	17.9	15.4	24.5	54.1

Notes:
1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
5. **DI** (Deep Infection) includes: Abscess aspirate, Pus aspirate, Deep Biopsy and Deep Tissue.
6. **CSF** (Cerebrospinal fluid)

Table 7: Susceptible percentages of *Pseudomonas aeruginosa* isolated from different specimen (except faeces).

AMA	All Specimen	Blood	LRT	SI	DI	CSF	Urine
	n=8856	n=776	n=2922	n=2573	n=561	n=47	n=922
Amikacin	68.8	63.3	77.9	66.7	69.8	42.9	51.7
Cefepime	63.5	65	72.5	59.9	64.8	31.9	44.3
Ceftazidime	65.9	70.4	73.5	62.4	68.9	34	46.1
Ciprofloxacin	60	57.8	68.2	59.5	60.6	31.1	41.9
Colistin	91.5	92.5	93.1	86.2	98.4	-	93.1
Gentamicin	63.1	61.4	71.7	62.9	63.6	43.6	46.1
Imipenem	67.2	70.6	71.7	67.9	70.5	47.6	51.2
Levofloxacin	58.4	58.5	69.5	54.9	60.8	31.9	37.4
Meropenem	69.2	72.9	72.1	70.3	73.1	41.3	50.4
Piperacillin-tazobactam	71	72.4	75	70.3	73.6	38.3	55.6
Tobramycin	68	59	80.2	64	71.6	42.9	43.3

Notes:
1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
4. **DI** (Deep Infection) includes: Abscess aspirate, Pus aspirate, Deep Biopsy and Deep Tissue.
5. **CSF** (Cerebrospinal fluid)

Table 8: Susceptible percentages for *Escherichia coli* isolated from different specimen

AMA	All Specimens	Blood	LRT	SI	SS	CSF	Urine
	n=18303	n=2335	n=880	n=3460	n=484	n=44	n=9391
Amikacin	81.1	81.3	76.8	78	80.1	70.7	83
Cefazolin	28	-	-	-	-	-	28
Cefotaxime	20.9	19.1	12.6	15	11.3	15.4	25
Ceftazidime	23.1	23.3	18.8	22.7	25.5	25.7	-
Ciprofloxacin	25.2	24.4	19.1	21.1	22.7	16.3	27.9
Colistin	98.5	99.5	97.8	98.6	100	-	98.1
Ertapenem	68.6	69.2	56.6	63.5	64.5	43.6	71.5
Fosfomycin	88.1	-	-	-	-	-	88.1
Imipenem	73	80.6	71.2	69.7	80.5	81.4	73.7
Levofloxacin	23.4	12	16.6	17.2	18.3	17.4	26.6
Meropenem	70.4	76.7	59.7	63.3	75.3	59.1	71.6
Nitrofurantoin	85.9	-	-	-	-	-	86
Piperacillin-tazobactam	60	59.6	44.9	52.1	54.1	57.1	66.2
Trimethoprim-sulfamethoxazole	39.4	-	-	-	-	-	39.4

Notes:

1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
5. **CSF** (Cerebrospinal fluid)

Table 9: Susceptible percentages for *Klebsiella pneumoniae* isolated from different specimen

AMA	All Specimens	Blood	LRT	SI	SS	CSF	Urine
	n=10387	n=1965	n=2404	n=2134	n=209	n=46	n=2446
Amikacin	52.9	43.9	53	51.8	44.4	34.1	60.4
Cefazolin	28.2	-	-	-	-	-	28.2
Cefotaxime	23.2	18.6	24.3	21.6	23	2.3	27
Ceftazidime	26.7	20.9	31.9	25.8	23.1	7.3	-
Ciprofloxacin	36.2	30.4	40.7	35	30	22.2	37.7
Colistin	91.5	90.6	93.2	95	95.8	-	89.9
Ertapenem	49.2	36.8	51.1	51.3	40.1	30.2	52.6
Imipenem	54	47.4	54.7	54.2	49.5	54.3	60.7
Levofloxacin	30.9	23.8	28.3	30.7	21.9	15.4	36.5
Meropenem	51.5	42.4	53.1	53.4	45	39.5	54.7
Nitrofurantoin	37.4	-	-	-	-	-	37.5
Piperacillin-tazobactam	41.1	33.2	42.7	40.2	36.1	15.2	46.6
Trimethoprim-sulfamethoxazole	40	-	-	-	-	-	40

Notes:

1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
5. **CSF** (Cerebrospinal fluid)

Table 10: Susceptible percentages for *Enterobacter cloacae* isolated from different specimen

AMA	All Specimens	Blood	LRT	SI	SS	Urine
	n=1037	n=216	n=103	n=333	n=23	n=171
Amikacin	78.3	82.4	91.3	74.3	82.6	73.8
Cefotaxime	36.6	24	46	43.6	-	35.3
Ceftazidime	42.8	35.9	37	45.9	-	-
Ciprofloxacin	63.5	67	77.3	62	78.3	54.2
Colistin	92.4	-	-	-	-	90
Ertapenem	75.9	71.6	90	78.2	90	70.6
Imipenem	77.9	79.4	88.3	76.6	82.6	76.6
Levofloxacin	58.4	54.5	82.6	56.3	-	56.6
Meropenem	76.2	76.7	87.2	74.3	90.9	72.9
Nitrofurantoin	53.6	-	-	-	-	53.3
Piperacillin-tazobactam	66	68.1	73.7	63.9	77.3	66.5
Trimethoprim-sulfamethoxazole	57.4	-	-	-	-	57.1

Notes:

1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.

Table 11: Susceptible percentages for *Staphylococcus aureus* isolated from different specimen

AMA	All Specimens	Blood	LRT	SI	SS	CSF	Urine
	n=8424	n=1217	n=681	n=4727	n=112	n=29	n=203
Cefoxitin	61.5	58.2	62.8	60.4	64.2	31	55.9
Ciprofloxacin	18.6	21.1	15.5	16.9	27.6	32	30.7
Clindamycin	76.1	74.8	69.8	76.4	78.7	74.1	71.4
Erythromycin	44.4	41.3	40.4	45.1	47.2	46.2	37.7
Linezolid	98.8	98	98.9	99	100	100	97.8
Mupirocin High Level	97.7	96.6	98.9	98.3	98.2	-	94.5
Oxacillin	55	58.4	52.3	51	51.6	-	74.4
Penicillin	6.2	8.5	10.1	4.7	7	-	7.4
Teicoplanin	97.7	96.2	98.1	98	100	95.7	96.5
Tetracycline	88.6	88.6	85.3	89.4	93.5	90.5	77.3
Tigecycline	99.5	100	97.6	99.5	100	-	100
Trimethoprim-sulfamethoxazole	62.7	65.8	66.5	61.4	61.2	70.8	63.2
Vancomycin	100	100	100	100	100	-	100

Notes:

1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
5. **CSF** (Cerebrospinal fluid)

Table 12: Susceptible percentages for Methicillin sensitive *Staphylococcus aureus* (MSSA) isolated from different specimen

AMA	All Specimens	Blood	LRT	SI	SS	Urine
	n=5009	n=5009	n=5009	n=5009	n=5009	n=5009
Cefoxitin	100	100	100	100	100	100
Ciprofloxacin	24.3	26.8	20.8	22.7	38.1	36.9
Clindamycin	86.2	84.4	84.4	86.3	84.4	87.5
Erythromycin	56.9	57	53.4	57.1	56.5	55.2
Linezolid	99.5	98.8	99.5	99.6	100	100
Mupirocin High Level	98.9	99.6	98.5	99	97.3	94.6
Oxacillin	100	100	100	100	-	100
Penicillin	10.7	14.5	17.8	8.5	14.8	13.3
Teicoplanin	98.9	98.8	98.9	99.1	100	97.9
Tetracycline	92.1	92.5	91.1	92	96.2	90.7
Tigecycline	100	100	100	100	-	-
Trimethoprim-sulfamethoxazole	67.1	73.4	70.1	64	67.2	74.8
Vancomycin	100	100	100	100	100	100

Notes:
1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.

Table 13: Susceptible percentages for Methicillin resistant *Staphylococcus aureus* (MRSA) isolated from different specimen

AMA	All Specimens	Blood	LRT	SI	SS	Urine
	n=3352	n=3352	n=3352	n=3352	n=3352	n=3352
Cefoxitin	0.2	0	0	0.2	2.6	0
Ciprofloxacin	10.1	14.1	7.8	8.8	11.9	23
Clindamycin	61.4	61.8	48.5	62.9	70.5	52.9
Erythromycin	25.6	21.5	19.9	27.8	34.1	16.7
Linezolid	97.9	96.9	98	98.1	100	95.4
Mupirocin High Level	95.4	91.6	100	97	-	94.4
Oxacillin	2.6	3.7	0	1.9	-	-
Penicillin	1.3	1.6	2	1	0	0
Teicoplanin	96.3	93.3	97.2	96.9	100	94.7
Tetracycline	83.6	83.3	76.6	85.9	90	62.7
Tigecycline	98.7	100	94.5	99	-	-
Trimethoprim-sulfamethoxazole	56.3	55.1	60.7	57.9	52.5	48.2
Vancomycin	100	100	100	100	100	-

Notes:
1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.

Table 14: Susceptible percentages for CoNS isolated from different specimen

AMA	All Specimens	Blood	LRT	SI	SS	CSF	Urine
	n=3915	n=2342	n=23	n=904	n=56	n=66	n=93
Cefoxitin	27.5	25.5	30	29.3	48.1	35.5	27.8
Ciprofloxacin	38	35.2	31.8	42.8	49.1	50.8	38.5
Clindamycin	54.3	51.6	40.9	57.7	68.5	64.6	56.1
Erythromycin	22.1	19.3	10	24.4	36.4	35.4	27.2
Linezolid	97.4	97.7	95.7	97.9	100	98.5	96.7
Penicillin	9.3	9.9	-	7.2	25.6	26.2	2.2
Teicoplanin	94.5	93.6	100	96	96.1	98.5	96.6
Tetracycline	79.5	80.3	-	80.6	88.2	87.7	62.6
Tigecycline	98.3	99.1	-	95.2	-	-	-
Trimethoprim-sulfamethoxazole	45.6	42.6	-	47.3	67.3	47.5	61.9
Vancomycin	100	100	-	100	100	-	100

Notes:

1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
4. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
5. **CSF** (Cerebrospinal fluid)

Table 15: Susceptible percentages for *Enterococcus faecalis* isolated from different specimen

AMA	All Specimens	Blood	SI	SS	Urine
	n=1990	n=261	n=506	n=44	n=763
Ampicillin	73.7	67.3	71.5	53.5	78.6
Ciprofloxacin	13.4	-	-	-	13.2
Fosfomycin	87.5	-	-	-	87.5
Gentamicin HL	52.1	46.6	53.1	53.5	54.2
Linezolid	98.3	97.1	99	100	98.5
Nitrofurantoin	93	-	-	-	93
Teicoplanin	95.9	89.9	96	93.2	97.6
Vancomycin	96.1	93.4	95.4	93.2	97.5

Notes:
1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.
3. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.

Table 16: Susceptible percentages for *Enterococcus faecium* isolated from different specimen

AMA	All Specimens	Blood	SI	SS	Urine
	n=1424	n=478	n=218	n=61	n=501
Ampicillin	18.1	20.8	18.6	14	16.7
Ciprofloxacin	6.1	-	-	-	6.1
Gentamicin HL	29.5	25.3	28	18.2	32.1
Linezolid	96	97.1	94.8	96.7	94.4
Nitrofurantoin	52.5	-	-	-	52.5
Teicoplanin	78.9	74.7	76.1	82	82.2
Vancomycin	78.1	75	73.4	82	81.3

Notes:
1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.

3. **SI** (Superficial Infection) includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.

Table 17: Susceptible percentages of *Candida spp.* isolated from all specimen

AMA	All Specimens						
	Candida albicans **n=395**	***Candida auris*** **n=25**	***Candida glabrata*** **n=143**	***Candida krusei*** **n=35**	***Candida parapsilosis*** **n=102**	***Candida tropicalis*** **n=384**	***Candida utilis*** **n=151**
Anidulafungin	99.2	-	84.9	100	100	96.8	98
Caspofungin	94.6	-	50.8	57.7	100	94.7	100
Fluconazole	92.4	0	70.4	22.9	82.4	94.8	98.7
Micafungin	100	-	-	-	96.6	98.8	-
Voriconazole	93.1	-	97.1	97.1	96.9	98.4	100

Table 18: Susceptible percentages of *Candida spp.* isolated from blood specimen.

AMA						
	Candida albicans **n=149**	***Candida glabrata*** **n=83**	***Candida krusei*** **n=22**	***Candida parapsilosis*** **n=94**	***Candida tropicalis*** **n=261**	***Candida utilis*** **n=150**
Anidulafungin	98.9	84.4	-	100	96.7	98
Caspofungin	95.1	48.5	60	100	94.9	100
Fluconazole	98.7	62.2	22.7	81.9	95.4	98.7
Micafungin	100	-	-	96.2	100	-
Voriconazole	99.3	96.3	100	96.7	98.4	100

Table 19: Susceptible percentages of *Candida spp.* isolated from urine specimen.

AMA		
	Candida albicans **n=57**	***Candida tropicalis*** **n=68**
Fluconazole	93	98.5
Voriconazole	96.4	100

Table 20: Susceptible percentages of *Candida spp.* isolated from genital specimen.

AMA		
	Candida albicans **n=140**	***Candida glabrata*** **n=22**
Fluconazole	83.6	90.9
Voriconazole	83.6	100

APPENDIX II

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