Treatment Guidelines for Antimicrobial Use in Common Syndromes

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Department of Health Research
New Delhi, India
2017

Foreword

Emergence of antimicrobial resistance(AMR) in pathogens of public health importance is globally recognised as a threat to human health. It is well known that Infections caused by antimicrobial-resistant micro-organisms in hospitals are associated with increased morbidity, mortality and healthcare costs. Antimicrobial resistance is closely linked to inappropriate antimicrobial use and selection and spread of resistant microorganisms in the presence of antimicrobials is facilitated by irrational use of drugs, self-medication and misuse of drugs.

Recognizing the need for having a nation wide evidence on AMR, ICMR initiated putting together AMR surveillance network in 2013. Using the data from the ICMR's AMR surveillance network of last two years, ICMR has developed evidence based treatment guidelines for treatment of ten syndromes of infections. It gives me immense pleasure to inform you that country's leading infectious disease physicians and clinical microbiologists, both from public and private sector, have contributed to the compilation of this document. We are thankful to all the experts who contributed to the guidelines as well as those who reviewed it.

It is estimated that 50% or more of hospital antimicrobial use is inappropriate. We hope that this document will be instrumental in guiding the treatment and will bring down inappropriate prescriptions. I hope that this document will be of immense help to medical practitioners, hospital administrators, doctors and will be helpful in bringing down the burden of AMR in the country.

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Guideline Development Process

The publication of the of the Antimicrobial Treatment Guidelines represents the culmination of the efforts of the Antimicrobial Stewardship Program of ICMR to publish treatment guidelines for common syndromes in India. These guidelines are targeted for the health care settings. It aims to rationalize the usage of antibiotics on our Essential Medicines Formulary (EMF) 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. A working group on Antimicrobial Stewardship Program (AMSP) was simultaneously constituted in late 2012 to provide overall direction to development of AMSP in the country. One of the key recommendations of the group was to devise standard treatment guidelines, based on Indian data, which can guide antibiotic usage in the country. The process began with identification of ten syndromes for which treatment guidelines was to be framed. The country's leading infectious disease physicians and clinical microbiologists from leading medical organisations were assigned this task of compilation and review. The data emanating out of the ICMR network was shared with all the teams. The document was compiled to give it the present shape.

All recommended therapies are either evidence-based or universally accepted standards. These are general guidelines; treatment of individual patients may vary depending upon local conditions and experience.

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Please send your comments or feedback on guidelines to icmr.project2015@gmail.com subject "ICMR treatment guidelines".

Instructions to users of Antimicrobial Guidelines

There is no denying the fact that our country lacks proper Anti microbial Guidelines (AMGL) for empiric management of infections. Most of AMGLs available are based on pathogenic bacteria and easily available authentic western literature. Instead AMGL should be syndromic and based on reliable Indian antimicrobial resistance (AMR) data. The empirical management must be altered in 48-72 hours according to antimicrobial susceptibility test report data on isolation of specific pathogen(s) causing infection.

With these issues in background, Indian Council of Medical Research (ICMR) embarked on preparation of AMGL for 10 more important infective syndromes based on ICMR Antimicrobial Resistance Surveillance Network (AMRSN) data as part of its Antimicrobial Stewardship Program. Basic components of these AMGLs are Definition of syndrome, Clinical aspects, likely Investigations, ICMR AMR data, Schedule of antimicrobial management, References, Editorial Board (consisting of Infectious Diseases Physician/Clinician, Clinical Microbiologist, Pharmacologist etc..).

However a clinician managing an infection is well advised not to follow these AMGLs blindly but customize these in accordance with local AMR data. AMR data is known to differ between different Health Care Institutes of the country and even between different clinical departments of same Health Care Institute. Hence each Health Care Institute and each Clinical department must customize their respective AMGL accordingly using ICMR AMGL as basic rational format.

Contents

Management of Community - onset Acute Undifferentiated Fever in Adults

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. Some general principles:

i. 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).

ii. The choice of medication may vary depending on differences in the case mix of patients, various drugs (of same or different class) listed in formulary or clinical practice guidelines already in place at different institutions in similar patient care locations.

iii. 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.

iv. Empiric antibiotic treatment for common infections should be limited to conditions where early initiation of antibiotics has been shown to be beneficial, eg severe sepsis and septic shock, acute bacterial meningitis, community acquired pneumonia, necrotizing fasciitis, etc.

v. Reassessment 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.

3. Case Definition

i. 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.

ii. Seen in ambulatory care settings at the primary level (PHC), doctor's office/clinic, emergency room in a community Hospital, including referrals from primary health care or community physicians.

iii. 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.*

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

i. 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.

ii. **Viruses** cause febrile illness or specific viral "influenza like- illness" (with mild sore throat and cough).

iii. If rash or exanthema is present without drug exposure (rule out drug allergy), consider mononucleosis syndrome (EBV, CMV, HIV) or an exanthematous viral illness (measles, rubella, etc).

iv. **Primary or secondary dengue** (sometimes 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 hemorrhage, bleeding gums, bleeding at puncture sites, hematuria, hematemesis, hemoptysis, blood in stools .

v. Scrub **typhus** or murine typhus may present with skin eschar, regional lymphadenopathy, and maculopapular rash.

vi. **Leptospirosis** can present with conjunctival suffusion, muscle tenderness and jaundice (ask for flood water or sewage exposure)

vii. **Typhoid** (continuous fever and splenomegaly are clues)

viii. Community acquired secondary bacteremia: Primary source may be occult. In most instances it is either from an underlying pneumonia, intra-abdominal infection or urosepsis. Symptoms related to these systems may not be manifest, especially in the elderly.

ix. **Hepatitis A or E** (fever usually subsides with onset of jaundice)

x. **Chikungunya** presents with arthralgia /polyarthritis.

xi. Consider **rheumatic fever** caused by Group A beta hemolytic streptococci if there is migratory arthritis with preceding significant "sore throat".

xii. **Tuberculosis** should be considered in any patient with prolonged undifferentiated fever, especially if there is weight loss or night sweats.

5. Diagnostic Investigations (where facilities are available)

i. One blood smear and/or RDT at least is required for malarial parasite detection (repeat blood smear once more if initial smear is negative in an endemic region).

ii. Complete blood count : Anemia, leucopenia /leukocytosis, elevated hematocrit or thrombocytopenia (dengue, leptospirosis)

iii. Diagnostic blood cultures for aerobic bacteria (at least two) to be drawn prior to start of empiric antibiotics

iv. Liver enzymes and bilirubin

v. Urinalysis – white blood cells, proteinuria and hematuria.

vi. Chest roentgenogram (if chest findings are present, to rule out early pneumonia or TB)

vii. Ultrasonography of abdomen if fever persists to rule out hepatic, renal or intra-abdominal sources of infection.

viii. 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.

- Dengue rapid NS1 antigen and IgM Combo test (SD bioline, USA)
- Scrub typhus IgM ELISA (In Bios, USA),
- Leptospira IgM ELISA (Alere, Australia),

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. Artemesinin (especially oral) monotherapy should be strongly discouraged as it leads to resistance this class.

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

Table 1. *Salmonella* Typhi ICMR AMR Data 2014

AMA	PGIMER, Chandigarh 'n' 109	AIIMS, New Delhi 'n' 22	CMC, Vellore 'n' 71	JIPMER, Puducherry 'n' 7	National 'n' 209
	No. R (%)	No. R	No. R (%)	No. R	No.R %)
Ampicillin	9 (8.3)	0	2 (2.8)	0	11 (5.3)
Cefixime	0 (0)	0	0 (0)	0	0 (0)
Ceftriaxone	0 (0)	0	0 (0)	0	0 (0)
Chloramphenicol	3 (2.8)	0	1 (1.4)	0	4 (1.9)
Ciprofloxacin	56 (51.4)	15	67 (94.4)	7	145 (69.4)
Trimethoprim-sulphamethoxazole	0 (0)	0	3 (4.2)	0	3 (1.4)

Note : If No. Tested is ≥30, No. R (%) given. If No. tested <30, only No. R given.

Table 2. *Salmonella* Paratyphi A ICMR AMR Data 2014

AMA	PGIMER, Chandigarh 'n' 2	AIIMS, New Delhi 'n' 6	CMC, Vellore 'n' 14	JIPMER, Puducherry 'n' 7	National 'n' 29
	No. R	No. R	No. R	No. R	No. R
Ampicillin	1	0	0	1	2
Cefixime	0	0	0	0	0
Ceftriaxone	0	0	0	0	0
Chloramphenicol	0	0	1	0	1
Ciprofloxacin	1	2	14	6	23
Trimethoprim-sulphamethoxazole	0	0	0	0	0

Note : If No. Tested is ≥30, No. R (%) given. If No. tested <30, only No. R given.

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.

Table 3. *Staphylococcus aureus* ICMR AMR Data 2014

AMA	JIPMER, Puducherry		AIIMS, New Delhi		PGIMER, Chandigarh		CMC, Vellore		National	
	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R
Cefoxitin	2217	863 (38.9)	644	116 (18.0)	360	171 (47.5)	0	0	3221	1150 (35.7)
Ciprofloxacin	2216	1394 (62.9)	644	399 (62.0)	359	241 (67.1)	27	21 (77.8)	3246	2055 (63.3)
Clindamycin	2200	501 (22.8)	644	180 (28.0)	362	120 (33.1)	0	0	3206	801 (25.0)
Erythromycin	2200	1073 (48.8)	644	367 (57.0)	362	190 (52.5)	112	42 (37.5)	3318	1672 (50.4)
Gentamicin	2196	386 (17.6)	0	0	0	0	206	42 (20.4)	2402	428 (17.8)
Linezolid	1596	0	644	6 (0.9)	82	0	134	0	2456	6 (0.2)
Muporicin	1588	30 (1.9)	0	0	0	0	0	0	1588	30 (1.9)
Penicillin	2217	2023 (91.2)	644	528 (82.0)	0	0	0	0	2861	2551 (89.2)
Teicoplanin	1588	0	644	0	276	0	0	0	2508	0
Tetracycline	2216	412 (18.6)	644	644 (100)	0	0	0	0	2860	1056 (36.9)
Trimethoprim-sulfamethoxazole	1427	685 (48.0)	0	0	0	0	239	76 (31.8)	1666	761 (45.7)
Vancomycin*	2217	4 (0.2)	644	0	362	0	0	0	3223	4 (0.1)

*The 4 numbers listed as Vancomycin Resistant (R) are VISA isolates.

No VRSA was isolated during the year 2014 at JIPMER.

Cefoxitin : Surrogate marker for Methicillin.

Gram negative organisms: On the other hand, 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 intra-abdominal infections (IAI), etc} should be with an agent active against ESBL producers eg beta-lactam/beta-lactamase inhibitors or with a carbapenem for more severely ill patients.

Table 4 . Enterobacteriaceae isolates from blood. ICMR AMR data 2014.

AMA	PGIMER, Chandigarh % Resistant			AIIMS, New Delhi % Resistant			JIPMER, Puducherry % Resistant			CMC, Vellore % Resistant			National % Resistant		
	Ec	Ks	Es	Ec	Ks	Es	Ec	Ks	Es	Ec	Ks	Es	Ec	Ks	Es
Amikacin	21	56	58	58	70	75	21	44	27	12	39	11	24	54	44
Cefepime	84	87	80	85	93	85	71	86	74	67	59		79	88	80
Cefoperazone-sulbactam	48	79	69				12	38	10	20	37	7	33	62	39
Cefotaxime	87	89	80	75	87	84	79	94	85	72	62	89	80	83	83
Ceftazidime	89	92	84	78	92	80	72	79	69	72	62	79	81	84	77
Ciprofloxacin	85	66	53	90	79	67	76	73	36	74	50	25	81	65	48
Colistin	1	1	0							1	0		1	1	0
Gentamicin	32	78	81	72	74	75	40	57	47	45	48	4	46	65	56
Imipenem	6	14	9	62	63	55	26	49	31	12	37	11	18	35	26
Meropenem	52	51	44	55	77	70	18	49	21	11	37	33	35	53	38
Netilmicin										12	42	18	12	42	18
Piperacillin-tazobactam	46	73	63	59	77	72	37	73	48	30	45	11	43	68	57
Tetracycline	64	42	16										64	42	16

Note : Ec : *Escherichia coli;* Ks : *Klebsiella* spp.; Es : *Enterobacter* spp.

7. Principles of empiric therapy:

- Supportive: Acetaminophen 500 or 650 mg every 6 hours round the clock is advisable, accompanied by tepid sponging for fever or with chills >103 F. Replace fluid and electrolytes as required.
- No antibiotics are required for the majority of patients with acute febrile illness without an obvious clinical diagnosis.
- Always draw two sets of blood cultures before start of empiric antibacterial therapy.
- 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.
- Reassess the situation within 48 hours based on test results and patient status.
- Corticosteroids are not recommended in the treatment of acute undifferentiated fever.

- In patients with fever and thrombocytopenia, platelet transfusions are not recommended in general.
- Consider platelet transfusion when platelet counts are <10,000 cumm or in the presence of clinical bleeding in cases of dengue hemorrhagic fever.
- Empirical treatment with **doxycycline** for patients with undifferentiated fever and negative rapid diagnostic tests for malaria and dengue is an option for the clinician. (*Lancet Glob Health. 2013 Jul;1(3):e46-e54.)*

Figure 1 Protocol for the management of adult patients with acute undifferentiated fever.

(Int J Emerg Med. 2011; 4: 57)

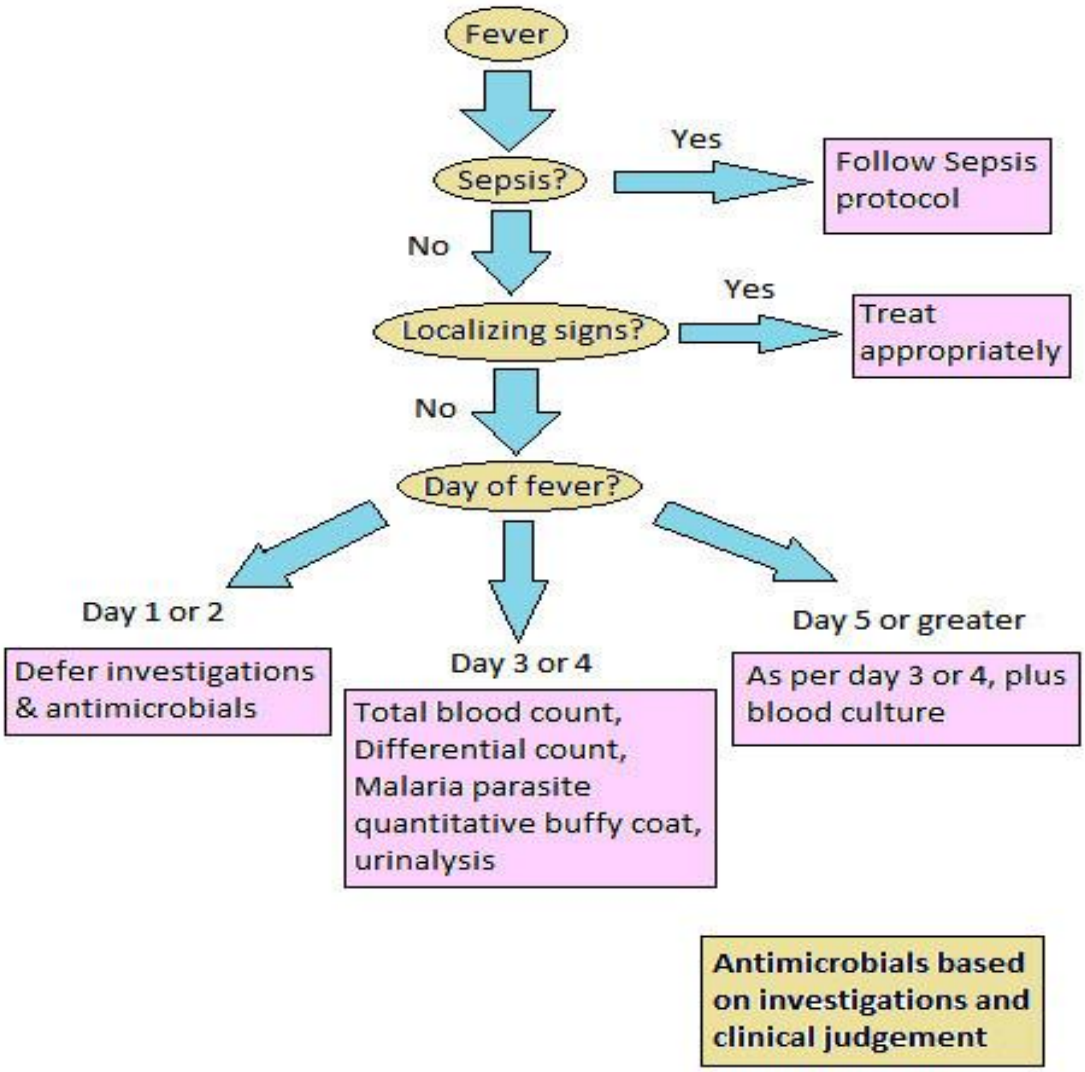

Table 5 Antimicrobial Choice for Disease conditions

	Type of disease	Organisms	Initial Treatment/ Preferred	Alternatives	Comments
1	Typhoid fever	*Salmonella* Typhi, *Salmonella* Paratyphi A	Oral: co-trimoxazole (1ds tab bd) or azithromycin (10 mg/kg/day) Parenteral: ceftriaxone 2 g IV od	Cefixime (20 mg/kg/day) or chloramphenicol 500 mg qid or ciprofloxacin 750 mg bd	Change empiric regimen based on susceptibility testing. Duration of treatment: 10-14 days.
2	Empiric therapy of suspected Gram positive infections	*S.pneumoniae, Streptococcus pyogenes, Staphylococcus aureus*	Cefazolin 2 g IV q8h or Cloxacillin 2 g IV q6h	Amoxicilin-clavulanate 1.2 g IV q8h or Penicillin G 20 laks IV q4h (if *S.aureus* excluded) or Vancomycin (if anaphylactic penicillin allergy or MRSA clinically possible)	Adjust regimen after receipt of culture and susceptibility data. Duration of treatment will depend on final diagnosis.
3	Empiric therapy for suspected Gram negative infections (eg pyelonephritis or intra-abdominal infections)	*E. coli, Klebsiella pneumoniae,* anaerobes especially *Bacteroides sp* in IAI	Piperacillin-tazobactam 4.5 g IV q6h or Cefoperazone-sulbactam 3 g IV q12h	Imipenem 1 g IV q8h or Meropenem 1 g IV q8h or Ertapenem 1 g IV od (carbapenems preferred for more seriously ill patients)	Separate anaerobic coverage unnecessary for IAI, when using BL-BLIs or carbapenems. De-escalate to ciprofloxacin, co-trimoxazole or third generation cephalosporin if isolate is sensitive. Duration of treatment: 10-14 days for pyelonephritis, 4-7 days for IAI.

4	Rickettsial infections	*Orientia tsutsugamushi, Rickettsia conori*	Doxycycline 100 mg po or IV bd	Azithromycin 500 mg po or IV od, chloramphenicol 500mg qid	Duration of treatment: 7 days
5	Leptospirosis	*Leptospira sp*	Penicillin G 20 laks IV q4h or doxycycline 100 mg po or IV bd	Ceftriaxone 2 g IV od	Duration of treatment: 7 days
6	Vivax malaria	*P.vivax*	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)	Followed by primaquine (0.25 mg/kg daily for 14 days)
7	Falciparum malaria	*P. falciparum*	Artesunate 4 mg/kg body weight daily for 3 days Plus Sulfadoxine (25 mg/kg body weight) and Pyrimethamine (1.25 mg/kg body weight) on first day.	Artemether-lumefantrine (1 tab bd for 3 days)	Followed by primaquine single dose (0.75 mg/kg). 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 centers

8. References

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9. **Editorial Board** (Name, Designation, Institution)

Antimicrobial Guidelines for the Management of Antibiotic Associated Diarrhea

Preamble and Case definition

AAD is a broad term that encompasses all diarrheal episodes, inflammatory and non inflammatory, related to the use of antibiotics. Of these, *Clostridium difficile* associated diarrhea (CDAD), or *Clostridium difficile* infection (CDI) /*Clostridium* associated colitis, is the one of the most clinical and public health importance and has become the commonest nosocomial infection in the west. There have been increasing reports of CDAD from India (1,2). Studies on CDAD from India reveals a prevalence range from 7.1 - 26.6%.

The different presentations of CDI are summarized below .

i. Asymptomatic: About 20% of hospitalised patient may be asymptomatic carrier, and have stool positive for *C. difficile* toxin. They act as reservoir for environmental contamination but do not have diarrhea.
ii. *C. difficile* associated diarrhea with colitis. This is characterised by multiple watery diarrhea > 10 times per day associated with abdominal pain, tenderness and systemic symptoms like, anorexia, nausea, fever and features of dehydration.
iii. Fulminant Colitis
iv. Recurrent disease - Recurrence of symptoms after successful initial therapy for *C. difficile*, due to relapse of the initial infecting strain or due to reinfection with a new strain, develops in 10 to 25 percent of cases

CDAD must be differentiated from

- Other causes of antibiotic associated diarrhea
- Unrelated causes of inflammatory diarrhea like Inflammatory bowel disease
- Other infective etiology like *Salmonella*, *Shigella*, *Entamoeba histolytica*
- Non inflammatory or osmotic diarrhea

Common Pathogens

Clostridium difficile

- Cases of hypervirulent strain with severe disease reported less than the west
- An asymptomatic carrier state was noted to be 6% in a hospital survey (3)
- Incidence of mild to moderate CDAD was 10%.
- Most of the cases were responsive to metronidazole.
- The hypervirulent strain NAP1/BI/027 has been responsible for dramatic increases in the frequency, severity, and refractoriness of *C. difficile* in multiple outbreaks around the world

Clinical Manifestation

C. difficile infection should be suspected in any patient who has one or more risk factors for developing this infection and has abdominal symptoms, predominantly diarrhea. The risk factors for developing CDI include:

- Antibiotics, especially
- Fluroquinolones
- Clindamycin
- Penicillins (Broad spectrum)
- Cephalosporins (Broad spectrum)
- Advanced age
- Severity of illness
- Gastric acid suppression (mainly with proton pump inhibitors)
- Enteral feeding
- Prolonged hospitalization
- Gastrointestinal surgery
- Obesity
- Cancer chemotherapyHematopoietic stem cell transplant

Antibiotic use is the most common cause for this infection and some antibiotics (listed above) are commonly associated with *C. difficile* colitis**.** Antibiotics least associated with CDAD include Macrolides, Sulphonamides, Trimethoprim, Aminoglycosides, Tetracycline, Tigecycline, Chloramphenicol, Metronidazole and Vancomycin. It is important to note that *C. difficile* infection may occur even in the absence of any risk factor .

Investigations

The mainstay of laboratory diagnosis of *C. difficile infection* (CDI) is toxin assay of a fresh sample of liquid or semiformed stool (to be performed within two hours at room temperature) or preserved at 4 degree Celsius in the refrigerator if the assay is delayed for any reason.

1. Enzyme immunoassay (EIA) for *C. difficile* toxins A and B
   - Most commonly performed assay in clinical practice.
   - The sensitivity of EIA for toxins A and B is about 75%; the specificity is high (up to 99%).
   - If the initial EIA test is negative, the value of repeating the test is limited and repeat testing is generally discouraged
2. Enzyme immunoassay (EIA) for *C. difficile* glutamate dehydrogenase (GDH)
   - Useful as an initial screening step
   - Highly sensitive, and results are available in less than one hour.
   - Cannot distinguish between toxigenic and nontoxigenic strains

- Positive results need to be confirmed by more specific tests like toxin assays and /or PCR.

3. Real-time PCR tests that detect toxin A and B genes
   Highly sensitive and specific for diagnosis of *C. difficile* related diarrhea for the 1st episode but cannot be used as a test of cure and may be less useful if a relapse or re-infection suspected.
4. Cell culture cytotoxicity assay
   - The 'gold standard' test for diagnosis of *C. difficile*
   - Labor intensive and takes approximately two days
   - Not performed routinely.
5. An algorithmic approach should be utilized for judiciously using these investigations.
6. If PCR assay is available
   - Most sensitive and specific test and is recommended.
   - If it is positive no further test is required
   - If negative and clinical suspicion is high, EIA for toxin or cell culture should be performed
7. If PCR is not available
   - EIA for GDH should be performed first
   - If positive, it should be confirmed with EIA toxin assay
     - positive result may be presumed in the setting of positive EIA for GDH and toxin
     - negative result if both EIAs are negative.

8. If EIA GDH and PCR both are not available as might be the case in many centres in India, a fresh sample of liquid stool tested within two hours should be performed for EIA toxin.
   - If it is negative and clinical suspicion is high repeat toxin assay should be performed
   - Repeat testing and test for cure are not warranted in patients with for diagnosis of *C. difficile* related diarrhea the 1st episode but cannot be used as a test of cure and may be less useful if a relapse or re-infection suspected.
9. Repeat testing and test for cure are not warranted in patients with positive PCR or toxin assay test who are a symptomatic. There is no clinical role for laboratory tests among asymptomatic patients or among patients on treatment for acute disease, as stool assays may remain positive during or after clinical recovery
10. Colonoscopy or sigmoidoscopy and biopsy (in the setting of diagnostic uncertainty) with visualization of pseudomembrane and ulceration, can be a useful adjunctive tool for diagnosis of *C. difficile* in the following settings:
    - Failure of *C. difficile* infection to respond to antibiotic therapy
    - Atypical presentation with ileus or minimal diarrhea
    - Prompt *C. difficile* diagnosis needed before laboratory results can be obtained
    - High clinical suspicion for *C. difficile* with negative laboratory assay(s)

Resistance Patterns

- The hypervirulent strain NAP1/BI/027 is not commonly reported in India
- Most strains respond to metronidazole

Table 1. Treatment Regimen for *C. difficile* Colitis

Clinical condition	Initial AMA	Alternate AMA	Comments
Mild disease	Metronidazole 400 mg orally three times daily for 10 to 14 days	Vancomycin 125 mg orally four times daily	Stop any ongoing antibiotic, if possible. Substitute with low-risk antibiotic if possible. Correction of fluid and electrolyte imbalance in all patients
Severe disease:	Vancomycin 125 mg orally four times daily for 10 to 14 days, can be increased to 500 mg 4 times daily	If not able to tolerate oral vancomycin, vancomycin retention enema (500 mg in 100 ml normal saline given six hourly) with intravenous metronidazole 500 mg 8 hourly.	Monitor organ function closely; Consider surgery for severe persistent symptoms, toxic megacolon, severe ileus, or peritonitis.
Relapsing Disease	Tapering and pulsed oral vancomycin 125 mg orally four times daily for 7 to 14 days If multiple relapses : Vancomycin125 mg orally twice daily for 10-14 days, then 125 mg orally q12h, 125 mg orally once daily for 7 days, then125 mg orally every other day for 4 doses, then125 mg orally every 3 days for 5 doses Fecal Microbiota Transplantation (FMT):	Fidaxomicin 200 mg orally twice daily for 10 days (not available in India) OR Rifaximin 200 mg three times daily OR Fecal bacteriotherapy (fecal microbiota transplant)	Probiotics (e.g.,*Saccharomyces boulardii* 500 mg orally twice daily). The probiotics may be overlapped with the final week of the taper and continued for two additional weeks in the absence of antibiotics.

All these regimens need to be tailored according to susceptibility patterns at individual centers

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Editorial Board

Antimicrobial Guidelines for prophylaxis and treatment of Infections in Bone Marrow Transplant setting

Preamble and Case definitions

i. **Allogeneic transplant:** A transplant that uses stem cells taken from a donor (rather than using the recipient's own stem cells).
ii. **Antimicrobial prophylaxis:** It refers to the administration of antimicrobial agent (antibiotic, antiviral, anti-fungal or anti-parasitic agent) to the patient usually in lower dose for prevention of infection. It may be administered before (e.g. for surgical intervention), during or after a procedure (e.g. bone marrow transplantation).
iii. **Autologous transplant:** A transplant that uses stem cells taken previously from the patient (rather than stem cells from a donor).
iv. **Bone marrow harvesting:** A surgical procedure in which doctors insert long needles through the skin to withdraw bone marrow from the crests of the pelvic bones. Donors receive general or spinal anesthesia for the procedure.
v. **CMV surveillance:** Early detection of CMV infection or disease by monitoring of CMV viral load at regular intervals in high risk patients (solid organ transplant and allogeneic bone marrow transplant recipients) for initiation of pre-emptive therapy. . Although previously done by CMV cultures and detection of pp65 antigenemia the current technology is to detect CMV viral load by quantitative real time PCR according to standard WHO guidelines for reporting of Quantitative CMV PCR.
vi. **Conditioning:** This is chemotherapy, total body irradiation, or both given before a bone marrow transplant. High-dose conditioning is intended to do one of three things:
   - Eliminate malignant cells in people with cancer
   - Disable the immune system in people with an autoimmune disease
   - Destroy the bone marrow in people with other marrow-related diseases

High-dose conditioning leaves patients without an immune system or the ability to form new blood cells.
Alternatively, some patients (typically those who are older or have additional health problems) get reduced-dose conditioning—designed to weaken, but not destroy, their bone marrow and immune system so their body can more readily accept the donor's stem cells.

i. **Engraftment:** Stage in which the bone marrow (or stem cells) of the donor have been taken up by the recipient.
ii. **Haploidentical transplant:** A transplant using stem cells from a donor whose HLA type is a half-match for the recipient. This may be an option for people who need a transplant but have not been able to find a more closely matched donor.
iii. **MUD transplant:** The genetically matched marrow or stem cells are from an unrelated donor. Unrelated donors are found through bone marrow registries.

iv. **Neutropenic fever:** Neutropenia with an absolute neutrophil count (ANC) of <500 cells/mm^3 along with single oral temperature measurement of >38.3°C (101°F) or a temperature of >38.0°C (100.4°F) sustained over a 1-hour period.

v. Pre-emptive therapy: It is the initiation of specific antimicrobial therapy based on an early diagnostic test with the aim of preventing morbidity due to established disease. For example rising values of a quantitative CMV PCR at weekly intervals precedes establishment of disease and is an indication for "Pre-emptive therapy" with an appropriate antiviral drug. At this time the clinical manifestations of CMV disease are not clinically manifest.

vi. **Stem cell mobilization and collection:** Stem cell mobilization means receiving medicine that causes stem cells to leave the tissues they normally occupy and to circulate in the bloodstream. Typically it takes a few days after receiving the medicine for the stem cells to mobilize. Then the stem cells are collected using a machine similar to those used for blood donation at blood banks. A catheter (tube) is placed in a donor's large vein so blood can flow out of the body and into the machine, which separates the stem cells from the blood and returns the blood through another catheter. Collection typically takes a few hours, and donors leave the same day.

vii. **Surveillance culture:** Surveillance cultures are cultures obtained from clinical specimens to determine the spectrum of antimicrobial flora and associated resistance patterns in the absence of an obvious clinical infection. In a high risk patient with breach of skin or mucosal barriers there is a possibility that these colonizing microbes would become pathogenic. For example stool surveillance cultures to determine which of these multi-drug resistant organisms (ESBL, AmpC, carbapenemase producers, vancomycin resistant enterococci) are likely to become pathogenic due to gut translocation in a bone marrow transplant recipient.

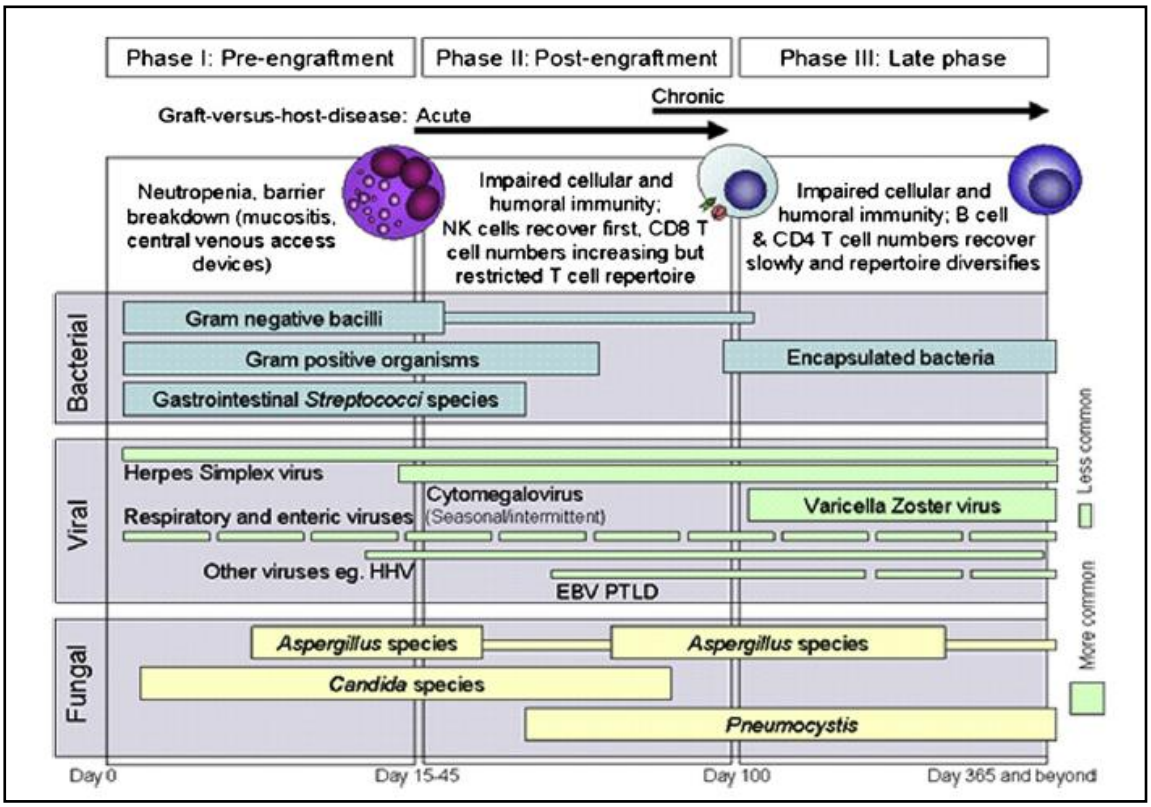
ix. **Total body irradiation (TBI):** TBI is a radiation treatment to the entire body. It is used to destroy cancer cells and bone marrow cells in preparation for a bone marrow transplant.

Table 1 Common pathogens:

Clinical condition	**Common pathogens**
Community acquired pneumonia	*Streptococcus pneumoniae, Haemophilus influenzae, atypical agents (Mycoplasma, Chlamydia, Legionella), respiratory viruses (influenza A, influenza B, RSV, parainfluenza, rhinovirus, human metapneumovirus)*
Hospital acquired pneumonia	*E. coli, Klebsiellla, Pseudomonas, Acinetobacter, Staphylococcus aureus (methicillin resistant and methicillin sensitive)*
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)*
Intravenous catheter	*Staphylococcus aureus, Staphylococcus epidermidis, Coliforms and non-fermentative Gram negative bacilli*

associated infection	
Skin and soft tissue infection	*Staphylococcus aureus, Streptococcus species, coliforms and non-fermentative Gram Negative Bacilli (in compromised host), candida, aspergillus and zygomycetes*
Intra-abdominal infection	*Coliforms and non-fermentative Gram Negative Bacilli, Anaerobes, Enterococcus species*
Antibiotic associated diarrhoea	*Clostridium difficile*
Tuberculosis	*Mycobacterium tuberculosis*

Figure:1 Phases of opportunistic infections among allogeneic HCT recipients Abbreviations: EBV, Epstein-Barr virus; HHV6, human herpesvirus 6;PTLD, post transplant lympho-proliferative disease



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 2 Investigations:

Diagnostic sector	Investigations relevant for management of infections and its complications
Hematology	Complete Blood Count, Differential count, prothrombin time, APTT, INR
Biochemistry	Urea, creatinine, electrolytes (sodium, potassium, calcium, magnesium, phosphorus), glucose, liver function tests (bilirubin- total, direct, indirect, SGOT, SGPT, alkaline phosphatase), C-reactive protein, procalcitonin
Microbiology	**Blood stream infection:** blood culture (from peripheral vein as well as through a central line if present) **Urinary tract infection:** urine microscopy and culture sensitivity (mid-stream or catheterized urine) **Gastroenteritis:** Stool microscopy for ova cysts parasites and culture sensitivity **Antibiotic associated diarrhea:** Clostridium difficile toxin detection **Upper respiratory tract infection:** Nose and throat swab or nasopharyngeal aspirate for respiratory virus PCR (influenza A and B, parainfluenza viruses, respiratory syncitial viruses, rhinovirus, human metapneumovirus), throat swab for bacterial culture **Lower respiratory tract infection (pneumonia, hospital acquired pneumonia, ventilator associated pneumonia):** Bacterial and fungal culture of sputum, broncho-alveolar lavage, endotracheal aspirate **Skin and soft tissue infection including surgical site infection:** Pus swab, aspirate or tissue for bacterial+/- fungal culture **CMV viremia:** CMV viral load determination by quantitative real time PCR **CMV disease (colitis/pneumonia/hepatitis/encephalitis):** CMV viral load determination by quantitative real time PCR **Detection of multidrug resistant bacteria:** **MRSA screening:** nose swab surveillance culture for MRSA **Stool surveillance culture:** for detection of ESBL, AmpC, carbapenemase producers and vancomycin resistant enterococci **Serological screening before transplantation of donor and recipient:** HIV, HBsAg, anti-HCV, HTLV, CMV IgG **Tuberculosis:** Mycobacterial culture from relevant samples
Imaging	Chest X-Ray, ultra sonography, CT scan, MRI, PET scan

a. Resistance pattern of common pathogens:

Table 3 . *Staphylococcus aureus* ICMR AMR Data 2014

AMA	JIPMER, Puducherry		AIIMS, New Delhi		PGIMER, Chandigarh		CMC, Vellore		National	
	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R
Cefoxitin	2217	863 (38.9)	644	116 (18.0)	360	171 (47.5)	0	0	3221	1150 (35.7)
Ciprofloxacin	2216	1394 (62.9)	644	399 (62.0)	359	241 (67.1)	27	21 (77.8)	3246	2055 (63.3)
Clindamycin	2200	501 (22.8)	644	180 (28.0)	362	120 (33.1)	0	0	3206	801 (25.0)
Erythromycin	2200	1073 (48.8)	644	367 (57.0)	362	190 (52.5)	112	42 (37.5)	3318	1672 (50.4)
Gentamicin	2196	386 (17.6)	0	0	0	0	206	42 (20.4)	2402	428 (17.8)
Linezolid	1596	0	644	6 (0.9)	82	0	134	0	2456	6 (0.2)
Muporicin	1588	30 (1.9)	0	0	0	0	0	0	1588	30 (1.9)
Penicillin	2217	2023 (91.2)	644	528 (82.0)	0	0	0	0	2861	2551 (89.2)
Teicoplanin	1588	0	644	0	276	0	0	0	2508	0
Tetracycline	2216	412 (18.6)	644	644 (100)	0	0	0	0	2860	1056 (36.9)
Trimethoprim-sulfamethoxazole	1427	685 (48.0)	0	0	0	0	239	76 (31.8)	1666	761 (45.7)
Vancomycin *	2217	4 (0.2)	644	0	362	0	0	0	3223	4 (0.1)

*The 4 numbers listed as Vancomycin Resistant (R) are VISA isolates.

No VRSA was isolated during the year 2014 at JIPMER.

Cefoxitin : Surrogate marker for Methicillin.

Table 4. *Enterococcus faecium* ICMR AMR Data 2014.

AMA	JIPMER, Puducherry		AIIMS, New Delhi		PGI, Chandigarh		NATIONAL	
	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R
Ampicillin	208	131 (63.0)	159	127 (79.9)	0	0	367	258 (70.3)
Ciprofloxacin	103	93 (90.3)	61	50 (82.0)	0	0	164	143 (87.2)
Gentamicin HL	181	86 (47.5)	159	109 (68.6)	241	188 (78.0)	581	383 (65.9)
Linezolid	164	0	159	0	0	0	323	0
Nitrofurantoin	79	5 (6.3)	61	34 (55.7)	0	0	140	39 (27.9)
Teicoplanin	158	16 (10.1)	159	20 (12.6)	170	32 (18.8)	487	68 (14.0)
Tetracycline	208	171 (82.2)	0	0	0	0	208	171 (82.2)
Vancomycin	208	31 (14.9)	159	18 (11.3)	131	20 (15.3)	498	69 (13.9)

Table5 . *Enterobacteriaceae* isolates from blood. ICMR AMR data 2014.

	PGIMER, Chandigarh % Resistant			AIIMS, New Delhi % Resistant			JIPMER, Puducherry % Resistant			CMC, Vellore % Resistant			National % Resistant		
AMA	**Ec**	**Ks**	**Es**	**Ec**	**Ks**	**Es**	**Ec**	**Ks**	**Es**	**Ec**	**Ks**	**Es**	**Ec**	**Ks**	**Es**
Amikacin	21	56	58	58	70	75	21	44	27	12	39	11	24	54	44
Cefepime	84	87	80	85	93	85	71	86	74	67	59		79	88	80
Cefoperazone-sulbactam	48	79	69				12	38	10	20	37	7	33	62	39
Cefotaxime	87	89	80	75	87	84	79	94	85	72	62	89	80	83	83
Ceftazidime	89	92	84	78	92	80	72	79	69	72	62	79	81	84	77
Ciprofloxacin	85	66	53	90	79	67	76	73	36	74	50	25	81	65	48
Colistin	1	1	0							1	0		1	1	0
Gentamicin	32	78	81	72	74	75	40	57	47	45	48	4	46	65	56
Imipenem	6	14	9	62	63	55	26	49	31	12	37	11	18	35	26
Meropenem	52	51	44	55	77	70	18	49	21	11	37	33	35	53	38
Netilmicin										12	42	18	12	42	18
Piperacillin-tazobactam	46	73	63	59	77	72	37	73	48	30	45	11	43	68	57
Tetracycline	64	42	16										64	42	16

Note : Ec : *Escherichia coli;* Ks : *Klebsiella* spp.; Es : *Enterobacter* spp.

Table 6. *Pseudomonas aeruginosa* ICMR AMR Data 2014

AMA	PGIMER, Chandigarh 'n' 75 R (%)	AIIMS, New Delhi 'n' 102 R (%)	JIPMER, Puducherry 'n' 113 R (%)	CMC, Vellore 'n' 84 R (%)	National 'n' 374 R %
Amikacin	27	49	38	21	35
Aztreonam		62	55	30	48
Cefepime		52	57	20	41
Cefoperazone-sulbactam		39	41	30	38
Ceftazidime	64	51	51	23	47
Colistin		34		2	10
Imipenem	17	54	48	25	37
Levofloxacin		44	42	23	36
Meropenem		74	41	23	47
Netilmicin		66	45	22	45
Piperacillin-tazobactam	44	67		25	46
Tobramycin		56	43	18	33

Table 7. *Acinetobacter baumannii* ICMR AMR Data 2014

AMA	PGIMER, Chandigarh 'n' 209 R (%)	AIIMS, New Delhi 'n' 143 R (%)	JIPMER, Puducherry 'n' 157 R (%)	CMC, Vellore 'n' 90 R (%)	National 'n' 599 R %
Amikacin	77	83	59	84	75
Aztreonam		87	93	84	87
Cefepime	98	86	75	61	81
Cefoperazone-sulbactam	89	23	22	47	57
Ceftazidime	99	86	68	68	84
Colistin	1	64		22	22
Imipenem	52	83	62	64	63
Levofloxacin		86	68	60	73
Meropenem	50	86	59	61	62
Netilmicin		79		56	69
Piperacillin-tazobactam	73	86		71	83
Tetracycline	61			52	55
Tobramycin	54		64	58	58
Trimethoprim-sulphamethoxazole			46	63	55

Table 8 . *Candida* spp. isolated at PGIMER, Chandigarh ICMR AMR Data 2014.

AMA	*C tropicalis* 'n' 101; % R	*C krusei* 'n' 98; % R	*C albicans* 'n' 50; % R	*C pelliculosa* 'n' 35; % R
Amphotericin B	1	5	0	0
Fluconazole	4	0	8	0
Voriconazole	1	3	8	0
Itraconazole	8	4	2	0
Posaconazole	1	0	0	0
Caspofungin	2	8	0	0
Anidulafungin	1	7	2	0
Micafungin	0	6	2	6

II. Table 9 Antimicrobial Agents (AMA) regime (based on ICMR/Indian resistance data) in the Bone Marrow Transplant setting:

Clinical Condition	Common Pathogens	Empirical Antimicrobial Agents	Alternate Antimicrobial Agents	Comments
Neutropenic fever/ sepsis	*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter species, Staphylococcus aureus,* Coagulase Negative *Staphylococci, Enterococcus species, Candida species*	Piperacillin-tazobactam + amikacin	Second line: Meropenem± Teicoplanin/Vancomycin. Third line or patient in septic shock: Meropenem+ Colistin± Teicoplanin/Vancomycin+ caspofungin	Continue broad-spectrum antibiotics until the patient has been afebrile for at least 2 days and the neutrophil count is >500 cells/mm3 on at least one occasion. Gram positive cover with Teicoplanin or Vancomycin to be discontinued once cultures are negative.
Community acquired pneumonia	*Streptococcus pneumoniae, Haemophilus influenzae, atypical agents (Mycoplasma, Chlamydia, Legionella), respiratory viruses (influenza A, influenza B, RSV, parainfluenza, rhinovirus, human metapneumovirus)*	Piperacillin-tazobactam+ clarithromycin or azithromycin	Meropenem+ clarithromycin or azithromycin+ Teicoplanin/Vancomycin	If viral infection is suspected send respiratory sample (nose and throat swab/BAL/endotracheal secretion) for respiratory viral PCR and consider early empirical use of oseltamivir to be discontinued once influenza PCR is negative
Hospital acquired pneumonia	*E. coli, Klebsiella, Pseudomonas, Acinetobacter, Staphylococcus aureus (methicillin resistant and methicillin sensitive)*	Piperacillin-tazobactam + amikacin	Meropenem+ 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. Also consider use of aerosolized colistin as an adjunct to intravenous antibiotics in the treatment of multi-drug resistant pathogens Where toxicity is a concern.
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)*	Piperacillin-tazobactam + amikacin Or Cefoperazone-Sulbactam+ amikacin	Second line: Meropenem± Teicoplanin/Vancomycin Third line or patient in septic shock: Meropenem+ Colistin± Teicoplanin/Vancomycin + caspofungin	Duration of treatment depends on the actual or the suspected source of blood stream infection
Intravenous catheter associated infection	*Staphylococcus aureus, Staphylococcus epidermidis, Coliforms and non-fermentative Gram negative bacilli*	Piperacillin-Tazobactam+ Vancomycin	Meropenem+ Teicoplanin/Vancomycin	Consider the use colistin or anti-fungal agents based on specific clinical/laboratory diagnosis
Skin and soft	*Staphylococcus aureus,*	Piperacillin-	Meropenem+	Consider the use of anti-fungal

tissue infection	*Streptococcus species, coliforms and non-fermentative Gram Negative Bacilli (in compromised host), candida, zygomycetes*	Tazobactam + Teicoplanin/ Vancomycin	Teicoplanin/Vancomycin + Clindamycin	agents based on specific clinical/laboratory diagnosis. For MRSA coverage consider use of Teicoplanin/Vancomycin combination. 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
Urinary Tract infection	*Coliforms and non-fermentative Gram Negative Bacilli, Enterococcus species, 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*	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), with or without Caspofungin	6-12 weeks. Treatment should be continued until lesions have resolved or clinically stable
Mucormycosis	*Apophysomyces, Basidiobolus, Conidiobolus, Cunninghamella, Mortierella, Mucor, Lichtheimia (Absidia), Rhizomucor, Rhizopus, Saksenaea, Syncephalestrum*	Liposomal Amphotericin B with Surgical debridement (wherever feasible)	Caspofungin may be considered along with liposomal amphotericin B	Surgical debridement as far as possible. Antifungal therapy for mucormycosis 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	Duration of therapy depends on organ involvement.
Varicella or disseminated zoster or localized zoster	Varicella Zoster Virus	Acyclovir or Valacyclovir	Foscarnet	Duration of therapy depends on organ involvement Requires a minimum of 7-10days of treatment with acyclovir/ valacyclovir in case of cutaneous involvement.
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)
***Pneumocystis jirovecii* pneumonia**	*Pneumocystis jirovecii*	Co-trimoxazole (high dose)	Clindamycin+ Primaquine	Duration of therapy:21 days

III. Foot Notes:

IIIa. Table 10 Antimicrobial prophylaxis, surveillance and therapy

Policy	Details	Comments
BMT pre-engraftment		
Antibiotics prophylaxis	No antibiotic prophylaxis is given	
Surveillance culture	Stool surveillance culture for multidrug resistant bacteria may be done though this should not be used to initiate prophylaxis	This detects ESBL, AmpC, carbapenemase producers and VRE. However resistant colonized pathogens should not be presumed to cause of fever without microbiological confirmation
Antibiotics for treatment of neutropenic fever	**First line:** Piperacillin-tazobactam + amikacin or Cefoperazone sulbactam+ amikacin (depending on local resistance patterns) **Second line:** Meropenem± Teicoplanin/Vancomycin **Third line or patient in septic shock:** Meropenem+ Colistin± Teicoplanin/Vancomycin + caspofungin	If blood cultures are negative at 3 days following initiation of antibiotic the Teicoplanin/Vancomycin is stopped
Antifungal prophylaxis	Posaconazole	Of utility when used as prophylaxis after AML induction therapy or at the time of GVHD.
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 (Sept-Oct) 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.	Pre-emptive therapy if 2 consecutive viral loads are showing an upward trend suggesting progression to disease Definitive therapy of CMV disease with ganciclovir or valganciclovir. 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 BID for twice weekly for 1 year, and • Penicillin 400 mg orally BID for 1 year.	Penicillin prophylaxis in those with splenectomy or those with sickle cell anemia to be continued till 14 years.
Antifungal prophylaxis	Posaconazole/ voriconazole/ liposomal amphotericin B or echnocandin based on oral medication, tolerability, requirement of mold active prophylaxis, intolerance of azoles, presence of GVHD. Posaconazole 600-800 mg/ day (200 mg Q8H or Q6H) Voriconazole: 200 mg twice daily (Q12H) Liposomal amphotericin B 3-5 mg/kg/day or 3 times weekly.	
Antiviral prophylaxis	Yearly Influenza vaccination	At the beginning of flu season (Sept-Oct) and at least 2 weeks before starting chemotherapy.

IIIb. Table 11 Standard adult doses of antimicrobial agents

Antimicrobial agent	Standard adult dose
Acyclovir	Prophylaxis: 400 mg Q12H (BID) for a month after BMT and then shift to 800 mg Q12H (BID) for a year. This is to prevent Herpes simplex initially but Herpes Zoster at a later stage Herpes simplex in immunocompromised requiring IV treatment: 5 mg/kg body weight per dose for Q8H (TID). Varicella zoster: 800 mg orally 5 times daily ; In immunocompromised 10 mg/kg body weight Q8H (TID)
Amikacin	15 mg/kg IV or IM Q24H (OD)
Amphotericin B (conventional)	0.5-1 mg/kg body weight IV Q24H (OD) in 5% dextrose over 4 hours after prehydration
Amphotericin B (liposomal)	3-5 mg/kg body weight IV Q24H (OD)
Anidulafungin	200 mg loading dose on Day 1 followed by 100 mg on Day 2 IV Q24H (OD)
Azithromycin	500 mg IV Q24H (OD)
Caspofungin	70 mg IV as loading dose followed by 50 mg IV Q24H (OD) from next day
Ciprofloxacin	400 mg IV Q8H (TID) or 750 mg PO Q12H (BID)
Clindamycin	300-600 mg IV Q6H (QID)
Colistin	9 MU loading followed 12 hours later by 4.5 MU IV Q12H (BID);
Co-trimoxazole	Treatment of *Pneumocytis jiroveci*: 20 mg/kg of trimethoprim with 100 mg/kg of sulphamethoxazole in 2-4 divided doses; Treatment of Nocardiosis: DS tab (960 mg) 3-4 times daily for 3-6 months. Cerebral disease is to be treated longer
Fluconazole	For invasive candidiasis: 800 mg loading dose followed 24 hours later by 400 mg Q24H (OD); For other indications please look up appropriate guidelines
Ganciclovir	5 mg/kg body weight Q12H (BID) (10 mg/kg per day)
Gentamicin	5 mg/kg IV Q24H (OD)
Imipenem	500 mg IV Q6H (QID)
Levofloxacin	500 mg-750mg IV Q24H (OD)
Linezolid	600 mg IV Q12H (BID)
Meropenem	1 gm IV Q8H (TID)
Metronidazole	500 mg IV Q8H (TID)
Micafungin	100 mg IV OD
Oseltamivir	75 mg orally Q12H (BID)
Piperacillin-tazobactam	4.5 gm IV Q8H (TID)
Posaconazole	Prophylaxis: 200 mg Q8H (TID) or Q6H (QID) orally with fatty food
Teicoplanin	400 mg IV Q12H (BID) for day 1 then 400 mg IV Q24H (OD)
Tigecycline	Initial dose of 100 mg followed by 50 mg IV Q12H (BID)
Valacyclovir	Varicella zoster: 1000 mg orally Q8H (TID) Herpes simplex: 1000 mg orally Q12H (BID)
Valganciclovir	900 mg orally Q12H (BID)
Vancomycin	1 gm IV Q12H (BID)
Voriconazole	400 mg IV Q12H (BID) on day 1 followed by 200 mg IV Q12H (BID) from next day

Note:

1) Dose of the antimicrobial agent depends on the age, indication, site and severity of infection, body weight, creatinine clearance/ renal and hepatic function
2) Modify dose and duration as required based on age, indication, site and severity of infection, body weight, creatinine clearance/ renal and hepatic function
3) Doses mentioned in the above table reflect those used in adults without renal or hepatic impairment and serious infections. Wherever applicable prophylactic dosing has been indicated
4) A higher dose of colistin has been recommended for critically ill patients [9 MU IV as the loading dose followed 24 hours later by 4.5 MU IV BID];
5) OD- once daily (Q24H); BID- twice daily (Q12h); TID- three times daily (Q8h); QID- four times daily (Q6h)
6) For extensively drug resistant organisms such as colistin-resistant *Klebsiella pneumoniae* please refer to antibiotic susceptibility test results and specific references

IIIc. Table 12 Duration of Antimicrobial Therapy

Category	Duration
Fever of unidentified etiology	Continue broad-spectrum antibiotics until the patient has been afebrile for at least 2 days and the neutrophil count is >500 cells/mm3 on at least one occasion.
Documented infections	The duration of antibiotic therapy should be appropriate for effective eradication of the identified infection.
Bacterial bloodstream infections, soft-tissue infections, and pneumonia	10–14 days of appropriate antibiotic therapy. Antibiotic treatment may therefore extend beyond resolution of fever and neutropenia.
Deep tissue infection, endocarditis and septic thrombosis, complicated central line associated blood stream infection (CLABSI) persistent bacteremia or fungemia occurring >72 hour after catheter removal	Treatment duration depends on the organism and extent of involvement. Please involve an ID physician to determine appropriate antibiotic and duration of therapy.
CLABSI caused by *Staphylococcus. aureus, Pseudomonas aeruginosa*, fungi, or mycobacteria	Systemic antimicrobial therapy for at least 14 days along with catheter removal if there are no metastatic complications
Candidemia without obvious metastatic complications	2 weeks after documented clearance of Candida from the bloodstream and resolution of symptoms attributable to candidemia and resolution of neutropenia
Deep seated infection with candida (endophthalmitis, septic arthritis, infection of prosthetic devices, endocarditis etc)	Prolonged treatment (minimum of 4–6 weeks) is recommended. For candida endocarditis valve replacement is recommended, and treatment should continue for at least 6 weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications
Antifungal prophylaxis	For the duration of the neutropenia
Invasive pulmonary aspergillosis	12 weeks. Treatment should be continued until lesions have resolved or are clinically stable
Mucormycosis	Antifungal therapy for mucormycosis should be continued until all of the following objectives are attained: (1) there is resolution of clinical signs and symptoms of infection, (2) there is resolution or stabilization of residual radiographic signs of disease on serial imaging, and (3) there is resolution of underlying immunosuppression.
Influenza	5 days of treatment with oseltamivir
Herpes simplex	5-10 days
Varicella zoster	7 days of treatment with acyclovir/ valacyclovir
CMV	As directed by viral load measurements
***Pneumocystis jirovecii* pneumonia**	14-21 days

IIId. De-escalation

If the patient is afebrile, signs of severe sepsis / septic shock and neutropenia have resolved, plan for targeted therapy based on culture and susceptibility reports.

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Antimicrobial Guidelines for Device Associated Infections

I. Introduction

Health care associated infections pose a major threat to patient safety contributing to significant morbidity, mortality and economic burden. The occurrence of these infections is associated with various factors among which an important one is the increasing use of invasive medical devices. These foreign devices which seem to be a blessing in disguise are responsible for device associated infections (DAIs). About 60-70% of nosocomial infections are associated with implanted medical devices (1). In this population of patients, 95% of cases of urinary tract infection are catheter related, 87% of cases of bloodstream infection are associated with indwelling vascular catheters, and 86% of cases of pneumonia are due to mechanical ventilation (2). The management of these infections is a big challenge as they may lead to persistent and resistant infections by providing a safe shelter to the microorganisms inside the biofilm formed on the device. These biofilms act as a nidus for chronic infections which are recalcitrant to antimicrobial therapy (3). A thick biofilm is formed within 24 hours on the entire surface of these plastic devices even with a small initial number of bacteria spreading at a rate of up to 0.5 cm per hour (4). The hazards associated with use of medical devices might far exceed those arising from device failures.

Though majority of studies on device-associated infections are from developed countries, the problem may even be grave in developing countries. The rates of DAIs have been assessed in a multicenter prospective cohort surveillance study of 46 hospitals in Central and South America, India, Morocco, and Turkey, between 2002 and 2005 (5). An overall rate of 14.7 percent or 22.5 infections per 1000 ICU days, was observed.

II. Case definitions:

Healthcare-associated infections: A localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) that occurs in a patient in a healthcare setting (*e.g*., a hospital or outpatient clinic), and was not found to be present or incubating at the time of admission unless the infection was related to a previous admission to the same setting (1).

Device associated infection (DAI): An infection in a patient with a device (*e.g*., ventilator or central line) that was used within the 48-hour period before onset of infection. If the interval is longer than 48 hours, there must be compelling evidence that the infection was associated with device use. There is no minimum period of time that these devices must be in place for the infections to be considered device-associated (6).

Central line associated blood stream infection (CLABSI): CLABSI is defined when a patient with a central line in place (or in the 48 hours after line removal)

has a recognized pathogen cultured from one or more blood cultures that is not related to an infection at another site, or has at least one of the following signs or symptoms: fever >38°C, chills, hypotension, and a common skin contaminant is cultured from two or more blood cultures drawn on separate occasions, when signs, symptoms, and positive laboratory results are not related to an infection at another site (7).

Catheter related bloodstream infections (CRBSI) are defined on the basis of following criteria:

- A positive semi quantitative (>15 colony-forming units [CFU]/catheter segment) or quantitative (>10^3 CFU/catheter segment) cultures whereby the same organism (species and similar antibiogram) is isolated from the catheter segment and peripheral blood
- Simultaneous quantitative blood cultures with a ≥5:1 ratio CVC versus peripheral
- For automated systems a differential period of CVC culture versus peripheral blood culture positivity where CVC culture flags positive before peripheral blood culture by >2 hours

III. Table 1 Common pathogens associated with DAIs:

Gram-positive cocci	**Gram-negative bacilli**	**Fungi**
Staphylococcus aureus	*Escherichia coli* and *Klebsiella* species	*Candida* species
Coagulase negative *Staphylococcus*	*Pseudomonas aeruginosa*	*Aspergillus* species
Enterococcus faecalis/E. faecium	*Enterobacter* species	*Malassezia furfur*
	Acinetobacter species	
	Stenotrophomonas maltophilia	

Uncommon pathogens are: *Mycobacterium* spp., *Flavobacterium* spp., *Corynebacterium* spp. and *Ochrobacterum anthropi* (8).

VAP

Ventilator-associated pneumonia (VAP) is a common complication of ventilatory support for patients with acute respiratory failure. Ventilator-associated pneumonia (VAP) is common in the intensive care unit (ICU), affecting 8 to 20% of ICU patients and up to 27% of mechanically ventilated patients. Common pathogens include *Pseudomonas* species and other highly resistant Gram-negative bacilli, the Enterobacteriaceae, staphylococci, streptococci, and *Haemophilus* species. Atypical bacteria, viruses, and fungi also have been implicated as causes of VAP, but their role is presently unclear (9).

Diagnosis and treatment: Several criteria have been proposed for diagnosing VAP in clinical settings, including clinical manifestations, imaging techniques,

methods to obtain and interpret bronchoalveolar specimens, and biomarkers of host response. But the accuracy of these methods in diagnosing VAP is controversial because of non-availability of a gold standard. Quantitative cultures of bronchoalveolar lavage (BAL) seem to be fairly equivalent in diagnosing VAP, while blood cultures are relatively insensitive. If VAP is suspected, obtain lower respiratory tract samples for quantitative and semi-quantitative cultures and microscopy. Begin empirical antimicrobial therapy, unless there is very low suspicion of pneumonia and microscopy of LRT sample is negative. Assess the clinical improvement at 48-72 hours. If patient shows improvement, and culture is negative, stop the antibiotics and if culture is positive reassess the patient after giving antibiotics for 7-8 days. If there is no clinical improvement, search for other pathogens or complications (10).

CRBSI and CLABSI

Intravascular devices are commonly used these days to administer IV fluids, medications, blood products, parenteral nutrition, and to monitor the hemodynamic status of critically ill patients. These patients usually have a compromised immune system making them predisposed to DAIs. Accurate diagnosis is essential in the management of these infections.

IV. Diagnostic investigations for CRBSI:

The diagnosis of CRBSI is very challenging. The clinical diagnosis is not a reliable method as the fever and chills associated with CRBSI are not specific and local catheter site inflammation has a sensitivity of ≤ 3%. Therefore, it is important to follow microbiological techniques to establish the catheter as the source of blood stream infections. These techniques include (11):

A. Catheter sparing diagnostic methods

1. Qualitative blood culture through the device
2. Quantitative blood cultures through the device
3. Simultaneous quantitative blood cultures
4. Differential time to positivity with automated culture systems
5. Acridine orange leukocyte spin
6. Endoluminal brush

B. Diagnostic methods requiring catheter removal

1. Semi-quantitative roll plate catheter culture
2. Quantitative catheter segment culture
3. Microscopy of stained catheters

Quantitative blood cultures through the device: The blood sample drawn only through the CVC is cultured by lysis centrifugation method and the colony count of >100 CFU/ml helps in diagnosing CRBSI. But, this method cannot distinguish CRBSI from high grade bacteremia especially in immunocompromised patients with high grade sepsis. Sensitivity of this method is 77% and specificity is 90%.

Simultaneous quantitative blood culture: Paired blood samples are obtained simultaneously from CVC and peripheral vein. If both the cultures show growth of similar organism with a colony count that is five-fold or greater from blood culture drawn through the CVC versus peripheral vein is indicative of CRBSI. The pooled sensitivity and specificity for short-term catheters 75% and 97%, respectively, and for long-term catheters 93% and 100%, respectively.

Differential time to positivity: It is a simple technique and involves simultaneous qualitative blood cultures drawn through the catheter and a peripheral vein. Definite diagnosis of CRBSI is established when the blood culture drawn from the CVC becomes positive at least 2 hours earlier than the blood culture drawn from the peripheral vein. A meta-analysis found the pooled sensitivity and specificity for this method of diagnosing CRBSI in short-term catheters to be 89% and 87%, respectively, compared with 90% and 72%, respectively, for long-term catheters. Automated blood culture systems used for this excludes any extra cost or labour for this method.

Acridine orange leukocyte cytospin: Acridine orange leukocyte cytospin (AOLC) is a rapid diagnostic microscopy method. In this 1 ml blood sample is drawn through CVC, centrifuged and stained with acridine orange. Under fluorescence microscope, if any bacteria are seen, it is considered to be positive. This method has a sensitivity of 87% and specificity of 94%. This is a recent method and currently under investigation.

Endoluminal brush technique: This is not a widely used method because of the various side effects associated with it. In this, a tapered nylon brush on a steel wire is passed through the catheter hub and lumen, withdrawn and placed in a buffered container. This solution is cultured onto blood agar plates after sonication and vortexing. Colony counts >100 CFU/ml are considered positive for CRBSI. Kite and colleagues reported sensitivity for this test of 95% and a specificity of 84%.

Semiquantitative roll plate culture technique: In this method, the distal segment of the CVC is cut and rolled against a blood agar plate at least four times and then the plate is incubated overnight. After incubation a colony count of ≥15 CFU/ ml suggests that the catheter is colonized with the organism grown. But the same organism must grow from the peripheral blood culture to label it as CRBSI. The pooled sensitivity and specificity for roll-plate catheter culture in was calculated to be 84% and 85%, respectively (9).

Quantitative catheter segment culture: Several methods such as centrifugation, vortexing, and sonication have been used to retrieve organisms from both the external and internal surfaces of the catheter. A 5 cm catheter segment is removed, flushed or sonicated with the broth, serially diluted and plated on blood agar. The plates are incubated at 35°C and a count of ≥100 CFU per catheter segment is deemed positive. The pooled sensitivity and specificity of quantitative catheter segment culture for short-term catheters were 82% and 89%, respectively, and 83% and 97% for long-term catheters, respectively (9).

Microscopy of stained catheters: Gram staining and acridine orange staining are also used for diagnosis of CRBSI. Gram staining has been reported to show 100% sensitivity and 97% specificity while acridine orange has a sensitivity of 84% and specificity of 99%.

A recent meta-analysis found that paired quantitative blood culture is the most accurate method for the diagnosis of CRBSI, followed by quantitative blood culture through the catheter and quantitative or semiquantitative catheter segment cultures(12).

Relevant IDSA guidelines (8) for diagnosis of CRBSI include:

Catheter culture:

- For central venous catheters (CVCs), the catheter tip should be cultured, rather than the subcutaneous segment.
- For cultures of an anti-infective catheter tip, use specific inhibitors in the culture media.
- When catheter infection is suspected and there is a catheter exit site exudate, swab the drainage to collect specimens for culture and Gram staining.

Blood Culture:

- The blood samples should be obtained prior to the initiation of antibiotic therapy, taking aseptic precautions.
- For suspected CRBSI, paired blood samples, drawn from the catheter and a peripheral vein, should be cultured before initiation of antimicrobial therapy, 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. It is unclear whether blood cultures should be drawn through all catheter lumens in such circumstances.
- A definitive diagnosis of CRBSI requires that the same organism grow from at least 1 percutaneous blood culture and from a culture of the catheter tip, or that 2 blood samples be drawn (one from a catheter hub and the other from a peripheral vein) that, when cultured, meet CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP).
- Alternatively, 2 quantitative blood cultures of samples obtained through 2 catheter lumens in which the colony count for the blood sample drawn through one lumen is at least 3-fold greater than the colony count for the blood sample obtained from the second lumen should be considered to indicate possible CRBSI. In this circumstance, the interpretation of blood cultures that meet the DTP criteria is an unresolved issue.
- For quantitative blood cultures, a colony count of microbes grown from blood obtained through the catheter hub that is at least 3-fold greater than the colony count from blood obtained from a peripheral vein best defines CRBSI.
- Before starting antimicrobial therapy, it is recommended to do quantitative blood cultures and/or DTP.

V. Prevalent antimicrobial resistance status among common pathogens:

According to the International Nosocomial Infection Control Consortium (INICC), the overall resistance pattern of the common pathogens was found as follows (13):

- 87.5% of all *Staphylococcus aureus* HCAIs were caused by methicillin-resistant strains,
- 71.4% of Enterobacteriaceae were resistant to ceftriaxone and 26.1% to piperacillin–tazobactam;
- 28.6% of the *Pseudomonas aeruginosa* strains were resistant to ciprofloxacin, 64.9% to ceftazidime and 42.0% to imipenem.

Table 2: The following table shows ICMR surveillance network reports in 2014:

Resistant Pathogen	**Resistance (%) in 2014**
Vancomycin Resistant Enterococci (VRE)	8.6 %
Methicillin resistan *Staphylococcus aureus* (MRSA)	35.7 %
P. aeruginosa resistant to imipenem	37 %
A. baumannii resistant to carbapenems	63 %
Enterobacteriaceae resistant to third generation cephalosporins, mainly extended-spectrum beta-lactamase producers	83 % (*K. pneumoniae)* 80 % (*Escherichia coli)*
Enterobacteriaceae resistant to carbapenems (CREs)	35 % (*K. pneumoniae)* 18 % (*Escherichia coli)*

This increasing trend of resistance points towards a dire need to strictly follow the infection control practices.

VI. Treatment of CRBSI (14):

The three important considerations in the management of CRBSIs include:

- Removal of the indwelling device or catheter
- Salvage of the device
- Antimicrobial chemotherapy (type and duration of therapy)
- Removal or salvage of the catheter depends upon various factors:
    - **The type of catheter used (tunnelled or non-tunnelled)** In most cases of non-tunnelled CVC–related bacteremia and fungemia, the CVC should be removed.For management of blood stream infections from a tunneled catheter or implantable device, such as

a port, the decision to remove the catheter or device should be based on the severity of the patient's illness, documentation that the vascular-access device is infected, assessment of the specific pathogen involved, and presence of complications, such as endocarditis, septic thrombosis, tunnel infection, etc.

- **The organism isolated in blood culture:**Catheter removal is recommended in all infections caused by *S. aureus*, gram negative bacilli, *Enterococcus* spp. and *Candida* spp. The catheter may be retained with CoNS, if systemic antimicrobial therapy is given along with antibiotic lock therapy.
- **Hemodynamic or immune status of the patient:** The importance of catheter for the survival of the patient also helps in deciding that whether the catheter can be removed or not.
- Long-term catheters should be removed from patients with CRBSI associated with any of the following conditions: severe sepsis; suppurative thrombophlebitis; endocarditis; bloodstream infection that continues despite >72 h of antimicrobial therapy to which the infecting microbes are susceptible; or infections due to *S. aureus, P. aeruginosa,* fungi, or mycobacteria.
- Short-term catheters should be removed from patients with CRBSI due to gram-negative bacilli, *S. aureus,* enterococci, fungi, and mycobacteria.For long-term and short-term CRBSI due to less virulent microbes that are difficult to eradicate (e.g., *Bacillus* species, *Micrococcus* species, or propionibacteria), catheters should generally be removed after blood culture contamination is ruled out on the basis of multiple positive culture results, with at least 1 blood culture sample drawn from a peripheral vein.

Catheter salvage: Removal of device is not always the preferred option, sometimes salvage of catheter is the preferred option. In uncomplicated CRBSI involving long-term catheters due to pathogens other than *S. aureus, P. aeruginosa, Bacillus* species, *Micrococcus* species, propionibacteria, fungi, or mycobacteria, patients undergoing hemodialysis or other patients who require long term intravascular access for survival, catheter should be retained in place with use of antimicrobial lock therapy.

- For patients with CRBSI for whom catheter salvage is attempted, additional blood cultures should be obtained, and the catheter should be removed if blood culture results (*e.g*., two sets of blood cultures obtained on a given day; one set of blood cultures is acceptable for neonates) remain positive with blood samples obtained 72 h after the initiation of appropriate therapy.
- If a catheterized patient has a single positive blood culture that grows coagulase-negative *Staphylococcus* species, additional cultures of blood samples obtained through the suspected catheter and from a peripheral vein should be performed before the initiation of antimicrobial therapy and/or catheter removal (8).
- Urokinase and other thrombolytic agents are not recommended as adjunctive therapy for patients with CRBSI(8).

- **Empirical antimicrobial therapy (8)**: After appropriate cultures of blood and catheter samples are done, empirical i/v antimicrobial therapy should be initiated. This therapy is based on the severity of illness and the potential pathogens involved.
    - Vancomycin is usually recommended as the empirical antimicrobial therapy in areas with an increased incidence of methicillin-resistant staphylococci.
    - Linezolid is not recommended as empirical therapy in patients suspected to have CRBSI.
    - Daptomycin acts as an alternative for institutions where MRSA isolates have vancomycin minimum inhibitory concentration (MIC) values of >2 μg/mL.
    - In the absence of methicillin-resistant *S. aureus,* penicillinase-resistant penicillins, such as nafcillin or oxacillin, or a first generation cephalosporin like cefazolin should be used.
    - Empirical coverage for gram-negative bacilli should be based on local antimicrobial susceptibility data and the severity of disease (e.g., a fourth-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination, with or without an aminoglycoside).
    - Empirical combination antibiotic coverage for multidrug-resistant (MDR) gram-negative bacilli, such as *Pseudomonas aeruginosa,* should be used when CRBSI is suspected in neutropenic patients, severely ill patients with sepsis, or patients known to be colonized with such pathogens, until the culture and susceptibility data are available and de-escalation of the antibiotic regimen can be implemented.
    - In cases of suspected CRBSI involving femoral catheters a broad coverage for gram-positive pathogens, gram-negative bacilli, as well as for *Candida* species is recommended.
    - Empirical therapy for suspected catheter-related candidemia should be used for septic patients with any of the following risk factors: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, hematologic malignancy, bone marrow or solid-organ transplant, femoral catheterization, or colonization due to *Candida* species at multiple sites.
    - For empirical treatment of suspected catheter-related candidemia, use an echinocandin or, in selected patients, fluconazole. Fluconazole can be used for patients without azole exposure in the previous 3 months and in health care settings where the risk of *Candida krusei* or *Candida glabrata* infection is very low.
    - Use of amphotericin B or, for selected patients, iv fluconazole should also be considered for empirical treatment when fungemia is suspected. Initial antimicrobial therapy should be given intravenously, but once the patient is clinically stable and

antibiotic susceptibilities are known, an oral quinolone, such as ciprofloxacin, trimethoprim-sulfamethoxazole, or linezolid, could be administered.

When a catheter-related infection is documented and a specific pathogen is identified, systemic antimicrobial therapy should be narrowed and consideration given for antibiotic lock therapy, if the CVC or implantable device is not removed.

Table 3 Pathogen-specific antimicrobial therapy according to the pathogen isolated (8).

Pathogen	Preferred therapy with dosage	Alternative therapy
MSSA (Methicillin Sensitive *Staphylococcus aureus*)	Oxacillin, 2 g q4h	Cefazolin, 2 g q8h; or vancomycin, 15 mg/kg q12h. For patients receiving hemodialysis, administer: Cefazolin, 20 mg/kg (actual weight), round to nearest 500-mg increment, after dialysis.
MRSA(Methicillin Resistant *Staphylococcus aureus*)	Vancomycin, 15 mg/kg q12h	Daptomycin, 6–8 mg/kg per day, or linezolid; or vancomycin plus rifampin (or gentamicin); or TMP-SMZ alone (if susceptible).
MS-CoNS (Methicillin Sensitive Coagulase negative staphylococci)	Oxacillin, 2 g q4h	First-generation cephalosporin or vancomycin or TMP-SMZ (if susceptible).
MR-CoNS (Methicillin Resistant Coagulase negative staphylococci)	Vancomycin, 15 mg/kg iv q12h	Daptomycin 6 mg/kg per day, linezolid, or Quinupristin-dalfopristin.
Enterococcus faecalis/E. faecium: Ampicillin susceptible: Ampicillin resistant vancomycin susceptible Vancomycin resistant	 Ampicillin, 2 g q4h or q6h; or Ampicillin+/-Gentamicin, 1 mg/kg q8h; Vancomycin, 15 mg/kg iv q12h+/-gentamicin, 1 mg/kg q8h Linezolid, 600 mg q12h; or daptomycin 6 mg/kg per day	 Vancomycin Linezolid or daptomycin 6 mg/kg per day Quinupristin-dalfopristin 7.5 mg/kg q8h
E. coli/ Klebsiella spp.: Extended spectrum beta	Ceftriaxone, 1–2 g per	Ciprofloxacin

lactamase (ESBL) negative: ESBL positive	day Cefoperozone Sulbactam 2g q8h Ertapenem, 1 g per day; imipenem, 500 mg q6h; meropenem, 1 g q8h; or doripenem, 500 mg q8h;	or aztreonam Ciprofloxacin or aztreonam
Enterobacter spp. and *Serratia marcescens*	Ertapenem, 1 g per day; imipenem, 500 mg q6h; meropenem, 1 g q8h;	Cefepime or ciprofloxacin
Pseudomonas aeruginosa	Cefepime, 2 g q8h; or imipenem, 500 mg q6h; or meropenem, 1 g q8h; or piperacillin-tazobactam, 4.5 g q6h, amikacin, 15 mg/kg q24h or tobramycin 5–7 mg/kg q24h	
Acinetobacter spp.	Ampicillin/sulbactam, 3 g q6h; or imipenem, 500 mg q6h; meropenem, 1 g q8h	
Stenotrophomonas maltophilia	TMP of 3–5 mg/kg q8h and 15 to 25 mg of SMX q8h	Ticarcilllin and clavulanic acid
Candida albicans or *Candida* spp.	Caspofungin, 70-mg loading dose, then 50 mg per day; micafungin, 100 mg per day; anidulafungin, 200 mg loading dose followed by 100 mg per day; or fluconazole, 400–600 mg per day (6-12 mg/kg/day)	Lipid AmpB preparations
Corynebacterium spp.	Vancomycin, 15 mg/kg q12h; alternative: linezolid (based on in vitro activity)	
Burkholderia cepacia	TMP-SMZ, 3–5 mg/kg q8h; or imipenem, 500 mg q6h; or meropenem, 1 g q8h	
Chryseobacterium spp. or *Flavobacterium* spp.	Levofloxacin750 mg q24h; alternative: TMP-SMZ or imipenem or meropenem	

Ochrobactrum anthropi	TMP-SMZ, 3–5 mg/kg q8h; or ciprofloxacin, 400 mg q12h; alternative: imipenem, meropenem, ertapenem, or doripenem plus aminoglycoside	
Malassezia furfur	Amphotericin B	Voriconazole
Mycobacterium spp.	Susceptibility varies by species	

VII. Duration of antimicrobial therapy in individual pathogens (11):

When denoting duration of antimicrobial therapy, day 1 is the first day on which negative blood culture results are obtained (8).

Coagulase-negative staphylococci

Vancomycin is the drug of choice for empirical treatment of CoNS related CRBSI and change to semisynthetic penicillin if the isolate is susceptible. The duration of therapy is 5-7 days if the catheter is removed, while the duration is 10-14 days along with antibiotic lock therapy, if the catheter is retained. Dalbavancin and daptomycin are alternative treatment options. Minocycline and EDTA, ethanol, or triple combination of minocycline and EDTA in 25% ethanol, constitutes alternative lock therapy (9).

Staphylococcus aureus

S. aureus is frequently associated with septic thrombosis and endocarditis. Trans-esophageal echocardiography (15) should be done to identify patients with complicated bacteremia and requiring 4-6 weeks of treatment. In cases of negative TEE, duration of therapy is two weeks. Catheter removal is usually recommended and is associated with a rapid response and a lower relapse rate. The antibiotics recommended for *S aureus* bacteremia are the β-lactam antibiotics (antistaphylococcal penicillin or cefazolin, if allergic to penicillin). For patients with serious allergy to β-lactams and for those with methicillin-resistant *S. aureus,* vancomycin is the drug of choice.

Gram-negative bacilli and miscellaneous pathogens

Catheter removal and appropriate antimicrobial therapy for 10-14 days is recommended for patients with catheter-related, gram-negative bacteremia with non-tunnelled CVCs. Catheter salvage can be done in suspected CRBSI in hemodynamically unstable patients with tunneled CVCs and can be treated for 14 days with systemic and antibiotic lock therapy. The preferred antibiotics include quinolones, such as ciprofloxacin with or without rifampin. This treatment duration is increased to 4-6 weeks if bacteremia is prolonged even after appropriate antimicrobial therapy and catheter removal, especially in the presence of underlying valvular heart disease.

Antibiotic lock therapy: Intraluminal colonization is the major mechanism for the occurrence of CRBSIs in patients with long-term devices. Parenteral antimicrobials or antiseptics (e.g., ethanol) with or without anticoagulants are infused into the catheter hub and allowed to dwell at supratherapeutic concentrations. Antibiotic lock solutions are not recommended to be used routinely to prevent CRBSI. These are indicated in patients with long-term cuffed or tunneled catheter, or port with a history of multiple infections and in CRBSI patients in whom catheter salvage is recommended (16). The antimicrobial concentration used in lock solution is 100-1000 times the minimum inhibitory concentration (MIC) to kill the bacteria within the biofilm. The risks of using antimicrobial lock therapy include potential toxicity and the potential to develop resistance. Various solutions used are; heparin (10 IU/ml), heparin-vancomycin (25µg/ml) and heparin-vancomycin-ciprofloxacin (2 µg/ml). A combination of minocycline hydrochloride and EDTA was found to be synergistic against resistant Gram-positive and Gram-negative bacteria and *C. albicans*. Other such solutions include: gentamicin and citrate, cefotaxime and heparin, taurolidine and citrate, and heparin (17).

Alternative treatment options: With the emergence of antimicrobial resistance, the enzymes like lysostaphin have been found to show good antistaphylococcal activity. Also ultrasound waves with a frequency of >20 KHz have been used to disrupt organisms from the surface of medical devices, especially if applied as high intensity ultrasound (>10W/cm^2)(14).

Conclusion: The medical devices are an indispensable part of our health-care system. A large number of patients have to be managed with indwelling medical devices. In such unavoidable situations, recommended guidelines must be followed for proper use and maintenance of these devices and removal when no longer indicated.

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Editorial Board

Antimicrobial guidelines in immune-compromised hosts and solid organ transplant recipients

1. Introduction

With advances in treatment of organ failure, auto-immune diseases and malignancies, an increasing population of immune compromised hosts and transplant recipients will develop infections and require care by the medical system. Such patients present unique challenges with regard to diagnosis and treatment, which often differ from the immune competent host. Moreover, these patients are likely to suffer repeated episodes of infections and consequently receive repeated courses of antimicrobial agents leading to higher level of antimicrobial resistance in pathogens.

2. Case definition

An immune compromised host includes the following:

- recipients of solid and stem cell organ transplants
- congenital immune deficiency disorders
- patients on medications that compromise cell mediated immunity eg corticosteroids, calcineurin inhibitors, mTOR pathway inhibitors, TNF-alpha antagonists, anti-thymocyte globulin and monoclonal antibodies like rituximab, adalimumab, etc.
- Patients suffering from cancer, cystic fibrosis etc.

3. Common pathogens

Immunocompromised hosts are at risk of developing opportunistic infections but also remain exposed to normal community acquired pathogens. Clinical presentation can be subtle and often difficult to diagnose in these hosts. 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 jiroveci, Cytomegalovirus* (CMV), *Cryptococcus, Aspergillus* spp, *Strongyloides stercoralis.*

4. Prevalent AMR status in common pathogens

Table 1. Enterobacteriaceae isolates from blood. ICMR AMR data 2014.

AMA	PGIMER, Chandigarh % Resistant			AIIMS, New Delhi % Resistant			JIPMER, Puducherry % Resistant			CMC, Vellore % Resistant			National % Resistant		
	Ec	Ks	Es	Ec	Ks	Es	Ec	Ks	Es	Ec	Ks	Es	Ec	Ks	Es
Amikacin	21	56	58	58	70	75	21	44	27	12	39	11	24	54	44
Cefepime	84	87	80	85	93	85	71	86	74	67	59		79	88	80
Cefoperazone-sulbactam	48	79	69				12	38	10	20	37	7	33	62	39
Cefotaxime	87	89	80	75	87	84	79	94	85	72	62	89	80	83	83
Ceftazidime	89	92	84	78	92	80	72	79	69	72	62	79	81	84	77
Ciprofloxacin	85	66	53	90	79	67	76	73	36	74	50	25	81	65	48
Colistin	1	1	0							1	0		1	1	0
Gentamicin	32	78	81	72	74	75	40	57	47	45	48	4	46	65	56
Imipenem	6	14	9	62	63	55	26	49	31	12	37	11	18	35	26
Meropenem	52	51	44	55	77	70	18	49	21	11	37	33	35	53	38
Netilmicin										12	42	18	12	42	18
Piperacillin-tazobactam	46	73	63	59	77	72	37	73	48	30	45	11	43	68	57
Tetracycline	64	42	16										64	42	16

Note : Ec : *Escherichia coli;* Ks : *Klebsiella* spp.; Es : *Enterobacter* spp.

Table 2. *Salmonella* Typhi isolates from blood ICMR AMR Data 2014

AMA	PGIMER, Chandigarh 'n' 109	AIIMS, New Delhi 'n' 22	CMC, Vellore 'n' 71	JIPMER, Puducherry 'n' 7	National 'n' 209
	No. R (%)	No. R	No. R (%)	No. R	No.R %)
Ampicillin	9 (8.3)	0	2 (2.8)	0	11 (5.3)
Cefixime	0 (0)	0	0 (0)	0	0 (0)
Ceftriaxone	0 (0)	0	0 (0)	0	0 (0)
Chloramphenicol	3 (2.8)	0	1 (1.4)	0	4 (1.9)
Ciprofloxacin	56 (51.4)	15	67 (94.4)	7	145 (69.4)
Trimethoprim-sulphamethoxazole	0 (0)	0	3 (4.2)	0	3 (1.4)

Note : If No. Tested is ≥30, No. R (%) given. If No. tested <30, only No. R given.

Table 3. *Staphylococcus aureus* ICMR AMR Data 2014

AMA	JIPMER, Puducherry		AIIMS, New Delhi		PGIMER, Chandigarh		CMC, Vellore		National	
	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R
Cefoxitin	2217	863 (38.9)	644	116 (18.0)	360	171 (47.5)	0	0	3221	1150 (35.7)
Ciprofloxacin	2216	1394 (62.9)	644	399 (62.0)	359	241 (67.1)	27	21 (77.8)	3246	2055 (63.3)
Clindamycin	2200	501 (22.8)	644	180 (28.0)	362	120 (33.1)	0	0	3206	801 (25.0)
Erythromycin	2200	1073 (48.8)	644	367 (57.0)	362	190 (52.5)	112	42 (37.5)	3318	1672 (50.4)
Gentamicin	2196	386 (17.6)	0	0	0	0	206	42 (20.4)	2402	428 (17.8)
Linezolid	1596	0	644	6 (0.9)	82	0	134	0	2456	6 (0.2)
Muporicin	1588	30 (1.9)	0	0	0	0	0	0	1588	30 (1.9)
Penicillin	2217	2023 (91.2)	644	528 (82.0)	0	0	0	0	2861	2551 (89.2)
Teicoplanin	1588	0	644	0	276	0	0	0	2508	0
Tetracycline	2216	412 (18.6)	644	644 (100)	0	0	0	0	2860	1056 (36.9)
Trimethoprim-sulfamethoxazole	1427	685 (48.0)	0	0	0	0	239	76 (31.8)	1666	761 (45.7)
Vancomycin*	2217	4 (0.2)	644	0	362	0	0	0	3223	4 (0.1)

*The 4 numbers listed as Vancomycin Resistant (R) are VISA isolates.

No VRSA was isolated during the year 2014 at JIPMER.

Cefoxitin : Surrogate marker for Methicillin.

Table 4. *Enterococcus faecalis* ICMR AMR Data 2014.

AMA	JIPMER, Puducherry		AIIMS, New Delhi		PGI, Chandigarh		NATIONAL	
	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R
Ampicillin	706	170 (24.1)	26	18 (69.2)	0	0	732	188 (25.7)
Ciprofloxacin	318	272 (85.5)	0	0	0	0	318	272 (85.5)
Gentamicin HL	569	214 (37.6)	26	18 (69.2)	78	60 (76.9)	673	292 (43.4)
Linezolid	501	0	26	0	0	0	527	0
Nitrofurantoin	230	7 (3.0)	0	0	0	0	230	7 (3.0)
Teicoplanin	483	8 (1.7)	26	1 (3.8)	34	3 (8.8)	543	12 (2.2)
Tetracycline	704	566 (80.4)	0	0	0	0	704	566 (80.4)
Vancomycin	707	33 (4.7)	26	1 (3.8)	63	8 (12.7)	796	42 (5.3)

Table 5. *Enterococcus faecium* ICMR AMR Data 2014.

AMA	JIPMER, Puducherry		AIIMS, New Delhi		PGI, Chandigarh		NATIONAL	
	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R	'n'	No. (%) R
Ampicillin	208	131 (63.0)	159	127 (79.9)	0	0	367	258 (70.3)
Ciprofloxacin	103	93 (90.3)	61	50 (82.0)	0	0	164	143 (87.2)
Gentamicin HL	181	86 (47.5)	159	109 (68.6)	241	188 (78.0)	581	383 (65.9)
Linezolid	164	0	159	0	0	0	323	0
Nitrofurantoin	79	5 (6.3)	61	34 (55.7)	0	0	140	39 (27.9)
Teicoplanin	158	16 (10.1)	159	20 (12.6)	170	32 (18.8)	487	68 (14.0)
Tetracycline	208	171 (82.2)	0	0	0	0	208	171 (82.2)
Vancomycin	208	31 (14.9)	159	18 (11.3)	131	20 (15.3)	498	69 (13.9)

Table 6. *Pseudomonas aeruginosa* ICMR AMR Data 2014

AMA	PGIMER, Chandigarh 'n' 75 R (%)	AIIMS, New Delhi 'n' 102 R (%)	JIPMER, Puducherry 'n' 113 R (%)	CMC, Vellore 'n' 84 R (%)	National 'n' 374 R %
Amikacin	27	49	38	21	35
Aztreonam		62	55	30	48
Cefepime		52	57	20	41
Cefoparazone-sulbactam		39	41	30	38
Ceftazidime	64	51	51	23	47
Colistin		34		2	10
Imipenem	17	54	48	25	37
Levofloxacin		44	42	23	36
Meropenem		74	41	23	47
Netilmicin		66	45	22	45
Piperacillin-tazobactam	44	67		25	46
Tobramycin		56	43	18	33

Table 7. *Acinetobacter baumannii* susceptibility pattern 2014

AMA	PGIMER, Chandigarh 'n' 209 R (%)	AIIMS, New Delhi 'n' 143 R (%)	JIPMER, Puducherry 'n' 157 R (%)	CMC, Vellore 'n' 90 R (%)	National 'n' 599 R %
Amikacin	77	83	59	84	75
Aztreonam		87	93	84	87
Cefepime	98	86	75	61	81
Cefoperazone-sulbactam	89	23	22	47	57
Ceftazidime	99	86	68	68	84
Colistin	1	64		22	22
Imipenem	52	83	62	64	63
Levofloxacin		86	68	60	73
Meropenem	50	86	59	61	62
Netilmicin		79		56	69
Piperacillin-tazobactam	73	86		71	83
Tetracycline	61			52	55
Tobramycin	54		64	58	58
Trimethoprim-sulphamethoxazole			46	63	55

Table 8 Central nervous system infections

Clinical condition	Common pathogens	Empiric antimicrobial agents	Alternative antimicrobial agents	Comments
Acute bacterial meningitis	*Pneumococcus, Listeria monocytogenes, H.influenzae, Meningococcus*	Ceftriaxone 2 gm IV q 12h/ Cefotaxime 2 gm IV q 4-6h + Ampicillin 2gm IV q4h	Moxifloxacin 400mg IV q 24h or Meropenem 2gm IV q 8h	Exclude TB, *Cryptococcus* Vancomycin not required due to low level of penicillin resistance in *Pneumococcus* If penicillin allergic, use cotrimoxazole 15 mg/kg/day (TMP component) or meropenem 2gm IV q 8h to cover for *Listeria* Duration: 10-14 days, 21 days for Listeria or Gram negative infection
Brain abscess, subural empyema	Streptococci, *Bacteroides,* Enterobacteriace-ae, *Staph aureus*	Ceftriaxone 2 gm IV q12h/ Cefotaxime 2 gm IV q 4-6h + Metronidazole 1 gm IV q 12h Duration based upon clinical & radiological response, minimum 8 weeks	Meropenem 2gm IV q 8h	Exclude TB, *Nocardia, Aspergillus* Aspiration/surgical drainage required unless abscess <2.5cm & patient neurologically stable
	Nocardia spp	Co-trimoxazole 15 mg/kg/dose (trimethoprim component) IV or PO, plus imipenem-cilastatin 500 mg q6h	Linezolid 600 mg IV or PO q12h	Duration: 3-6 weeks of IV therapy, followed by 12 months of oral therapy

Table 9 Respiratory tract infections

Condition	Organisms	Empiric antibiotics	Alternative antibiotics	Comments
Pneumonia	*S. pneumoniae, H.influenzae, Legionella, E.coli, Klebsiella, Pseudomonas, S.aureus*	Ceftriaxone 2 g IV od or Piperacillin-tazobactam 4.5 gm IV q 6h plus either azithromycin 500 mg PO/IV OD or doxycycline 100 mg PO BD Duration 5-8 days	Imipenem- cilastatin 500 mg q6h	If MRSA is a concern, add linezolid 600 mg IV/PO BD Avoid fluoroquinolones unless TB excluded Exclude TB, influenza, *Nocardia*, fungi (*Aspergillus, Mucor, Cryptococcus*), *Strongyloides* hyperinfection De-escalate to narrow spectrum agent on receipt of senstivity report
	Pneumocystis	Cotrimoxazole (trimethoprim component 15 mg/kg /day) Duration: 14 days, 21 days in patients with HIV	Clindamycin 600 mg IV q8h+ Primaquine 15 mg q12h(if sulpha allergy)	
Lung abscess, empyema	*Pneumococcus, Strep milleri* group, *E.coli, Klebsiella, Pseudomonas, S.aureus,* anaerobes	Piperacillin-tazobactam 4.5 gm IV q 6h Duration: 3-4 weeks	Cefoperazone-sulbactam 3 gm IV q 12h + clindamycin 600-900 mg IV q 8h	Drainage of pleural space essential for empyema
Acute bacterial pharyngitis	Group A ß-hemolytic streptococci (GABHS)	Benzathine penicillin 12 laks units IM or amoxicillin 500 mg PO q8h for 10 days		Most cases viral, confirm GABHS on culture before treating
Head and neck space infections	Polymicrobial (*Str pyogenes, Staph aureus*, oral anaerobes)	Clindamycin 600 mg IV q8h or Amox-clav 1.2 gm IV/PO q8h	Piperacillin-tazobactam 4.5 gm IV q 6h	Duration: At least 1 week
Acute sinusitis	Viral, *S.pneumoniae, H.influenzae, M. catarrhalis*	Amox-clav 1.2 gm IV/PO q8hfor 7 days	Piperacillin-tazobactam 4.5 gm IV q 6h	Exclude fungi (*Aspergillus, Mucor*)
Acute bronchitis	Viral	-	-	Antibiotics not required

Table 10 Gastrointestinal & intra-abdominal infections

Condition	Organisms	Empiric antibiotics	Alternative antibiotics	Comments
Acute gastroenteritis Food poisoning	Viral, entero toxigenic & entero pathogenic *E. coli* *S. aureus, B. cereus, C. botulinum*	none	none	Rehydration (oral/IV) essential
Cholera	*V.cholerae*	Doxycycline 300 mg PO stat	Azithromycin 1 gm PO stat or Ciprofloxacin 500 mg BD for 3 days	Rehydration (oral/IV) essential Antibiotics are adjuvant therapy
Bacterial dysentery	*Shigella, Campylobacter*, non typhoidal salmonellosis, Shiga toxin producing *E. coli*	Ceftriaxone 2 gm IV OD for 5 days	Azithromycin 1 gm od x 3d	
Amoebic dysentery	*E. histolytica*	Metronidazole 500 to 750 mg IV q8h for 7-10 days	Tinidazole 2 gm PO OD for 3 days	Add diloxanide furoate 500 mg tds for 10d
Enteric fever	*S.*Typhi, *S.*Paratyphi A	Outpatients: TMP-SMX4 1 DS tablet BD for 2 weeks or azithromycin 500 mg BD for 7 days	Inpatients: Ceftriaxone 2 g IV OD for 2 weeks	
Biliary tract infections (cholangitis, cholecystitis)	Enterobacteriacea (*E.coli, Klebsiella*)	Piperacillin-tazobactam 4.5 gm IV q 6h or Cefoperazone-sulbactam 3 gm IV q 12h or Ertapenem 1 gm IV OD	Imipenem-cilastatin 500 mg q6h or meropenem 1 gm IV q8h	Surgical or endoscopic intervention to be considered if there is biliary obstruction. De-escalate to narrow spectrum agent on receipt of sensitivities.

Hospital acquired diarrhea	*C. difficile*	Mild-moderate: Metronidazole 400 mg po qid for 10 days Severe: vancomycin 250 mg po q 6h empirically		Confirm by PCR or GDH-EIA test
Spontaneous bacterial peritonitis	Enterobacteriaceae (*E.coli, Klebsiella*)	Piperacillin-tazobactam 4.5 gm IV q 6h or Cefoperazone-sulbactam 3 gm IV q 12h or Ertapenem 1 gm IV OD Duration: 7-10 days	Imipenem-cilastatin 500 mg IV q6h or meropenem 1 gm IV q8h	De-escalate to narrow spectrum agent on receipt of sensitivities.
Secondary peritonitis, intra-abdominal abscess	Enterobacteriaceae (*E.coli, Klebsiella*), *Bacteroides*	Piperacillin-tazobactam 4.5 gm IV q 6h or Cefoperazone-sulbactam 3 gm IV q 12h or Ertapenem 1 gm IV OD	Imipenem-cilastatin 500 mg IV q6h or meropenem 1 gm IV q8h	Source control is important. De-escalate to narrow spectrum agent on receipt of sensitivities.

Table 11 Skin & soft tissue infections

Condition	Organisms	Empiric antibiotics	Alternative antibiotics	Comments
Cellulitis	*Strep. pyogenes, S.aureus*	Cefazolin 2 gm IV q8h.	Clindamycin 600-900 mg IV q8h	Duration: 5-7 days. Can switch to oral therapy once improving
Abscess, carbuncle	*S.aureus*	Cefazolin 2 gm IV q8h	Clindamycin 600-900 mg IV TDS or Linezolid 600 mg q 12h	Get pus cultures. MRSA coverage advisable for children <5 or severe infections
Necrotizing fasciitis	*Strep. pyogenes, Staph aureus* (monomicrobial), Anaerobes, Enterobacteriaceae (polymicrobial)	Piperacillin-tazobactam 4.5 gm IV q 6h or Cefoperazone-sulbactam 3 gm IV q 8h plus Clindamycin 600-900 mg IV q8h	Imipenem-cilastatin 500 mg IV q6h or meropenem 1 gm IV q8h + Clindamycin 600-900 mg IV q8h	Early surgical intervention crucial. De-escalate to narrow spectrum agent on receipt of sensitivities.

Table 12 Urinary tract infections

Condition	Organisms	Empiric antibiotics	Alternative antibiotics	Comments
Cystitis	Enterobacteriaceae (*E.coli, Klebsiella*)	Nitrofurantoin 100 mg BD for 5 days	Co-trimoxazole DS BD or ciprofloxacin 500 mg BD for 3 days	Obtain urine cultures before antibiotics & modify therapy based on senstivity report
Acute pyelonephritis	Enterobacteriaceae (*E.coli, Klebsiella*)	Piperacillin-tazobactam 4.5 gm IV q 6h or Cefoperazone-sulbactam 3 gm IV q 12h or Ertapenem 1 gm IV OD. Treat for 10-14 days.	Imipenem-cilastatin 500 mg IV q6h or meropenem 1 gm IV q8h	Obtain urine cultures before antibiotics & switch to a narrow spectrum agent based on senstivity report
Acute prostatitis	Enterobacteriaceae (*E.coli, Klebsiella*)	Piperacillin-tazobactam 4.5 gm IV q 6h or Cefoperazone-sulbactam 3 gm IV q 12h or Ertapenem 1 gm IV OD or	TMP/SMX DS PO q12h	Obtain urine and blood cultures before antibiotics & switch to narrow spectrum agent based on sensitivities. Treat for 4 weeks.
Chronic bacterial prostatitis	Enterobacteriaceae (*E.coli, Klebsiella*)	Ciprofloxacin 750 mg po bid		Therapy based on urine and prostatic massage cultures obtained before antibiotics. Treat for 4-6 weeks

Table 13 Bone & joint infections

Condition	Organisms	Empiric antibiotics	Alternative antibiotics	Comments
Acute osteomyelitis, septic arthritis	*S.aureus, Strep. pyogenes,* Enterobacteriaceae	Cefazolin 2 g IV q8h or Ceftriaxone 2 g IV od	Piperacillin-tazobactam 4.5 gm IV q 6h or Cefoperazone-sulbactam 3 gm IV q 12h plus Clindamycin 600-900 mg IV TDS	Treat based on culture of blood/synovial fluid/bone biopsy. Surgical debridement essential. Duration: 3-4 weeks (from initiation or last major debridement)
Chronic osteomyelitis, chronic infective arthritis		No empiric therapy		Definitive treatment guided by bone/synovial biopsy culture.

Table 14 Severe sepsis and septic shock of undetermined source

Condition	**Organisms**	**Empiric antibiotics**	**Comments**
Community acquired	Enterobacteriaceae, *Pseudomonas*, *Staph aureus*	Imipenem- cilastatin 1 g IV q8h or meropenem 1 g IV q8h	Add vancomycin if *Staph aureus* is a concern. Add colistin if high local prevalence of carbapenem resistant organisms or previously colonized.
Hospital acquired	Entero-bacteriaceae, *Pseudomonas, Acinetobacter, Staph aureus*	Imipenem 1g IV q8h or meropenem 1g IV q8h plus Vancomycin 1g IV q12h plus Colistin 9 mu IV stat then 4.5 mu IV q12h	Broaden spectrum if prior antibiotic exposure. De-escalate to narrow spectrum agent on receipt of sensitivities.

Table 15 Post-op infections following solid organ transplant (kidney, liver, heart, lung)

Condition	Organisms	Empiric antibiotics	Alternative antibiotics	Comments
Post-op fever with hemodynamic stability	Usually not due to infection	None		Look for hematoma, DVT, transfusion related fever, rejection
Surgical site infection	*Staph aureus*, Entero-bacteriaceae, *Pseudomonas*			Treat based on culture and sensitivities
VAP/HAP	Entero-bacteriaceae, *Pseudomonas*, *Acinetobacter*	Piperacillin-tazobactam 4.5 g IV q6h or Cefoperazone-sulbactam 3 g IVq8h. Add colistin if high local prevalence of carbapenem resistant organisms.	Imipenem-cilastatin 1g IV q8h or meropenem 1g IV q8h	De-escalate to narrow spectrum agent on receipt of sensitivities.
CLABSI	Entero-bacteriaceae, *Pseudomonas, Acinetobacter, Staph aureus*	Piperacillin-tazobactam 4.5 g IV q6h or cefoperazone-sulbactam 3 g IVq8h plus vancomycin 1g IV q12h. Add colistin if high local prevalence of carbapenem resistant organisms.	Imipenem-cilastatin 1g IV q8h or meropenem 1g IVq8h	Obtain blood cultures before starting antibiotics. De-escalate to narrow spectrum agent on receipt of sensitivities.

CA-UTI	ntero-bacteriaceae, enterococci	Piperacillin-tazobactam 4.5 g IV q6h or cefoperazone-sulbactam 3 g IVq12h	Imipenem-cilastatin 1g IV q8h or meropenem 1g IV q8h	Obtain blood and urine cultures before starting antibiotics. De-escalate to narrow spectrum agent on receipt of sensitivities.

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Antimicrobial Guidelines for Infections in Obstetrics and Gynaecology

1. Preamble:

The purpose of these guidelines is to ensure appropriate antimicrobial prophylaxis and treatment while at the same time limiting unnecessary use of antibiotics. Common gynaecological conditions which need treatment with antibiotics are pelvic inflammatory disease, bacterial vaginosis, vaginal candidiasis, vaginal trichomoniasis. Serious conditions include surgical site infection (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. Prophylactic antibiotics should be safe, inexpensive and effective against organisms likely to be encountered. Adequate serum and tissue levels should be present before an incision is made and therapeutic levels should be maintained during surgery and for a few hours after it is over.

2. Case definition:

Infectious complications following obstetric & gynaecologic surgery (eg caesarean section and hysterectomy) include SSI, urinary tract infection, endometritis, vaginal cuff cellulitis, perineal infection, and septicaemia.

Surgical Site Infection (SSI): These are defined by the centre for disease control, USA (CDC) and may be superficial, deep or involving organ/space.

i) Superficial incisional SSI: It occurs within 30 days after operation and involves only skin and subcutaneous tissue of the incision with at least one of the following:

- Purulent drainage, with or without laboratory confirmation, from the superficial incision
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
- At least one of the following: pain or tenderness, localised swelling, redness, or heat
- Diagnosis of superficial incisional SSI made by a surgeon or attending physician.

ii) Deep incisional SSI: It occurs within 30 days after operation if no implant is left or within one year if implant is in place. The infection appears related to the operation and involves deep soft tissue (*e.g.* fascia, muscle) of the incision with at least one of the following:

- Purulent drainage from deep incision but not from organ/space component of surgical site

- A deep incision dehisces spontaneously or is deliberately opened plus at least one of the following features: fever (>38°C), localised pain or tenderness (unless culture-negative)
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiological examination
- Diagnosis of deep incisional SSI made by a surgeon or attending physician

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

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

Puerperal sepsis: It is 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 foul odour
- Delay in the rate of reduction of the size of the uterus (<2cm/day during the first 8 days)

Pelvic inflammatory disease (PID) comprises inflammatory disorders of 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

- Sexually active young women
- Symptoms of pelvic or lower abdominal pain
- Presence of cervical motion tenderness OR uterine tenderness OR adnexal tenderness on clinical examination.
- . No other cause identified for the above symptoms and signs

Vaginitis & cervicitis: comprises a spectrum of inflammatory disorders of the lower female genital tract characterised by vaginal discharge, odor, pruritus, and dyspareunia.

3. Common Pathogens:

The common organisms causing sepsis in the **puerperium** are mostly from endogenous microbiota of vagina and include streptococci (Group B), enterococci, lactobacilli, diphtheroids, *Escherichia coli, genital mycoplasma, , Bacteroides* sp and other anaerobes.

Following a CS – Organisms to cover would be Staphylococci, Streptococci, Enterococci, Lactobacilli, Diptheroids, *E.coli*, Anaerobic streptococci, *Bacteroides* and *Fusobacterium* spp. A meta-analyses showed that prophylaxis is definitely recommended and reduces fever, endometritis, SSI, UTI etc [Hofmeyr GJ, Smaill F. Antibiotic prophylaxis for cesarean section. Cochrane Database Syst Rev 2002; 3: CD000933]

The common organisms causing sepsis in **gynaecologic surgery** are polymicrobial and include enterococci, aerobic gram negative bacilli, gram positive cocci, *Bacteroides* spp and other anaerobes. Antibiotic resistant organisms include methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococcus* (VRE), and extended-spectrum beta-lactamase-producing organisms. For majority of SSI, the endogenous flora of the vagina or the skin are responsible. Aerobic gram positive cocci, like staphylococci, are causative agents in majority of the cases but faecal flora (*Enterobacter* spp and *E coli*) may also contribute when the incision is near the perineum or groin.

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 centers 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%).[Chongsomchai C, Lumbiganon P, Thinkhamrop J et al. Placebo-controlled, double-blind, randomized study of prophylactic antibiotics in elective abdominal hysterectomy. J Hosp Infect 2002; 52:302–306.]

The staphylococci may be MSSA (methicillin senstitive *Staphylococcus aureus*) or MRSA, the latter more likely when the patient is referred after treatment at some other health care 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 vagina has less number of anaerobes and aerobes of proteobacteria which are responsible for majority of infections.

Common pathogens causing pelvic inflammatory disease (PID) are, *C. trachomatis, N. gonorrhoeae, 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*, anaerobes, ureaplasma and mycoplasma. Common pathogens causing cervicitis are chlamydia and *N. gonorrhoeae.*

4. Investigations: Blood culture and other samples are guided by clinical suspicion of focus of infection, 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.

5. Resistance pattern of common pathogens: in % susceptible (ICMR data 2014)

Enterobacteriaceae

Amikacin	53
Cefepime	17
Cefoperazone/Sulbactam	40
Cefotaxime	13
Ceftazidime	14
Chloramphenicol	72
Ciprofloxacin	35
Colistin*	97
Gentamicin	46
Imipenem	71
Meropenem	46
Piperacillin/Tazobactam	42
Tetracycline	55
Ertapenem	48

Staphylococcus aureus

Ciprofloxacin	68
Erythromycin	58
Clindamycin	68
Cefoxitin	51
Netilmicin	99
Vancomycin	100
Teicoplanin	100

Pseudomonas aeruginosa

Amikacin	93
Ceftazidime	68
Cefepime	51
Pip-taz	99
Imipenem	83
Cefoperazone	68
Meropenem	70
Cefo-sulbactam	56
Colistin	100
Ciprofloxacin	80
Tobramycin	63

Acinetobacter baumannii

Amikacin	18
Cefepime	2
Cefoperazone/Sulbactam	10
Cefotaxime	6
Ceftazidime	2
Chloramphenicol	26
Ciprofloxacin	10
Colistin	100
Imipenem	41
Meropenem	46
Piperacillin/Tazobactam	11
Tetracycline	32
Tobramycin	36
Ampicillin/Sulbactam	21
Ertapenem	0
Gentamicin	18

6. Antibiotic prophylaxis regimens:

I. 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 I V initial dose followed by 1gm IV 4-6 hrly till delivery for GBS prophylaxis. If allergic, Vancomycin 1 gm IV 12 hrly
- Third / fourth degree perineal tear: Single dose Cefotetan or Cefoxitin 1 gm IV, after sensitivity testing (or clindamycin 600-900 mg IV , if allergic). The alternates are: IV cefuroxime 1.5 gm plus metronidazole 500 mg or IV amoxicillin-clavulanic acid 1.2 gm.

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

c. Caesarean Delivery: Antibiotic prophylaxis is recommended for all caesareans

- Single dose of first generation cephalosporin, iv Cefazolin, 2 gm, within 60 minutes before incision. Minimum interval before incision should be 15 min, preferably 30 min
- If allergic to Cefazolin, give single dose of iv Clindamycin 600-900 mg + Gentamicin 80 mg

After single dose, therapeutic drug level is maintained for 3-4 hrs; repeat dose if duration of surgery is >3 hrs 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.

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

II. <u>Gynaecological Surgery</u>

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.

- Single dose of cefazolin 2 gm IV. Dose is 3 gm if weight is >100 kg. The alternate is a second-generation cephalosporin like cefuroxime.
- If allergic to cephalosporins, use Clindamycin 600 mg IV
- Administer 15 to 60 minutes prior to incision. Additional dose is given 3 hours after the initial dose if surgical procedure is lengthy (e.g. >3 hours), or blood loss is >1500 mL
- Give oral metrogyl 500 mg 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 1 gm IV (if allergic, use clindamycin 600 mg). Alternate is a second-generation cephalosporin like cefuroxime. Give oral doxycycline 100 mg twice daily for 5 days post-operatively if there is history of PID or if fallopian tubes are dilated at 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 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 abortion
- HSG: oral doxycycline 100 mg prior to procedure, to be continued twice daily for 5 days if there is history of PID or fallopian tubes are found dilated at procedure

III. <u>Emergency area (septic cases)</u>

a. Puerperal sepsis / Septic induced abortion / chorioamnionitis: Inj. Piperacillin + Tazobactam 4.5 gm IV 8 hrly X 7-14 days. If patients have received antibiotics elsewhere OR have septic shock OR are intubated, consider optimum and appropriate antibiotics like Vancomycin , Imipenem and Teicoplanin to cover MRSA. Important to consider and cover *C. sordelli* and *C. perfringens*

Table I Antimicrobial spectrum of AMAs:

Antimicrobial drug	**Organisms sensitive**	**Organisms resistant**
Ampicillin	Gram positive bacteria: *Streptococcus pneumoniae*, *Streptococcus pyogenes*, some isolates of *Staphylococcus aureus* (but not penicillin-resistant or methicillin-resistant strain), and some Enterococci. Gram negative bacteria: *Neisseria meningitidis*, some strains of *Haemophilus influenzae*, and Enterobacteriaceae Actinomyces spp.	MSSA, MRSA
Cefazolin	MSSA, Aerobic gram positive (*S. aureus, S. epidemidis, S. pyogenes, S. pneumoniae*), Aerobic gram negative if not ESBL or CRE (*E. coli, Proteus*) ESBL: Extended Spectrum Beta Lactamase producing Bacteria CRE: **Carbapenem Resistant Enterobacteriaceae**	MRSA, Enterococci, anaerobes
Cefuroxime	Aerobic gram positive (pneumococci, *S. pyogenes, S. aureus*), aerobic Gram negative if not ESBL or CRE (*E. coli, H influenzae, K. pnemoniae, N. gonorrhoeae*)	MRSA, Enterococci, anaerobes
Cefotetan	Like second generation: additional = anaerobes: *Bacteroides*	
Metronidazole / Tinidazole	Broad array of gut anaerobes, protozoa, and microaerophilic bacteria. *Bacteroides* spp, *Clostridium* spp, *Prevotella* spp, *Porphyromonas* spp, *Fusobacterium* spp, *Clostridium* spp	*Propionibacterium acnes*, and *Lactobacillus* species are resistant to

	Also anaerobic protozoa: *T. vaginalis*, *E.histolytica, Giardia lamblia*, *Blastocystis hominis*, *Balantidium coli*	metronidazole
Piperacillin + Tazobactum	MSSA, Coagulase negative Staphylococci if Methicillin susceptible, *Streptococcus pneumoniae (penicillin susceptible), Streptococcus spp., Haemophilus influenzae, Neisseria gonorrhoeae, Enterobacteriaceae, E. coli, Pseudomonas aeruginosa*	MRSA
Clindamycin	Staphylococci, *Streptococcus viridans*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* Potent activity against anaerobes such as *B. fragilis*, *Clostridium perfringens*, *Fusobacterium* spp, *Prevotella melaninogenicus*, *Peptostreptococcus* spp, Actinomyces spp	*H. influenzae*, enterococci, *Neisseria meningitides, Mycoplasma pneumoniae* and aerobic gram-negative bacilli
Vancomycin	MRSA	

Table 2 Summarizing use of Anti Microbial 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 previous baby with GBS infection • Bladder or kidney infection due to GBS	Group B Streptococci	Ampicillin 2 gm IV followed by 1gm IV 4-6 hrly till delivery	Cefazolin 2 g IV followed by 1 g 8 hrly till delivery If allergic, Vancomycin 1 gm IV 12 hrly till delivery	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** *Staph. aureus,* **Gram negative** Enterobacteriaceae, **Anaerobes**	Single dose cefoxitin or cefotetan 1gm IV	Single dose Cefazolin 1 gm IV plus metronidazole 500 mg IV OR single dose IV cefuroxime 1.5 gm plus metronidazole 500 mg IV OR single dose IV 1.2 gm amoxicillin-clavulanic acid .	Prophylaxis is considered to prevent adverse outcomes arising from infection eg fistulas

				if allergic, single dose IV clindamycin 600-900 mg	
3.	Preterm pre-labour rupture of membranes	**Gram positive** GBS **Gram negative:** Enteric gram-negative bacilli, Ureaplasma, mycoplasma **Anaerobes** (including *G. vaginalis*),	IV Ampicillin 2 gm followed by 1 gm 4-6 hourly for 48 hours followed by oral amoxycillin 500 mg 8 hourly for 5 days PLUS oral erythromycin 333 mg 8 hourly for 7 days	If erythromycin 333 mg is not available, use erythromycin stearate 250 mg 6 hourly for 7 days	
4.	Caesarean delivery	**Gram positive aerobes:** GBS, Staphylococci, enterococci, **Gram negative Aerobes:** *E. coli, Klebsiella, Proteus* **Anaerobic Gram-positive cocci** Peptococci, peptostreptococci **Anaerobic Gram-negative bacilli**: *Bacteroides, Prevotella* spp. **Facultatively anaerobic Gram-variable rod:** *G. vaginalis*	Single dose cefazolin 2gm IV Dose is 3gm if patient is >100kg	If allergic, single dose clindamycin 600-900 mg IV + Gentamicin 1.5mg/kg IV	Puerperal endometritis is polymicrobial, (aerobic–anaerobic). These organisms are part of vaginal flora and are introduced into the upper genital tract coincident with vaginal examinations during labour and/or instrumentation during surgery Tita et al showed the addition of 500-mg azithromycin to cefazolin for cesareans (in labor 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).
5.	Rescue cervical encerclage	Vaginal flora	Inj Ampicillin 2 gm single dose		To prevent ascending infection from vaginal flora to

					exposed membranes
6.	Puerperal sepsis / Septic abortion / chorioamnionitis	**Gram positive***:* Streptococci *(A,B,D), Staph. aureus* **Gram negative***:* *E.coli,* Enterobacteria ceae *including Klebsiella, Enterobacter, Citrobacter, Pseudomonas aeruginosa, Proteus mirabilis, Gardnerella vaginalis, Bacteroides Clostridium perfringes,* **Anaerobes**	Inj. Piperacillin + Tazobactem 4.5 gm IV 8 hrly X 7-14 days	Clindamycin 600-900 mg IV 8 hourly+ Gentamicin 60 mg IV 8 hourly+ metronidazole 500 mg IV 8 hourly or Ampicillin-Sulbactam 3 g IV Q6H	Usually polymicrobial
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 2 gm IV single dose Dose is 3 gm if patient is >100kg	Cefuroxime 1.5 g IV single dose OR If allergic to cephalosporin, Clindamycin 600 -900 mg IV + gentamicin 1.5mg/kg IV	In AH & LH, vagina is opened at end of procedure & exposure to vaginal flora is brief. In VH, there is greater colonisation of 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 500 mg 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: *Staph. aureus*	Cefazolin 1 gm IV single dose.	Cefuroxime 1.5 g IV sinlge dose If allergic, use IV clindamycin 600 mg	
9.	Abortions (medical and surgical)	*Chlamydia, Neisseria gonorrhoeae*	Azithromycin 1 g orally plus metronidazole 800 mg orally	Doxycycline 100 mg orally twice daily for 7 days, starting on day of abortion, plus	No prophylaxis for missed / incomplete abortion

			at time of abortion	metronidazole 800 mg orally at time of abortion	
10.	HSG	*Chlamydia, Neisseria gonorrhoeae*	Doxycycline 100 mg orally before procedure		Doxycycline continued twice daily for 5 days if there is history of PID or fallopian tubes are dilated at procedure
11.	Pelvic Inflammatory disease (mild to moderate)	*N. gonorrhoeae*, *C. trachomatis* and anaerobes. *E. coli, Bacteroides* GBS, GAS, S. aureus, respiratory pathogens (eg, *H. influenzae*, *S. pneumoniae*,	NACO: Tab. Cefixime 400 mg orally STAT **PLUS** Tab. Metronidazole 400 mg BD X 14D **PLUS** Cap. Doxycyline, 100 mg bd X 14 D	CDC: Levofloxacin 500 mg OD X 14 days OR Ofloxacin 400 mg OD X 14 days With or without Metronidazole 500 mg BD X 14 days OR Ceftriaxone 250 mg IM single dose plus Doxycycline orally 100 mg BD X 14 days with or without Metronidazole 500 mg BD X 14 days	
12.	Pelvic Inflammatory disease (severe) eg tubo-ovarian abscess, pelvic abscess		Cefotetan 2 g IV BD PLUS doxycycline 100 mg orally or IV BD	Cefoxitin 2 g IV every 6 hours PLUS Doxycycline 100 mg orally or IV every 12 hours OR Clindamycin 900 mg IV every 8 hours PLUS gentamicin loading dose IV or IM (2 mg/kg), followed by maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted	An attempt should be made to obtain cultures and de-escalate based on that. Duration is two weeks, but can be extended depending upon 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 150 mg orally single dose **OR** local Clotrimazole 500 mg vaginal tablet once only	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 2 gm oral, single dose **OR** Tab. Tinidazole 500 mg orally, twice daily for 5 days **OR** Tab. Metronidazole 400 mg, twice daily for 7 days		Alcohol avoided during treatment and 24 hours after metronidazole or 72 hours after completion of tinidazole to reduce possibility of disulfiram-like reaction. Partner treatment essential
15.	Bacterial vaginosis	Overgrowth of anaerobes *(Gardnerella vaginalis)*	**Metronidazole** 400 mg orally BD X 7 days OR **Metronidazole** gel 0.75%, one applicator (5 g) intravaginal x 5 days OR **clindamycin** Cream 2%, one applicator (5 g) intravaginal x 7 days	**Secnidazole** 2 g orally OD X one day OR **Tinidazole** 2 g orally OD X 2 days OR **Tinidazole** 1 g orally OD X 5 days OR c**lindamycin** orally 300 mg BD X 7 days OR c**lindamycin** ovules 100 mg intravaginally OD HS for 3 days*	Refrain from sexual activity or use condoms during the treatment. Clindamycin cream is oil-based and might weaken latex condoms

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Principles of Initial Empirical Antimicrobial Therapy in Patients with Severe Sepsis and Septic Shock in The Intensive Care Units

1. Definitions.

Systemic inflammatory response syndrome (SIRS)

Two or more of the following variables

i. Fever > 38°C (100.4°F) or hypothermia < 36°C (96.8°F)
ii. Tachypnea (>20 breaths/min) or PaCO2 < 32 mmHg
iii. Tachycardia (heart rate >90 beats/min)
iv. Leukocytosis or leucopenia : WBC > 12,000 cells/mm3, <4,000 cells/mm3 or > 10% immature band forms

Sepsis : Systemic inflammatory response syndrome that occurs due to a "known or suspected" pathogen (bacteria, viruses, fungi or parasites)

Severe sepsis

Sepsis plus evidence of organ dysfunction or tissue hypoperfusion as follows –

i. Altered mental status.
ii. Hypoxemia, with PaO2/FIO2 <250
iii. Thrombocytopenia < 100,000/cmm
iv. Bilirubin >2mg/dl
v. INR >1.5 or aPTT> 60 seconds.
vi. Urinary output of 0.5 ml/kg for at least 2 hours or Serum creatinine >2mg/dl despite fluid resuscitation.
vii. Tissue hypoperfusion as suspected by mottled skin, capillary refilling time ≥ 2 seconds or lactate >4 mmol/l
viii. Hypotension : Systolic blood pressure (SBP) ≤90 mmHg or mean arterial pressure ≤70 mm Hg.

Sepsis induced hypotension SBP <90 mm Hg or MAP <70 mm HG or SBP decrease >40 mm Hg

Septic shock Sepsis induced hypotension that persists despite adequate fluid resuscitation, requiring vasopressors to maintain the blood pressure.

Recently, the definitions have been updated as follows:

Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be

represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more.

In patients admitted from the community or emergency department, it can be assumed that patients had no pre-existing organ dysfunction, baseline SOFA score assumed to be zero. Organ dysfunction can be identified in these patients by the quick SOFA or qSOFA. The presence of any two of respiratory rate ≥22, altered mentation or systolic blood pressure ≤100 mm Hg identified high risk of patients. qSOFA is an extremely useful screening tool for organ dysfunction, especially in patients outside the ICU. It can be used to suspect sepsis and initiate further investigations and treatment.

Septic shock should be defined as 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. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

2. INVESTIGATIONS

Clinical history and Investigations should be directed at diagnosis, assessing the focus of sepsis, the severity of the sepsis and the risk of resistant organisms.

Tests to diagnose Infection

i. Hemoglobin
ii. White blood cell count (total and differential)
iii. Relevant cultures with gram stain
iv. Urine (Routine and microscopic examination)
v. Chest X-Ray
vi. Other relevant radiological investigations (ultrasound, CT scan)
vii. Lumbar puncture when clinically indicated
viii. Blood and other relevant cultures, sensitivity, MIC testing
ix. Procalcitonin (PCT), C-reactive protein (CRP)
x. Investigations for Tropical Infections (see below)

Tests to diagnose and quantify severity of organ dysfunction

i. Renal function tests (SE, BUN, Cr)
ii. Liver function test (Bilirubin, AST, ALT, ALKP, GGT, PT, INR, PTT)
iii. Arterial Blood gas analysis
iv. Serum lactate

Other tests

i. ECG, Echocardiography
ii. Therapeutic drug monitoring
iii. Blood Glucose.

Patients at risk for infections from resistant organisms include:
Antimicrobial therapy in preceding 90 days

- Current hospitalization of 5 days or more
- High frequency of community or hospital antibiotic resistance
- Immunosuppressive disease or therapy
- Presence of multiple risk factors for Health Care Associated Infections
    - Hospitalization for ≥2 days in preceding 90 days
    - Residence in nursing home or long term care facility
    - Home infusion therapy
    - Chronic dialysis within 90 days
    - Family member with MDR pathogen

3. Common Pathogens
Common resistant organisms include:

Gram negative:
Pseudomonas aeruginosa
E. coli
Klebsiella pneumoniae
Acinetobacter spp

Gram Positive:
Methicillin resistant *Staphylococcus aureus* (MRSA)
Entercoccus faecium
Vancomycin resistant enterocccci

Fungi:
Candida spp

3. Resistance Patterns: ICMR AMR Data 2014

Table 1. *Staphylococcus aureus and Enterococcus* ICMR AMR National Data 2014.

AMA	*Staphylococcus aureus*		*Enterococcus faecalis*		*Enterococcus faecium*	
	'n'	**% R**	**'n'**	**%R**	**'n'**	**%R**
Ampicillin	-	-	732	25.7	367	70.3
Cefoxitin	3221	35.7	-	-	-	-
Ciprofloxacin	-	-	318	85.5	164	87.2
Clindamycin	3206	25.0	-	-	-	-
Gentamicin	2402	17.8	-	-	-	-
Gentamicin HL	-	-	673	43.4	581	65.9
Linezolid	2456	0.2	527	0	323	0
Nitrofurantoin	-	-	230	3.0	140	27.9
Teicoplanin	2508	0	543	2.2	487	**14.0**
Vancomycin	3223	0.1*	796	5.3	498	**13.9**

* Vancomycin Resistant (R) are VISA isolates.
Cefoxitin : Surrogate marker for Methicillin.

Table2. Enterobacteriaceae isolates. ICMR AMR National data 2014.

	From Blood % Resistant			**From Lower Respiratory Tract, % Resistant**		
AMA	**Ec**	**Ks**	**Es**	**Ec**	**Ks**	**Es**
Amikacin	24	54	44	37	68	47
Cefepime	79	88	80	91	83	81
Cefoperazone-sulbactam	33	62	39	-	-	-
Cefotaxime	80	83	83	86	85	85
Ceftazidime	81	84	77	88	83	74
Ciprofloxacin	81	65	48	80	72	65
Colistin	1	1	0	-	-	-
Gentamicin	46	65	56	38	69	54
Imipenem	**18**	**35**	**26**	**25**	**60**	**52**
Meropenem	**35**	**53**	**38**	**33**	**62**	**55**
Netilmicin	12	42	18	-	-	-
Piperacillin-tazobactam	43	68	57	43	70	60
Tetracycline	64	42	16			

Note: Ec:*Escherichia coli;* Ks:*Klebsiella*spp.; Es : *Enterobacter* spp.

Table 3. *Pseudomonas aeruginosa* and *Acinetobacter baumannii* ICMR AMR National Data 2014

AMA	***Pseudomonas aeruginosa*** **'n' 374** **R %**	***Acinetobacter baumannii 'n' 599*** ***R %***
Amikacin	35	75
Aztreonam	48	87
Cefepime	41	81
Cefoparazone-sulbactam	38	57
Ceftazidime	47	84
Colistin	10	22
Imipenem	37	63
Levofloxacin	36	73
Meropenem	**47**	**62**
Netilmicin	**45**	**69**
Piperacillin-tazobactam	**46**	**83**
Tobramycin	33	58

Table 4. *Candida* spp. isolated at PGIMER, Chandigarh ICMR AMR Data 2014.

AMA	***C. tropicalis*** **'n' 101** **% R**	***C. krusei*** **'n' 98** **% R**	***C . albicans*** **'n' 50** **% R**	***C. pelliculosa*** **'n' 35** **% R**
Amphotericin B	1	5	0	0
Fluconazole	4	0	8	0
Voriconazole	1	3	8	0
Itraconazole	8	4	2	0
Posaconazole	1	0	0	0
Caspofungin	2	8	0	0
Anidulafungin	1	7	2	0
Micafungin	0	6	2	6

Indian Society of Critical Care Medicine Multi-center Observational Study to evaluate Epidemiology and Resistance patterns of common ICU-Infections (MOSER Study) 2012

Table 5. Ventilator Associated Pneumonia organisms – Resistance Pattern of top 5 organisms

Organisms	'n'	Pan sensitive	Carbapenem resistant	ESBL positive	Multi-drug resistant	Data NA	Amp C producer	Methicillin Resistant	Vanco resistant
Acinetobacter	88	3	1	2	77	5			
Klebsiella	59	1	1	8	47	2			
Pseudomonas	48	8	0	2	30	8			
Staphylococcus	15					5	2	7	1
E. coli	12	1	0	2	8	1			

Table 6. Catheter Related Bloodstream Infection Organisms – Resistance pattern of top 5 organisms

Organisms	'n'	Pan sensitive	Carbapenem resistant	ESBL positive	Multidrug resistant	Data NA
Klebsiella	18	5	0	4	9	
Pseudomonas	11	2	1	4	3	1
Acinetobacter	11	3	0	1	7	
E. coli	9			5	4	
Candida	8					

4. Initial Empirical Antibiotic Therapy

Clinical condition	Common pathogens	Empirical AMA	Alternate AMA	Comments
Early onset VAP	*Streptococcus pneumoniae,* *Haemophilus influenzae,* MRSA, *E. coli, Klebsiella pneumoniae,* *Enterobacter* spp, *Proteus* spp, *Serratia marscecens*	2nd or 3rd generation cephalosporin eg. Ceftriaxone	BL-BLI eg. Ampicillin+sulbactam 3 gm every 8 hourly Or Ertapenem 1 gm daily	Fluoroquinolone eg. Levofloxacin or, Moxifloxacin should be avoided due to high prevalence of tuberculosis
Late onset VAP or with risk factors for MDR	As in Early VAP, *Pseudomonas* spp, *Klebsiella pneumoniae, E. coli,* *Acinetobacter* spp, MRSA	BL-BLI Piperacillin+tazobactam 4.5 gm 6 hrly or Cefoperazone-sulbactam 3 gm 12 hrly, OR Antipseudomonal Carbapenem **PLUS** Aminoglycoside eg.amikacin 20 mg/kg/day, gentamicin 7 mg/kg/day, tobramycin 7 mg/kg/day Or Antipseudomonal fluoroquinolone e.g. Ciprofloxacin 400 mg 8 hrly, levofloxacin 750 mg daily **PLUS** Coverage for MRSA e.g. Vancomycin 15 mg/kg every 12 hrs or Linezolid 600 mg 12 hrly	Colistin **PLUS** Antipseudomonal Carbapenem Or Cefoperazone-sulbactam **PLUS** Coverage for MRSA eg. Vancomycin 15 mg/kg every 12 hrs or Linezolid 600 mg 12 hrly	For pseudomonas double coverage is recommended BL-BLI first choice if sensitivity is >70% For ESBL producing gram- negative strains, carbapenems are appropriate drugs Colistin where carbapenem resistance is high (>70%)
Urosepsis	*E. coli, Pseudomonas* spp, *Enterococcus* spp., *Klebsiella* spp., *Proteus* spp., Anaerobes *Candidia* spp	BL-BLI or Meropenem or Imipenem-cilastatin. Fluconazole if *Candida* spp. isolated	Colistin with Meropenem;	In pyelonephritis with sepsis, Echiocandins may be considered if *Candida* species are likely to be fluconzole resistant
Intra-abdominal sepsis	*E. coli, Pseudomonas* spp, *Enterococcus* spp., *Acinetobacter* spp, *Klebsiella* spp., *Proteus* spp. *Candida* spp	BL-BLI or Meropenem or Imipenem-cilastatin OR	Colistin with Meropenem;	Source control vital Vancomycin or Teicoplanin if *Enterococcus* spp isolated Fluconazole or Echinocandins

				if *Candida* spp isolated. Echinocandins if prior history of azole exposure or if *Candida* species are likely to be fluconzole resistant
Catheter related blood-stream infection	Gram –negative pathogens • *Escherichia coli* • *Klebsiella* spp • *Enterobacter* spp • *Pseudomonas aeruginosa* Gram-positive pathogens • Coagulase-negative staphylococci • *Staphylococcus aureus*, including methicillin-resistant strains Fungi • *Candida* spp	Carbapenem, or BL-BLI, with or without an aminoglycoside Vancomycin in settings of high MRSA prevalence; Echinocandin or fluconazole if fungal infection suspected	Add colistin for Gram-negative cover where carbapenem resistance rates are high	Where MRSA isolates have vancomycin MI ≥2 mg/mL, daptomycin, should be used
Invasive candidiasis	*C. albicans* *C. tropicalis* *C. glabrata* *C. parapsilosis* *C. krusei*	Echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) as initial therapy	Fluconazole, intravenous or oral, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species Lipid formulation amphotericin B (AmB) (3–5 mg/kg daily) if there is intolerance, limited availability, or resistance to other antifungal agents OR Amphotericin deoxycholate (in patients with normal renal function)	Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (eg, *C. albicans*), and have negative repeat blood cultures following initiation of antifungal therapy
Febrile neutropenia	Gram-negative pathogens • *Escherichia coli* • *Klebsiella* spp • *Enterobacter* spp • *Pseudomonas*	Ccarbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam or cefaperazone-sulbactam PLUS aminoglycosides or fluoroquinolones (if judged	• MRSA: Consider early addition of vancomycin, linezolid, or • daptomycin. • VRE: Consider early addition of	Modify treatment depending on clinical condition of patient and culture and

	aeruginosa • *Citrobacter* spp • *Acinetobacter* spp • *Stenotrophomonas maltophilia* • Gram-positive pathogens • Coagulase-negative staphylococci • *Staphylococcus aureus*, including methicillin-resistant strains • *Enterococcus* spp, including vancomycin-resistant strains • Viridans group streptococci • *Streptococcus pneumoniae* • *Streptococcus pyogenes* • Fungi*Candida* spp Moulds	necessary) PLUS Vancomycin if suspected catheter-related infection, skin and soft-tissue infection, pneumonia, or hemodynamic instability PLUS Initial Antifungal therapy: Echinocandin (In high-risk patients who have persistent fever after 4–7 days ofa broad-spectrum antibacterial regimen and no identified fever source)	linezolid or daptomycin • ESBLs: Consider early use of a carbapenem • KPCs, *Acinetobacter*: Consider early use of polymyxin-colistin or • tigecycline • Alternate Antifungal therapy • Lipid formulation AmB, 3–5 mg/kg daily, is an effective • but less attractive alternative • Fluconazole for patients who are not critically ill and have had no prior azole exposure • Voriconazole, 400 mg (6 mg/kg) twice daily for 2 doses,then 200–300 mg (3–4 mg/kg) twice daily, when additional mold coverage is desired	sensitivity reports

Note : (1)Antibiotic therapy must be guided by local susceptibility patterns. First line empirical treatment for Gram-negative organisms could be BL-BLI if local susceptibility is 70% and above. For Pseudomonas, Klebsiella and Acinetobacter,use Meropenem or Imipenem if local susceptibility is 70% and above and a combination of Colistin and Meropenem if carbapenem resistance is high (> 70%)

(2)In general, for settings with a higher incidence of ESBL producing organisms, BL-BLI combinations may be used for less ill patients, and carbapenems for patients with greater severity of illness

BL-BLI: beta lactam plus B-lactamase inhibitor: eg; Piperacillin-Tazobactam, Cefaperazone-Sulbactam

Choice of empirical therapy

- The initial management of infection requires forming a probable diagnosis, obtaining cultures, and initiating appropriate and timely empirical antimicrobial therapy and source control (i.e., draining pus, if appropriate)
- Because patients with severe sepsis or septic shock have little margin for error in the choice of therapy, the initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis.
- Administration of effective intravenous antimicrobials should occur within the first hour of recognition of septic shock and severe sepsis without septic shock.
- Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin.

The choice of empirical therapy depends on:

- the suspected site of infection
- the clinical syndrome
- the setting in which the infection developed (i.e., home, nursing home, or hospital
- medical history
- Epidemiology, susceptibility patterns of bacteria in the hospital and ICU, local microbial-susceptibility patterns, resistance potential
- Prior antibiotic therapy(previous 3 months)
- Immunological competence of patient
- Severity of underlying illness
- Microbes that previously have been documented to colonize or infect the patient.
- Pharmacokinetics of the chosen antimicrobial agent
- Drug allergies / toxicities
- Cost

De-escalation

- As soon as the causative pathogen has been identified, de-escalation should be performed by selecting the most appropriate antimicrobial agent that covers the pathogen and is safe and cost-effective.
- The antimicrobial regimen should be reassessed daily for potential de-escalation to prevent the development of resistance, to reduce toxicity, to reduce costs and to reduce the likelihood that the patient will develop superinfection with other pathogenic or resistant organisms, such as *Candida* species, *Clostridium difficile*, or vancomycin-resistant *Enterococcus faecium*.
- Use of low procalcitonin levels or similar biomarkers can assist the clinician in the discontinuation of empiric antibiotics in patients who appeared septic, but have no subsequent evidence of infection

Tropical Infections

Tropical diseases are diseases that are prevalent in, or unique to tropical and subtropical regions. These commonly include dengue hemorrhagic fever, rickettsial infections/scrub typhus, Malaria (usually falciparum), typhoid, and leptospirosis;

Bacterial sepsis and viral infections. It was recognized that sometimes the patients may have dual or triple infections and can present with atypical manifestations

There can be no uniform guidelines for empiric therapy but trends of tropical infections should guide the treating physician. The idea is to **hit wide and hit early** with intention to deescalate once the definitive diagnosis is established.

A syndromic approach to tropical infections can guide the intensivists regarding the commonest etiologies, investigative modalities and help them to choose early empiric therapy. For ease of diagnosis these infections can be divided into 5 major syndromes:

Undifferentiated fever

Malaria (*P. falciparum*), scrub typhus, leptospirosis, typhoid, dengue fever and other viral illness

Fever with rash/ thrombocytopenia

Bacterial infections, dengue hemorrhagic fever, rickettsial infections/scrub typhus, meningococcal infection, Malaria (usually falciparum), leptospirosis, typhoid, Crimean-Congo hemorrhagic fever and other viral fevers

Fever with ARDS

Falciparum malaria, H1N1 influeza, leptospirosis, hantavirus infection, scrub typhus, Melioidosis, Tuberculosis, severe pneumonias due to legionella and pneumococci, Diffuse alveolar hemorrhage **Febrile encephalopathy**

Bacterial infections, Herpes simplex virus encephalitis, Japanese B encephalitis, cerebral malaria, typhoid encephalopathy, fulminant hepatic failure due to viral hepatitis

Fever with multi-organ dysfunction

Bacterial sepsis, Falciparum malaria, Leptospirosis, Scrub typhus, Dengue, Hepatitis A or E with fulminant hepatic failure and hepato-renal syndrome, Hanta virus, Hemophagocytosis and Macrophage activation syndrome

Flow chart 1: An algorithmic approach for the diagnosis and management of critical tropical infections

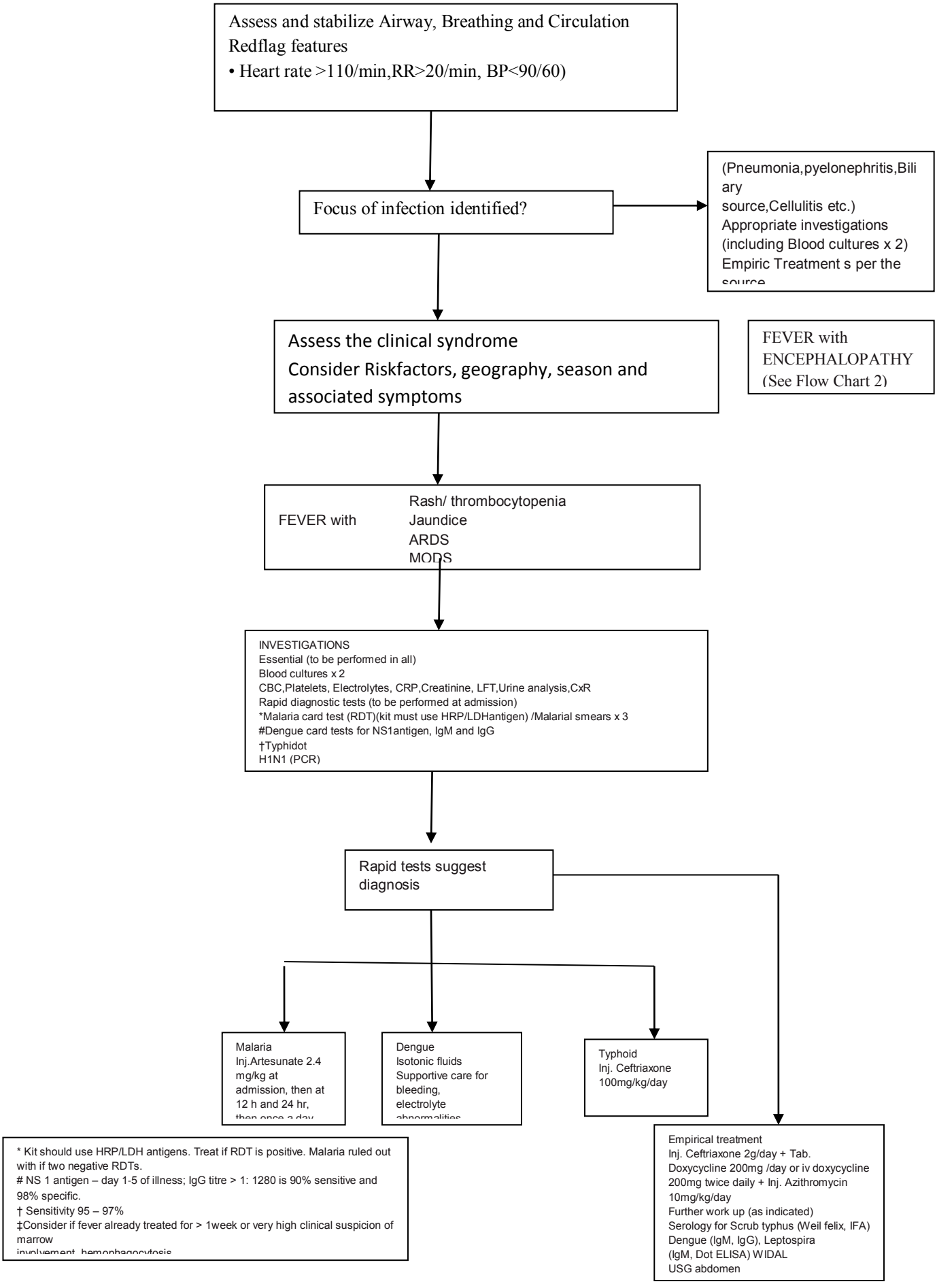
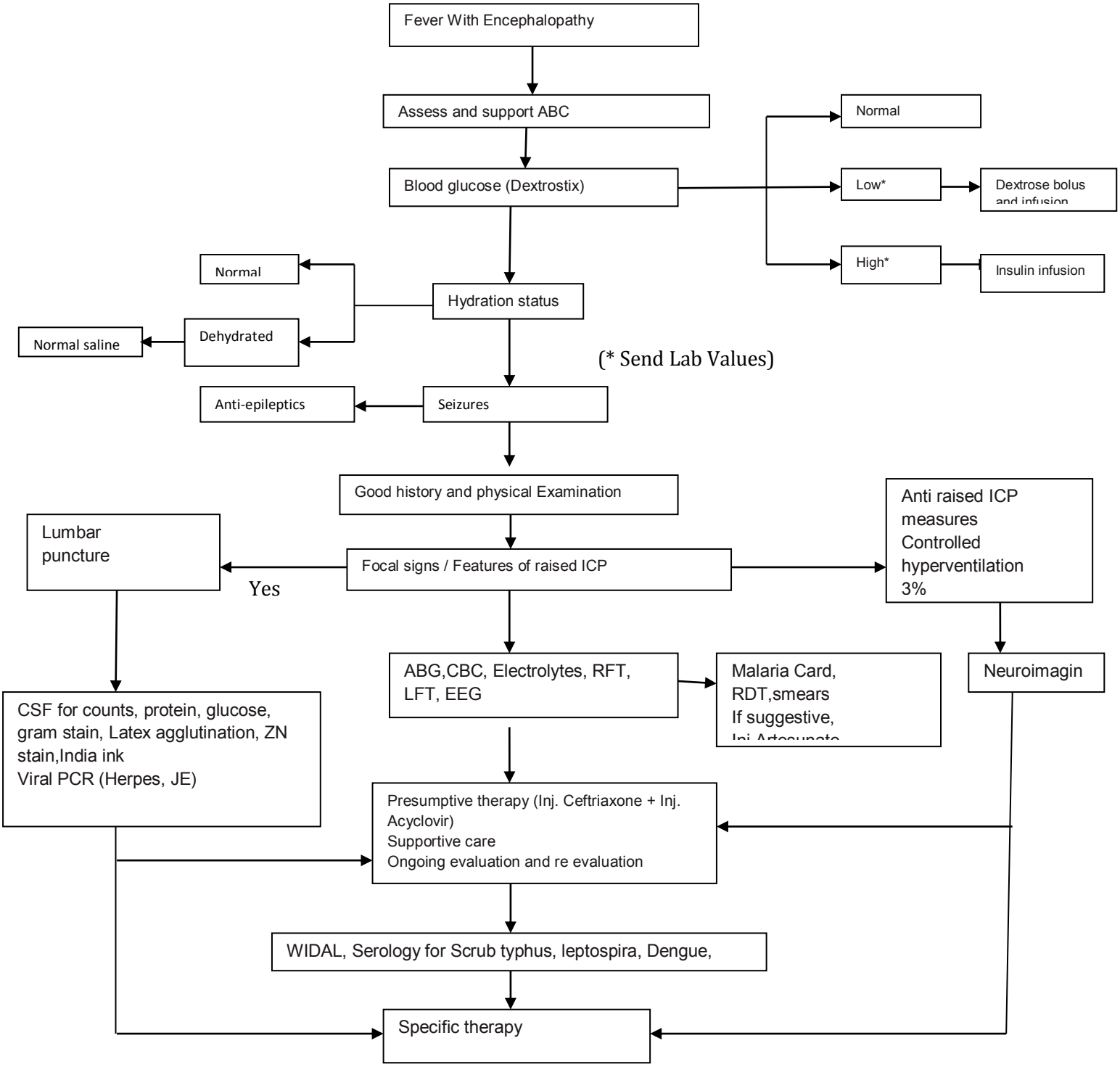


Figure -2 : Algorithmic approach to Fever With Encephalopathy



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Editorial Board

Antimicrobial guidelines for prophylaxis and treatment of Surgical Site Infections

1. Preamble

Surgical site infections (SSIs) are one of the most common health care associated infections (HCAIs) and represent a substantial cause of morbidity with 2-11-fold higher mortality. Patients developing SSIs are 60% more likely to be admitted to an ICU, are more than five times more likely to be readmitted to the hospital, and are twice as likely to die as similar patients without SSIs. SSIs complicate 3,00,000-5,00,000 surgeries per year in the USA alone, and are believed to result in US$5-10 billion of excess health expenditures, with 7- 10 days of increased length of hospital stay. SSI rates have become a universal measure of quality in hospital-based surgical practice, since they are probably the most preventable type of HCAI.

Peri-operative antimicrobials administered as prophylaxis for SSIs account for the majority of in-hospital antimicrobial prescriptions. Usually, long courses of antibiotic prophylaxis are administered, which are often associated with increasing antimicrobial resistance, super-infection with resistant pathogens, toxicity and unnecessary cost. Rampant and unnecessary administration of antibiotics is one of the major contributors for development of drug resistance.

In a systematic review on antibiotic prophylaxis for surgery for proximal femoral and other closed long bone fractures, a single dose antibiotic prophylaxis was found to significantly reduce the risk of deep surgical site infections. Several studies have justified the use of short courses of a single cephalosporin for clean surgeries, since these act on the most likely organisms causing SSIs.

2. Case d**efinitions**

Surgical Wound Classification

- Class I/Clean: uninfected operative wound in which no inflammation is encountered & respiratory, alimentary, genital, or uninfected urinary tract is not entered. Operative incisional wounds following blunt trauma are included here.
- Class II/ Clean-Contaminated: Operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination.
- Class III/Contaminated: Open, fresh, accidental wounds. Operations with major breaks in sterile technique or gross spillage from the GIT.
- Class IV/Dirty-Infected: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera.

Table 1 Criteria for Defining a Surgical Site Infection (SSI)[CDC ; ref 1]

Superficial Incisional SSI

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:

- Purulent drainage, with or without laboratory confirmation, from the superficial incision.
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
- At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
- Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do not report the following conditions as SSI:

- Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
- Infection of an episiotomy or newborn circumcision site.
- Infected burn wound.
- 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.

Deep incisional 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 deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
- 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 (>38ºC), localized pain, or tenderness, unless site is culture-negative.
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
- Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

i. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
ii. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

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:

- Purulent drainage from a drain that is placed through a stab wound into the

organ/space.

- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
- 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.
- Diagnosis of an organ/space SSI by a surgeon or attending physician.

3. Table 2 Operations and Likely Surgical Site Infection (SSI) Pathogens

Operations	**Likely Pathogens**
Placement of all grafts, prostheses, or implants	Staphylococcus aureus; Coagulase negative Staphylococci (CoNS)
Cardiac	*Staphylococcus aureus;* CoNS
Neurosurgery	*Staphylococcus aureus;* CoNS
Breast	*Staphylococcus aureus;* CoNS
Ophthalmic	*S. aureus*; CoNS; streptococci; gram negative bacilli (GNBs)
Orthopedic: Total joint replacement, closed fractures/use of nails, bone plates, other internal fixation devices, functional repair without implant/device, Trauma	*Staphylococcus aureus*; CoNS; gram-negative bacilli
Noncardiac thoracic, Thoracic (lobectomy, pneumonectomy wedge resection, other noncardiac mediastinal procedures), closed tube thoracostomy	*Staphylococcus aureus*; CoNS; *Streptococcus pneumoniae*; gram-negative bacilli
Vascular	*Staphylococcus aureus*; CoNS
Appendectomy	Gram-negative bacilli; anaerobes
Biliary tract	Gram-negative bacilli; anaerobes
Colorectal	Gram-negative bacilli; anaerobes
Gastroduodenal	GNBs; streptococci; oropharyngeal anaerobes (e.g.,peptostreptococci)
Head and neck (major procedures with incision through oropharyngeal mucosa)	*Staphylococcus aureus*; streptococci; oropharyngeal anaerobes (e.g., peptostreptococci)
Obstetric and gynecologic	GNBs; enterococci; group B streptococci; anaerobes
Urologic	Gram-negative bacilli

4. Investigations

- **Samples:**
    - Pus in sterile, wide mouth screw cap containers (if deep seated abscess, collect samples in anaerobic vials also)
    - If pus is not available, wound swabs (deep swabbing)

Samples should be taken from the depth of the wound or the advancing edge, avoiding contamination from surrounding skin.

- **Transport**: Immediate transport to the lab

- **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 as in obvious contamination with soil etc): SDA with appropriate antibiotics/ BHI-BA with appropriate antibiotics and incubation temperatures (25 and/or 37 degrees)

Resistance pattern of common pathogens (ICMR Data)

Following is the Indian data of AMR from soft tissue infections/SSI

***Table 3 Staphylococcus aureus* ICMR AMR Data 2014**

AMA	JIPMER, Puducherry		AIIMS, New Delhi		PGIMER, Chandigarh		CMC, Vellore		National	
	'n'	% R	'n'	% R	'n'	% R	'n'	% R	'n'	% R
Cefoxitin	2217	38.9	644	18.0	360	47.5	0	0	3221	35.7
Ciprofloxacin	2216	62.9	644	62.0	359	67.1	27	77.8	3246	63.3
Clindamycin	2200	22.8	644	28.0	362	33.1	0	0	3206	25.0
Erythromycin	2200	48.8	644	57.0	362	52.5	112	37.5	3318	50.4
Gentamicin	2196	17.6	0	0	0	0	206	20.4	2402	17.8
Linezolid	1596	0	644	0.9	82	0	134	0	2456	0.2
Muporicin	1588	1.9	0	0	0	0	0	0	1588	1.9
Penicillin	2217	91.2	644	82.0	0	0	0	0	2861	89.2
Teicoplanin	1588	0	644	0	276	0	0	0	2508	0
Tetracycline	2216	18.6	644	100	0	0	0	0	2860	36.9
Trimethoprim-sulfamethoxazole	1427	48.0	0	0	0	0	239	31.8	1666	45.7
Vancomycin*	2217	0.2	644	0	362	0	0	0	3223	0.1

*The 4 numbers listed as Vancomycin Resistant (R) are VISA isolates; No VRSA was isolated during the year 2014 at JIPMER.; Cefoxitin : Surrogate marker for Methicillin.

Table 1**Enterobacteriaceae isolates from skin and soft tissue. ICMR data 2014.**

	PGIMER, Chandigarh % Resistant			AIIMS, New Delhi % Resistant			JIPMER, Puducherry % Resistant			CMC, Vellore % Resistant			National % Resistant		
AMA	**Ec**	**Ks**	**Es**	**Ec**	**Ks**	**Es**	**Ec**	**Ks**	**Es**	**Ec**	**Ks**	**Es**	**Ec**	**Ks**	**Es**
Ciprofloxacin				84	76	65	71	49	31				78	61	58
Cefotaxime				89	85	81	63	61	73				80	74	79
Ceftazidime				84	82	80	49	52	58				72	67	74
Cefepime				86	83	81	58	56	57				77	70	74
Imipenem				37	54	58	13	25	22				27	39	44
Meropenem				48	62	59	15	27	21				33	43	44
Gentamicin				52	63	68	25	33	34				40	46	54
Netilmicin															
Amikacin				51	63	70	22	25	20				37	43	49
Piperacillin-tazobactam				51	63	59	24	41	37				41	52	52
Tetracycline															
Colistin															
Cefoperazone-sulbactam							8	18					8	18	

Note: Ec: *Escherichia coli;* Ks : *Klebsiella* spp; Es : *Enterobacter* spp.

***Table 2 Pseueudomonas aeruginosa* ICMR AMR data 2014**

AMA	**PGIMER, Chandigarh 'n' 75 R (%)**	**AIIMS, New Delhi 'n' 102 R (%)**	**JIPMER, Puducherry 'n' 113 R (%)**	**CMC, Vellore 'n' 84 R (%)**	**National 'n' 374 R %**
Amikacin	27	49	38	21	35
Aztreonam		62	55	30	48
Cefepime		52	57	20	41
Cefoparazone-sulbactam		39	41	30	38
Ceftazidime	64	51	51	23	47
Colistin		34		2	10
Imipenem	17	54	48	25	37
Levofloxacin		44	42	23	36
Meropenem		74	41	23	47
Netilmicin		66	45	22	45
Piperacillin-tazobactam	44	67		25	46
Tobramycin		56	43	18	33

- **Perioperative prophylaxis**

a. Choosing prophylactic antibiotics

- 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 florae (eg, *Staphylococcus* organisms) are the usual target, so first-generation cephalosporins are recommended (cephalexin, cephalothin) in most studies. Few studies also recommend cefuroxime.
- Patients with a history of anaphylaxis or urticaria after penicillin therapy should not receive prophylaxis with a beta-lactam antibiotic. Vancomycin or clindamycin should be used as alternative.

b. Timing of prophylactic antibiotics

- Give first dose 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.
- Prophylaxis should be started preoperatively in most circumstances, ideally within 30-60 minutes before incision, except for Vancomycin and Fluoroquinolones which need to be given 120 minutes before incision.

c. Route of administration

- Prophylactic antibiotics for surgical procedures should be administered intravenously.

d. Dose selection

- The dose of an antibiotic for prophylaxis is same **as for therapy of infectio**n.

e. Duration

- **Continue no longer than 24 hours postoperatively (Except cardiac surgery where data is conflicting)**
- Most studies have demonstrated efficacy of postoperative 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 24 hours is not only ineffective in reducing infections but increases antimicrobial resistance and the risk of colitis due to *Clostridium difficile*.

f. Redose for longer surgeries

- Patients undergoing surgery that extends beyond two half-lives of an antibiotic should be re-dosed intraoperatively.
- 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 3 **Pathogen-specific antimicrobial therapy according to the pathogen isolated**

Surgical Wound Classification	**Common Organisms**	**Antimicrobial prophylaxis**
Class I/Clean	Gram Positive cocci (*S. aureus*, CoNS)	None or single perioperative dose of cefuroxime/ cephalexin (Ideally 2 grams)
Class II/ Clean-Contaminated	Gram Negative Bacilli Anaerobes *S. aureus*	**1stLine:** Cefazolin or Ampicillin-sulbactam or Ceftriaxone (in patients of acute cholecystitis or acute biliary tract infections) **Alternative: In case of allergies;** if mixture of GP and GN is suspected: Ceftriaxone only if not ESBL clindamycin or vancomycin with cefazolin, aztreonam, gentamicin, or single-dose fluoroquinolone in b-lactam allergic
Class III/Contaminated	Gram Negative Bacilli Anaerobes	**1st line:** Cefazolin + Metronidazole **2nd Line:** Metronidazole+ Aminoglycoside/ Fluoroquinolone
Class IV/Dirty-Infected	Gram Negative Bacilli Anaerobes May be mixed with Gram positive bacteria	**1st Line:** Cefazolin + metronidazole, **Treatment for infected surgical wounds** Ertapenem + Clindamycin + aminoglycoside/aztreonam **Or** fluoroquinolone+ metronidazole + aminoglycoside/fluoroquinolone

- **Table 4 Antibiotics for Treatment of Incisional Surgical Site Infections**

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

Surgery	**Common organisms**	**Peri-op antimicrobial prophylaxis**
Surgery of Intestinal or Genitourinary Tract	Gram Negative Bacilli, anaerobes	**1st Line:** Piperacillin-tazobactam 3.375 g every 6 h or 4.5 g every 8 h IV Or Imipenem-cilastatin 500 mg every 6 h IV **2nd Line (as in case of non ESBL organisms)** : Ceftriaxone 1 g every 24 h + metronidazole 500 mg every 8 h IV
Surgery of trunk or extremity away from axilla or perineum	*S. aureus*, CoNS	**1st Line:** Oxacillin/ nafcillin 2 g every 6 h IV Or Cefazolin 0.5–1 g every 8 h IV 2nd Line: Cefotaxime 500 mg every 6 h IV
Surgery of axilla or perineum	*S.aureus*, GNBs, anaerobes	**1st Line**: Metronidazole 500 mg every 8 h IV plus Levofloxacin 750 mg every 24 h **2nd Line**: Metronidazole 500 mg every 8 h IV plus Ceftriaxone 1 g every 24 h

Table 5 Antimicrobial guidelines for treatment of Skin and Soft Tissue Infections

Clinical Syndrome/ condition	**Most likely pathogens**	**Antibiotic**	**Comments**
Impetigo and skin soft-tissue infections	Staphylococci & Streptococci	**1st Line** Clindamycin 300-400 mg qid PO **Alternative:** Amoxicillin-clavulanate 875/125 mg bid po	Local: Mupirocin ointment Apply to lesions bid
Erysipelas, Cellulits, Necrotising fasciitis	Streptococci (usually GAS)	Penicillin 2–4 million units X 4–6 h IV or Alternative Clindamycin 600–900 mg X 8 h IV	In penicillin allergic patients: Clindamycin, vancomycin or linezolid,
Cutaneous anthrax	*Bacillus anthracis*	1st Penicillin G8–12 MU/day IV in divided doses every 4-6 h or Erythromycin 250 mg PO every 6 hours	
Necrotizing infections of the skin, fascia, and muscle	Mixed infections	**1st Line** Piperacillin-tazobactam + Vancomycin 3.37 g every 6–8 h IV+ 30 mg/kg/d in 2 divided doses **Alternative** Carbapenems	
Water related injuries (water sports etc)	*Aeromonas hydrophila* *Vibrio vulnificus*	Doxycycline100 mg every 12 h IV+ ciprofloxacin500 mg every 12 h IV or Ceftriaxone1 to 2 g every 24 h IV	
Bubonic plague	*Yersinia pestis*	**1st Line** Streptomycin 1 g IM twice per day or Gentamicin 2 mg/kg loading dose, then 1.7 mg/kg/day in 3 divided doses IV Alternative Tetracycline 500 mg po every 6 h	

Diabetic Foot Infections			
Mild (treated with oral agents)	MSSA; *Streptococcus* spp	Cloxacillin/ cephalexin	
	MRSA	Linezolid, Daptomycin, Vancomycin	
Moderate (treated with oral or initial parenteral agent) or severe (treated with parenteral agents)	MSSA; *Streptococcus* spp; Enterobacteriaceae; obligate anaerobes	Ceftriaxone, Ampicillin/sulbactam, Moxifloxacin, Ertapenem, Tigecycline	

Table 6 Standard Doses of Antimicrobial Agents Active Against Multidrug-Resistant Organisms

Antimicrobial	**IV Dose**	**Comments**
Vancomycin	30–60 mg/kg/d in 2–4 divided doses	Target serum trough concentrations of 15–20 μg/mL in severe infections
Daptomycin	4–6 mg/kg/d	Covers VRE, strains nonsusceptible to vancomycin may be cross-resistant to daptomycin
Linezolid	600 mg every 12 h	100% oral bioavailability; so oral dose same as IV dose. Covers VRE and MRSA
Colistin	5 mg/kg load, then 2.5 mg/kg every 12 h	Nephrotoxic; does not cover gram-positives or anaerobes, *Proteus, Serratia, Burkholderia*

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11. Editorial Board

Antimicrobial Guidelines for Upper Respiratory Tract Infections

The upper respiratory tract infections (URTI) are mostly due to viral infections and therefore role of empirical antibiotics is limited . In pharyngitis a throat swab is collected but in other conditions mostly sampling for culture is not possible and not routinely done.

a. OTITIS MEDIA

Case Definition : It is an infection or inflammation of the middle ear.

Common bacterial pathogens : *Streptococcus pneumoniae, Haemophilus influenzae*, *Moraxella catarrhalis*.

Investigations
Tympanocentesis is not required. Usually it is an empirical therapy. It is important that if there is a perforation we realize that it is likely the organism isolated is a colonizer, and treatment based on that will not be appropriate..

Prevalent Resistance
S. pneumoniae in India is susceptible to penicillin (usually < 4 %) and so β Lactams can be given.
H. influenzae and *M. catarrhalis* produce β Lactamase (around 23% and 73% respectively) and need treatment with amoxycillin-clavulanic acid.

b. BACTERIAL SINUSITIS

Case Definition: This is an infection of the sinuses.

Common pathogens

Viral etiology is more common and amongst bacteria common causes are *Streptococcus pneumoniae, H. influenzae* , *Moraxella catarrhalis*.. If symptoms are < 10 days in duration and resolving, there is no need for antibiotics.

Investigations

These are not helpful as there is lack of a simple diagnostic test. Diagnosis is clinical. X-ray PNS is done usually only if there is a chronic sinusitis to look for a fluid level. Bacterial etiology is same as in otitis media. If duration of illness is >10 days with purulent nasal discharge, nasal obstruction and facial pain, then a bacterial cause should be considered

Prevalent Resistance
S. pneumoniae in India is susceptible to penicillin (usually < 4 %) and so β Lactams can be given.

H. influenzae and *M. catarrhalis* produce β Lactamases (around 23% and 75% respectively) and need treatment with amoxycillin-clavulanic acid.

c. ACUTE PHARYNGITIS

Case Definition : This is an infection or inflammation of the pharynx or tonsils.

Common Pathogen
Viruses cause the majority of these infections. Amongst bacterial causes, Group A Beta Hemolytic streptococci is responsible for pharyngitis. Other bacteria to worry about are *Fusobacterium necrophorum* which can cause Lemierre's syndrome and *Corynebacterium diptheriae* which causes a membranous tonsillitis causing respiratory compromise and other manifestations like myocarditis.

Investigations and Treatment
A throat swab is collected (if possible 2 swabs should be collected) using a sterile cotton swab, under direct visualisation without touching the tongue or buccal mucosa. The swab should be transported to the lab at room temperature. Most often no treatment is required. But if the patient is febrile for more than 3 days with pus points on tonsils, painful cervical lymphadenopathy only then a short course of antibiotics may be warranted.

Prevalent Resistance
S. pyogenes remain sensitive to Penicillin/Ampicillin. The reports on erythromycin resistance from India are now increasing (>45%) and therefore antimicrobial susceptibility should be done.
Rarely follicular tonsillitis and peritonsillar abscess may occur due to *Staphylococcus aureus* and can also present as URTI. This should be confirmed with culture and antibiotic to be given accordingly.

Table 1 **Table for AMA regimen**

Condition	**Common pathogens**	**Empiric antibiotics (presumptive antibiotics)**	**Alternative antibiotics**	**Comments**
Acute pharyngitis	Commonly viral.	None required		As most cases are viral no antimicrobial therapy required
	Common bacterial cause is *Streptococcus pyogenes*	Oral Penicillin V 500 mg BD or Amoxicillin 500 mg Oral TDS for 7 days	In case of penicillin allergy, Azithromycin 500 mg OD for 5 days	Erythromycin resistance from India reported
Acute bacterial rhinosinusitis	*Streptococcus pneumoniae, H.influenzae,*	Amoxicillin-clavulanate 1gm oral BD for 7	Azithromycin 500 mg OD for 5 days.	If nasal discharge headache or

	M. catarrhalis	days	Ciprofloxacin 500 mg BD for 7 days	cough persisit antibiotics are indicated.
Acute otitis media	*Streptococcus pneumoniae, H.influenzae, M. catarrhalis*	Amoxicillin clavulanate 1gm oral BD for 7 days	Azithromycin 500 mg OD for 5 days. Ciprofloxacin 500 mg BD for 7 days	Ear discharge swab may isolate colonizer
Acute bronchitis	Viral	Antibiotics not required		
Ludwig's angina Vincent's angina	Polymicrobial (Cover oral anaerobes)	Clindamycin 600 mg IV 8 hourly or Amoxicillin clavulanate 1.2 gm IV	Piperacillin tazobactam 4.5 gm IV 6 hourly	10-14 days and then can be prolonged based on response.

Note

Diphtheria may be present in rare cases but due to universal immunization is not included in differential diagnosis unless specific history, symptoms and signs are suggestive.

All these regimens need to be tailored according to susceptibility patterns at individual centers

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Editorial Board

Antimicrobial Guidelines for Urinary Tract Infections

Urinary tract infection (UTI) is one of the common community acquired infections and is seen more commonly in females.

Definition: Infections of the urinary tract caused by pathogens consistent with the clinical picture

Divide as

Anatomy - Upper UTI –Pyelonephritis

- Lower UTI – Cystitis

Clinical syndrome – Asymptomatic bacteruria

- Symptomatic bacteruria

- Pyelonephritis

CAUTI in catheterized/ hospitalized/complicated cases the management has to be done based on the specific situations (more details are discussed in section on device associated infections)

Common pathogens:

E. coli is responsible for about 80-90% of UTI in the community. This is followed by *Proteus* sp., *Klebsiella* sp., *Staphylococcus aureus*, etc. *Staphylococcus saprophyticus* causes infection in young women in many countries but this is rare in India.

In hospital acquired UTIs or in the presence of devices, *Pseudomonas aeruginosa, Acinetobacter* sp, Enterococci etc., are causative agents depending on the setting. In patients on long term catheters and antibiotic therapy, *Candida* sp is also implicated.

Investigations

Urine Specimen

- Clean catch mid stream- most common and convenient
- Suprapubic aspirate- only in cases of small children where voided urine is difficult to collect or in adults in case diagnosis is not getting confirmed by voided specimen.

Transport of specimen

Urine specimen must be transported as early as possible. For up to 4 hours delay, the urine should be refrigerated. But it is unsuitable beyond that time when 0.8% boric acid as preservative can be used to store urine for up to 24 hours if transported from distance.

Examination

- Direct Microscopy- Pus cells, RBC, Casts etc.
- Rapid- Presence of pus cells by leucocyte esterase/nitrate reduction tests.
- Culture- Semiquantitare culture for determining significant counts.

Bacterial Culture

It is the gold standard and is done by semi quantitative culture. The diagnosis is based on the presence of "significant bacterial" counts in the urine specimen. Urine is otherwise a sterile fluid in the bladder but during the passage through the urethra can get contaminated with perineal flora colonizing the lower urethra. A count of 10^5 bacteria/ml of urine in a clean catch mid stream specimen is "Significant bacteriuria" in a person with symptoms of the lower urinary tract like dysuria, frequency, suprapubic pain and hematuria.

On a urine microscopy, pus cells > 10,000/ml along with positivity for nitrite or leucocyte esterase in a symptomatic individual indicates probable UTI. In children commonly, one bacteria per oil immersion field in an uncentrifuged urine sample is considered a possible indication of a UTI. Rarely due to the inflammation red blood cells may be present and thus falsely increase the number of pus cells.

Even if urine microscopy or urine cultures are not indicative of a UTI, caution should be exercised in case of obstructive uropathy, patient on antibiotics, hematogenous route of infection, in suprapubic aspirate specimen if the patient is clearly symptomatic..

In children suprapubic aspirate may be needed due to the problem in collecting an appropriate specimen. Any count in this sample is considered significant.

Recurrent UTIs may suggest an underlying anatomic abnormality and a urological evaluation with contrast imaging may be required for delineation of the same.

Prevalent Resistance

E. coli and other members of family Enterobacteriaceae remain the most common cause of UTI, however antimicrobial resistance is very high to the commonly prescribed antibiotics in various Indian studies and the ICMR AMR network data (Table).
Most Enterobacteriaceae isolates are ESBL or extended spectrum betalactamase producing curbing the utility of 3rd and 4th generation cephalosporins and most beta lactam antibiotics. Most often we have to resort to Carbapenems.

Table 1. Antimicrobial Susceptibility of Enterobacteriaceae isolates from urinary tract. ICMR, AMRSN data 2014.

AMA	PGIMER, Chandigarh % Resistant			AIIMS, New Delhi % Resistant			JIPMER, Puducherry % Resistant			CMC, Vellore % Resistant			National % Resistant		
	Ec	Ks	Es	Ec	Ks	Es	Ec	Ks	Es	Ec	Ks	Es	Ec	Ks	Es
Amikacin	21	56	58	58	70	75	21	44	27	12	39	11	24	54	44
Cefepime	84	87	80	85	93	85	71	86	74	67	59		79	88	80
Cefoperazone-sulbactam	48	79	69				12	38	10	20	37	7	33	62	39
Cefotaxime	87	89	80	75	87	84	79	94	85	72	62	89	80	83	83
Ceftazidime	89	92	84	78	92	80	72	79	69	72	62	79	81	84	77
Ciprofloxacin	85	66	53	90	79	67	76	73	36	74	50	25	81	65	48
Colistin	1	1	0							1	0		1	1	0
Gentamicin	32	78	81	72	74	75	40	57	47	45	48	4	46	65	56
Imipenem	6	14	9	62	63	55	26	49	31	12	37	11	18	35	26
Meropenem	52	51	44	55	77	70	18	49	21	11	37	33	35	53	38
Netilmicin										12	42	18	12	42	18
Piperacillin-tazobactam	46	73	63	59	77	72	37	73	48	30	45	11	43	68	57
Tetracycline	64	42	16										64	42	16

Note : Ec : *E. coli* ; Ks : *Klebsiella* sp. : Es : *Enterobacter* sp.

Table2 : Treatment regimens for urinary tract infections

Clinical Condition	Common Pathogens	Empiric AMA	Alternate AMA	Comments
Acute Cystitis (in absence of cultures)	*E.coli, Proteus* sp *Klebsiella* sp.	●Nitrofurantoin 100 mg BD for 7 days ●Cotrimoxazole 500/125 mg BD for 3-5 days ●Ciprofloxacin 500 mg BD for 3-5 days	●Cefuroxime 250 mg BD for 3-5 days ● Cefixime 400mg BD for 5 days	*Staphylococcus saprophyticus* (in sexually active young women) but is not common in India. In pregnancy the duration of treatment is longer
Acute Pyelonephritis (individualized based on data from each center) If blood culture is positive, a carbapenem is preferred)	*E.coli, Klebsiella* sp *Proteus* sp *S. aureus*	●Piperacillin tazobactam 4.5 gm IV 6 hourly for 10 days ● Ertapenem 1 g IV OD for 7 days	●Imipenem 500 mg IV 8 hourly for 10 days or ●Inj Amikacin 5mg/kg IV once daily x 10 days	Urine and blood culture should be done before start of treatment. Amikacin 1gm OD IV or Gentamicin 7 mg/kg as prescribed doses . Close monitor on renal parameters is needed and watch out for relapse
Acute prostatitis	Enterobacteriaceae *(E. coli, Klebsiella* sp.*)*	●Doxycycline 100 mg BD for 2-3 wks ●Co-trimoxazole 960 mg BD for 2-3 wks Ciprofloxacin 500 mg BD for 2-3 wks	●Piperacillin tazobactam 4.5 gm IV 6 hourly ●Cefoperazone sulbactam 3 gm IV 12 hourly ● Ertapenem 1 gm IV OD or Imipenem 1 gm IV 8 hourly or Meropenem 1 gm IV 8 hourly	Get urine and prostatic massage cultures before antibiotics. Treatment may be needed for longer duration

All these regimens need to be tailored according to susceptibility patterns at individual centers

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