Brief Overview of Antibacterial Agents

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In choosing the appropriate antimicrobial agent for therapy for a given infection, a number of factors must be considered. Physical and chemical properties, compounding, biochemical and physiological effects, pharmacokinetics, spectrum of activity and therapeutic and other uses need to be considered to arrive at the optimal choice of antimicrobial agent.

The various antibacterial agents used in India are discussed briefly in this section.

Penicillins

The basic structure of the penicillins is a nucleus consisting of a thiazolidine ring, the β-lactam ring, and a side chain.

Mechanism of Action: The bactericidal activity of penicillin, like all β-lactam antibiotics, is due to its inhibition of bacterial cell wall synthesis.

Bactericidal activity depends upon the duration of time during which drug concentrations exceed the MIC (Time above MIC).

Classification: Penicillins can be divided into five classes on the basis of antibacterial activity: (1) natural penicillins, penicillin G and penicillin; (2) penicillinase-resistant penicillins, methicillin, nafcillin, and isoxazolyl penicillins; (3) aminopenicillins, ampicillin and amoxicillin; (4) carboxypenicillins, carbenicillin and ticarcillin; and (5) acyl ureidopenicillins, azlocillin, mezlocillin, and piperacillin. The carboxypenicillins and ureidopenicillins are also referred to as antipseudomonal penicillins.

Antimicrobial Activity: The natural penicillins are most active against non-β-lactamase–producing gram-positive bacteria, anaerobes, and selected gram-negative cocci, such as Neisseria.

Semisynthetic penicillinase resistant penicillins are the drugs of choice only for penicillinase resistant Staphylococcus aureus and Staphylococcus epidermidis, although they are also active against streptococci including S. pneumoniae but lack activity against methicillin-resistant staphylococci (MRSA), high level penicillin-resistant streptococci, Enterococcus Spp., Listeria monocytogenes and gram-negative cocci or bacilli.

Aminopenicillins possess the same spectrum as penicillin G, plus they are active against enterococci, gram-negative cocci and Enterobacteriaceae that do not produce β-lactamase.

Aminopenicillins lack activity against Klebsiella spp., Serratia, Acinetobacter, indole-positive Proteus, Pseudomonas spp., Shigella and strains of Bacteroides fragilis.

Carboxypenicillins and ureidopenicillins have activity against gram-negative aerobic rods, such as P. aeruginosa, which are resistant to ampicillin.

Anaerobic bacteria are susceptible to most penicillins (with the exception of isolates of Bacteroides fragilis, other Bacteroides spp., and some Prevotella spp., which produce chromosomal class A β-lactamase).

Clinical Use: Penicillin G remains the primary agent for treatment of infections due to Streptococcus pyogenes, penicillin-

susceptible strains of Streptococcus pneumoniae, and enterococci. For S. pneumoniae, Penicillin, ampicillin, and amoxicillin are the most active compounds, with MICs rarely exceeding 4 μg/mL.

Aminopenicillins are indicated for treatment of upper respiratory tract infections, lower respiratory tract infections, bacterial gastroenteritis (ampicillin only), bacterial endocarditis, meningitis, urinary tract infections caused by susceptible (i.e., non–β-lactamase–producing) organisms and treatment of ulcers and gastric infections caused by Helicobacter pylori.

β-lactam and β-lactamase Inhibitor Combinations

These are clavulanic acid and penicillinic acid sulfone derivative with mild antibacterial activity. These are potential inhibitors of Class A β-lactamases. The β-lactamase inhibitors do not inhibit Class C β-lactamases, Class D β-lactamases and Class B metallo-β-lactamases. Clavulanic acid, sulbactam, and tazobactam are the three β-lactamase inhibitors. Sulbactam also has modest activity in vitro against strains of A. baumannii.

Cephalosporins

The basic structure includes a β-lactam ring fused to a six-member sulphur-containing dihydrothiazine ring.

Classification of Parenteral and Oral Cephalosporins

1. First-generation: Parenteral - Cefazolin, Cephalothin, Cephalpirin, and Cephradine
   Oral - Cefadroxil, Cefalexin, and Cefadroxil

2. Second-generation: Parenteral- Cefamandole, Cefonicid and Cephalothin
   Oral - Cefadroxil, Cefprozil, Cefuroxime, and Loracarbef

3. Cephapirin: Cefoxitin, Cefmetazole, and Cefotetan

4. Third-generation: Parenteral- Cefoperazone, Cefotaxime, Ceftriaxone, and Moxalactam
   Oral- Cefixime, Cefdinir, Cefditoren, Cefpodoxime and Cefotuben

5. Fourth-generation: Cefepime, and Cefpirome

6. MRSA- Active: Ceftaroline, and Ceftobiprole ( not yet available in India)

The third- and fourth-generation drugs combined are also called the extended-spectrum cephalosporins.

Mechanism of Action: Bactericidal activity is due to inhibition of the cell wall synthesis, primary target being the peptidoglycan cross linkage structure. Time above MIC (T>MIC) is the major determinant of the antibacterial activity.

Spectrum of Activity: The first-generation cephalosporins exhibit activity focused primarily on gram-positive bacteria. They also have poor activity against B. Fragilis. The second-generation drugs have enhanced activity against gram-negative bacilli but maintain varying degrees of activity against gram-positive cocci. The cephamycin group is included in the second-generation classification. Cephamycins are noted for their additional activity against gram-negative anaerobic bacteria, such as Bacteroides spp. The third-generation group

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has markedly increased potency against gram-negative bacilli. Ceftazidime, cefoperazone and moxalactam have activity against *P. aeruginosa*. The third- and fourth-generation cephalosporins also exhibit enhanced potency against strains of *Salmonella*, *Shigella*, and *spirochetes*. However, for some compounds in the third-generation class (like ceftazidime), activity against gram-positive cocci is reduced. The fourth generation has the widest spectrum of activity of the five groups. These drugs, such as cefepime and cefpirome, have activity against most gram-negative bacilli including *P. aeruginosa* and maintain their potency against gram-positive cocci. Most cephalosporins are active against streptococci and staphylococci. Ceftriaxone and ceftobiprole have the greatest potency against this organism, followed by cefditoren, ceftriaxone, cefotaxime, cefepime, and cefpirome.

Many cephalosporins are active against penicillin-susceptible gram-positive anaerobes, such as peptostreptococci. Against *B. fragilis*, drugs such as the cephemycins, cefotaxime, ceftriaxone, and cefotaxime have the best activity.

No Activity Against: As a group, the cephalosporins have very poor activity against *Enteroocci*, *Chlamydia*, *Mycoplasma*, *Listeria* species.

Pharmacologic Properties: Cephalosporins have relatively poor intracellular concentrations. Clinical Uses:

First-Generation Cephalosporins are extensively used as alternatives to penicillin for staphylococcal and nonenterococcal streptococcal infections, most commonly for skin and soft tissue infections and surgical prophylaxis.

Second-Generation Cephalosporins are used extensively for the treatment of respiratory tract infections and surgical prophylaxis.

Cefotaxime and ceftriaxone are two of the most potent cephalosporins against penicillin-resistant pneumococci, *H. influenzae*, *N. meningitides*, *salmonella* and various Enterobacteriaceae.

Ceftazidime is useful for serious infections with *P. aeruginosa* as in febrile neutropenia and meningitis.

### Carbapenems

Four carbapenems—ertapenem, doripenem, imipenem, and meropenem—are approved for clinical use.

Mechanism of Action: Carbapenems are bactericidal. They bind with high affinity to penicillin-binding proteins (PBPs) of gram-positive and gram-negative bacteria and inhibit cell wall synthesis.

Pharmacokinetics and Pharmacodynamics: The bactericidal activity depends on T>MIC. It should be >30% of the dosing interval and can be achieved by giving prolonged infusions of 3 hours for carbapenems in saline.

Antibacterial Activity: Carbapenems are similar in their antibacterial spectra—good gram-positive, gram-negative and anaerobic coverage. Doripenem is the most active carbapenem against *P. aeruginosa*.

Among carbapenems, only imipenem has activity against *Enterococcus faecalis* (Imipenem is bacteriostatic for enterococci).

*Nocardia spp.*, *Actinomyces*, *B. anthracis* and *Mycobacterium* spp. are inhibited by meropenem or imipenem.

No activity against: Carbapenems lack activity against MRSA, *enterococci*, *S. maltophilia*, *Burkholderia cepacia* and *C. difficile*.

Among carbapenems, Ertapenem is not active against *P. aeruginosa* and *Acinetobacter*.

### Aminoglycosides

Mechanism of Action: Aminoglycosides are concentration-dependent bactericidal agents, have a post-antibiotic effect (PAE) and synergism with other drugs.

Aminoglycoside antibiotics inhibit protein synthesis by binding to the 30S subunit of prokaryotic ribosomes.

Antimicrobial Activity: These are active against aerobic and facultative gram-negative bacilli (*Enterobacteriaceae to Pseudomonas* spp. and *Acinetobacter* spp.) and aerobic gram-positive bacteria.

No Activity Against: these agents lack activity against *S. maltophilia*, *B. cepacia*, *enterococci*, and most streptococci, including *S. pneumoniae* and all anaerobes are resistant.

Toxicity includes nephrotoxicity, damage to the cochlea or vestibular apparatus or both, and neuromuscular blockade.

### Clinical use

The aminoglycosides (gentamicin, tobramycin, amikacin) are effective in the empirical treatment of infections due to aerobic gram-negative bacilli, including *P. aeruginosa*. It is useful for *Enterococcal* endocarditis along with cell wall–active drug, such as ampicillin or vancomycin.

Specific therapy when the patient is stabilized, the disease process is better understood, and the results of cultures performed on admission are available.

### Tetracyclines

**Tetracyclines** are a class of broad-spectrum bacteriostatic antibiotics active against gram-positive and gram-negative bacteria as well as against intracellular organisms such as *Legionella*, *Chlamydia*, *Mycoplasma*, *Rickettsiae*, and protozoan parasites (*Plasmodium* spp and *Entamoeba hystolytica* spp). Tigecycline, a glycyclcline, is a minocycline derivative and is bactericidal in nature.

This class includes short acting—oxytetracycline, tetracycline HCl, intermediate acting demclocycline HCl, long acting—doxycycline, minocycline and long acting, third generation tigecycline.

Mechanism of action: Tetracyclines inhibit bacterial protein synthesis by binding the 30S ribosomal subunit.

Tetracyclines also inhibit mitochondrial protein synthesis by binding the 70S ribosome subunits in mitochondria, which has been cited to help explain the efficacy of tetracyclines in eukaryotic parasites (like *Plasmodium* spp.). Doxycycline also acts against the *Wolbachia* endosymbionts present in most human filariae and exhibits a filaricidal activity.

Pharmacokinetics and Pharmacodynamics: For tetracyclines, including tigecycline, the area under the curve (AUC/MIC) ratio represents the best parameter of antimicrobial efficacy over 24-hour period. Furthermore, tigecycline exhibits postantibiotic effect for *S. aureus*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *E. coli*.

Spectrum of activity: All the tetracyclines, with the exception of tigecycline, are almost identical. Tigecycline has broad gram positive, gram negative and anaerobic coverage. It is active against multi drug resistant pathogens resistant to older tetracyclines like *methicillin* resistant *Staphylococcus aureus* (MRSA), *Vancomycin* resistant *enterococci* (VRE), resistant
**Macrolides**

Macrolide antibiotics are bacteriostatic in nature.

**Mechanism of Action:** The lincosamide antibiotics have the same or overlapping 50S ribosomal binding sites as those for the macrolides and chloramphenicol, and they may compete with these drugs for binding.

**Clinical Use:** Azithromycin is useful for acute otitis media, community-acquired pneumonia, uncomplicated enteric fever, acute nongonococcal urethritis and *M. avium* complex infections in patients with AIDS

**Lincomycin and Clindamycin**

Mechanism of Action: The lincosamide antibiotics have the same or overlapping 50S ribosomal binding sites as those for the macrolides and chloramphenicol, and they may compete with these drugs for binding.

Bacteriostatic efficacy is time dependent with moderate postantibiotic effect. AUC/MIC ratio is the most important parameter.

**Antimicrobial Activity:** Clindamycin is more potent than lincomycin but similar in potency to erythromycin against *staphylococci*, *pyogenes*, and streptococci of the viridans group when strains are sensitive to both. Clindamycin has been one of the most active antibiotics available against *B. Fragilis*. It is also effective against susceptible community-acquired methicillin-resistant *S. aureus*.

Clindamycin has activity against *T. gondii*, *P. jirovecii* and *P. falciparum*.

**Quinolones**

A bactericidal broad spectrum activity, good oral absorption, and generally good overall tolerability has resulted in extensive clinical use of the newer fluoroquinolones.

Mechanism of Action: The quinolones rapidly inhibit bacterial DNA synthesis by inhibiting the activities of two enzymes-DNA gyrase and DNA topoisomerase IV.

**Pharmacokinetic and Pharmacodynamic Parameter:** Bactericidal activity of quinolones is determined by concentration dependent kinetics and postantibiotic effect (PAE) of 1-2 hours.

Quinolones have high volume of distribution.

Antimicrobial Activity: Current quinolones are most active against aerobic gram-negative bacilli, particularly members of the family *Enterobacteriaceae*, *M. catarrhalis*, *Haemophilus* and against gram-negative cocci such as *Neisseria* species. Ciprofloxacin and levofloxacin are the only available quinolones with sufficient potency against *P. aeruginosa*.

Among quinolones, levofloxacin, gatifloxacan, moxifloxacin, and gemifloxacin have potency against *S. pneumoniae*.

All quinolones have activity against the agents of atypical pneumonias, and against genital pathogens such as *C. trachomatis*, *U. urealyticum*, and *M. hominis*.

Among quinolones, gatifloxacin, moxifloxacin, and sitafloxacin have activity against anaerobes.

Ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin are active against *M. tuberculosis*, *M. fortuitum*, *M. kansasi*, and some strains of *M. chelonae* but have poor activity against *M. avium-intracellulare*.

No Activity Against: For norfloxacin, ciprofloxacin, and ofloxacin, activity against *streptococci* and many *anaerobes* is limited.

**Glycopeptides (Vancomycin and Teicoplanin) and Lipopeptides (Daptomycin)**

**Vancomycin**

Structure and Mechanism of Action; Vancomycin is a bactericidal tricyclic glycopeptide which inhibits cell wall synthesis in dividing bacteria. The target of glycopeptides are peptidoglycan precursors composed of two amino sugars, *N*-acytelymuramic acid and *N*-acytelyglucosamine, with a D-alanyl-D-alanine terminating pentapeptide.
Spectrum of Activity: Vancomycin has broad activity against gram-positive microorganisms and are susceptible to vancomycin with minimal inhibitory concentrations (MIC) less than or equal to 2 μg/mL and minimal bactericidal concentrations (MBC) within twofold of the MIC. Glycopeptides remain active against most Enterococcus faecalis and a variable percent of Enterococcus faecium, but are not bactericidal even against susceptible isolates. All strains of Streptococci and almost all gram-positive anaerobes are susceptible to vancomycin.

No Activity Against: Vancomycin lacks in vitro activity against gram-negative organisms, except for some nongonococcal Neisseria spp.

Pharmacodynamics and Pharmacokinetics: It has concentration-independent activity against S. aureus, the primary predictive pharmacodynamic parameter for efficacy is AUC/MIC >400. To achieve this target, larger vancomycin doses (loading dose of 25–30 mg/kg followed by 15–20 mg/kg every 8–12 h) is given to attain a recommended trough serum concentrations of 15–20 μg/mL for most patients if the MIC is < 1 μg/mL.

S. aureus exposure to trough serum concentrations of < 10 μg/mL can produce strains VISA-like characteristics.

Vancomycin trough levels should be done before the fourth dose of vancomycin.

Dosing in Renal Insufficiency: Because vancomycin is not removed by haemodialysis and the serum half-life of vancomycin in anephric patients is 7.5 days, the recommended dose of vancomycin in these patients has been 15 mg/kg every 7 to 10 days. However, if high-flux membranes are used, a significant reduction of vancomycin serum levels might occur.

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

Adverse Reactions: Infusion-related reactions are the most common side effects (3.4% to 11.2%), “red man syndrome,” have been reported. Nephrotoxicity (0-12%) which is associated with vancomycin trough levels greater than or equal to 15 μg/mL, in those receiving high dose vancomycin (greater or equal to 4 gm/day), concomitant use of nephrotoxic agents, and duration of vancomycin therapy.

Clinical Uses: Useful for skin and soft-tissue infections, bacteremia and endocarditis, meningitis, ventriculitis, pneumonia, osteomyelitis, pseudomembranous colitis, febrile neutropenia, and antibiotic lock therapy etc.

Teicoplanin

Its mechanism of action and spectrum of activity is similar to that described for vancomycin, although some differences, mostly quantitative, exist. Teicoplanin can be administered by intravenous bolus or by the intramuscular route. The most common side effects are maculopapular rash (7%) and drug-related fever (6%). Thrombocytopenia, neutropenia and eosinophilia appear to be more frequent at higher doses (more than 12 mg/kg/day).

Higher doses of teicoplanin, sometimes more than 12 mg/kg/day, appear to be needed in patients with staphylococcal arthritis.

Lipopeptides

Daptomycin

Daptomycin (Cubicin; Cubist Pharmaceuticals) is a cyclic lipopeptide antibiotic. One vial has 350 mg.

Mechanism of Action, Antimicrobial Activity, and Resistance: Daptomycin exhibits rapid concentration-dependent bactericidal activity. Hence, given as intravenous infusion over 30 min.

Active against most gram-positive pathogens, including isolates resistant to methicillin, vancomycin, and linezolid including Staphylococci, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae subsp. equisimilis, and vancomycin-susceptible Enterococcus faecalis.

Its plasma protein binding is 92% and mean elimination half life is 8.1 hours.

Mechanism of Action: Antibacterial activity involves binding to bacterial membranes and rapid depolarization of membrane potential; the resultant inhibition of protein, DNA, and RNA synthesis results in bacterial cell death. Hence, cross-resistance with other antimicrobial classes has not been reported. The activity of daptomycin is dependent on the presence of calcium ions; it is two- to four fold more active when tested in 50 mg/liter of calcium (similar to the normal human serum concentration of ionized calcium).

The breakpoint susceptibility for staphylococci and streptococci is equal to or less than 1 μg/mL where as breakpoint susceptibility is equal to or less than 4 μg/mL for E. faecalis.

Clinical Pharmacodynamics, Pharmacokinetics, and Uses: Its efficacy is best correlated with the peak/MIC ratio and the 24-hour-AUC/MIC ratio. Daptomycin appears to have moderate postantibiotic effect (mean 2.5 and 1.7 hours) against staphylococci and pneumococci, respectively.

The drug is not compatible with the dextrose containing solutions. In patients with creatinine clearance < 30 ml/hr, receiving haemodialysis or CAPD, daptomycin is recommended every 48 hrs.

Adverse effect: Myopathy (2.9 %). Hence, CPK levels to be done after 7 days. Statins should be avoided with daptomycin.

Clinical uses: It is useful for bacteremia, right sided endocarditis, staphylococcal osteoarticular infections, and enterococcal infections. It can be used for haematogenous lung abscess but not for S. aureus bronchopneumonia as it is degraded by surfactant.

Linezolid and Oxazolidinones

Mechanism of Action: These agents bind to the 50S ribosome at its interface with the 30S unit, thereby preventing the formation of the 70S initiation complex, inhibit protein synthesis and are bacteriostatic against most bacteria.

Antimicrobial Activity: of linezolid is consistent against the majority of clinically important gram-positive organisms including Nocardia and Mycobacterium tuberculosis.

No activity against: These agents lack activity against gram-negative organisms. Pharmacokinetic/pharmacodynamic parameter: Best predictive of efficacy are the time above MIC (T > MIC exceeding 85%) and the ratio of the area under the serum concentration-time curve (AUC) to the MIC (AUC/MIC between 80 and 120).

Adverse Effects: This includes reversible bone marrow suppression (thrombocytopenia- 47 % in patients receiving
linezolid for > 10 days), neurotoxicity, optic neuritis (permanent), lactic acidosis, headache, and hypertension. It can cause serotonin syndrome in patients receiving concurrent serotonergic agents.

Clinical Use: Linezolid has been shown to be as effective as intravenous oxacillin in patients with complicated skin and soft tissue infections including susceptible strains of staphylococci and streptococci. In infections with MRSA, linezolid was shown to be comparable to vancomycin for therapy of skin and soft tissue infections, pneumonia, and urinary tract infections with or without bacteremia. It is also effective for Infections caused by VRE, *S. pneumoniae*, non-tubercular mycobacteria and nocardiosis.

**Polymyxin and Colistin**

Polymyxins are cyclic cationic polypeptide detergents. The two parenteral polymyxins that have been used are polymyxin B and polymyxin E (colistin). Colistin is available in two preparations—colistin sulphate, which can be used topically or orally and colistimethate sodium (the usual formulation) for use in intramuscular, intravenous or the nebulised form.

Colistimethate sodium is less active and less nephrotoxic in vitro than polymyxin B. Colistimethate sodium must be hydrolyzed to be active as an antibiotic.

Mechanism of action: They penetrate into cell membranes, interact with phospholipids in the membranes, and quickly disrupt the membranes. They also bind to the lipid A portion of and block many of the biologic effects of endotoxin.

Pharmacokinetics and Pharmacodynamics: Polymyxins are bactericidal in a concentration-dependent manner and have a post-antibiotic effect (PAE). PAE is for *Pseudomonas* and not *Acinetobacter* spp. The half-life of polymyxin B in serum is about 4.5 - 6 hours and that of colistimethate is about 3 hours. Half-lives are much longer in patients with renal insufficiency.

Antimicrobial Activity is against a broad array of gram-negative aerobic bacilli.

No activity against: Among gram-negative bacilli, *Proteus* spp is most resistant, and also have poor activity against *Providencia, Serratia, M. Morganii, Burkholderia, and Salmonella*. Gram-positive organisms and anaerobes are resistant to colistin.

Toxicity: There is dose-related nephrotoxicity and also dose-related reversible neurotoxicity. Hypersensitivity is unusual.

Clinical use: Colistimethate has been used via parenteral, inhalational and intraventricular route to treat systemic infections caused by multi-drug resistant (MDR) gram-negative bacilli. Colistin sulfate has been used orally for intestinal decontamination.

**Recommended Reading**