Chapter

Bactericidal and Bacteriostatic Antibiotics

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Abstract

Of all the medications available to physicians worldwide, antibiotics play an essential role in inpatient and outpatient settings. Discovered in the early nineteenth century by Alexander Fleming, penicillin was the first antibiotic isolated from a mold. Dr. Gerhard Domagk developed synthetic sulfa drugs by altering the red dye used in chemical industries. Since then, multiple antibiotic classes have been discovered with varying antimicrobial effects enabling their use empirically or in specific clinical scenarios. Antibiotics with different mechanisms of action could be either bactericidal or bacteriostatic. However, no clinical significance has been observed between cidal and static antibiotics in multiple trials. Their presence has led to safer deep invasive surgeries, advanced chemotherapy in cancer, and organ transplantation. Indiscriminate usage of antibiotics has resulted in severe hospital-acquired infections, including nosocomial pneumonia, *Clostridioides difficile* infection, multidrug-resistant invasive bacterial infections, allergic reactions, and other significant side effects. Antibiotic stewardship is an essential process in the modern era to advocate judicial use of antibiotics for an appropriate duration. They play a vital role in medical and surgical intensive care units to address the various complications seen in these patients. Antibiotics are crucial in severe acute infections to improve overall mortality and morbidity.

Keywords: Sepsis, antibiotics, bactericidal, bacteriostatic, stewardship

1. Introduction

Antibiotic is a term used to define a chemical substance produced by one microorganism that stunts the metabolism and development of other organisms [1]. The antibiotic term was used initially for naturally acquired substances; however, now the term encompasses both natural and synthetic antimicrobial substances. Although penicillin was the first antibiotic isolated from the mold, it was superseded by sulfa drugs used by physicians to treat infections successfully [2]. Due to antibiotic use, the infectious disease death rate has declined from 280 per 100,000 to 60 per 100,000 in the 1950s [3]. A common belief is that cidal antibiotics are efficient than static antibiotics with no clinical evidence supporting it. Both cidal and static are invitro terms which, refer to the effect of antibiotic concentrations affecting bacterial growth at a predefined threshold. They cannot predict the infection outcome in vivo. Antibiotics targeting the organism's cell wall are mostly bactericidal, whereas those targeting protein syntheses are bacteriostatic. MIC (minimum inhibitory concentration) is the lowest antibiotic concentration, which

prevents visible growth at 24 hours. MBC (minimum bactericidal concentration) is the minimal concentration of antibiotics that causes bacterial death. Breakpoints for antibiotic MIC's are set by the the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and National Committee for Clinical and Laboratory Standards Institute (CLSI). A bactericidal antibiotic MBC is less than or equal to four folds above the MIC, accounting for a 1000-fold decline in bacterial density [4]. A bacteriostatic antibiotic achieves a > 1000-fold reduction at eight-fold above MIC or a 500-fold reduction in bacterial density at 4-fold above its MIC. They are still labeled as static despite the clear demonstration of bacterial killing. An antibiotic becomes more bactericidal as the MIC moves closer to the MBC. Bacteriostatic agents have an MBC to MIC ratio > than that for bactericidal antibiotics.

A systematic literature review revealed no confirmation that cidal agents are better than static agents [5]. In addition, there was no substantial difference in efficiency, including critically ill patients with severe infections and sepsis. Six trials demonstrated the superiority of static agent linezolid over cidal agents such as vancomycin [5]. A single trial showed the efficiency of cidal agent imipenem over tigecycline; however, the dose of tigecycline was small, and with increased appropriate dosing, the efficacy disappeared [6, 7]. A rapidly bactericidal agent such as daptomycin does not perform better than a slowly cidal agent such as vancomycin to treat right-sided infective endocarditis (IE) and staphylococcal bacteremia [8] . A synergistic combination of beta-lactam with aminoglycosides enhances the bactericidal effect with rapid blood clearance [9]. However, this synergistic combination has not improved clinical outcomes or mortality [10]. In the initial studies, static agents such as tetracyclines and macrolides were inferior to cidal agents in IE therapy [11]. This assumption can be erroneous as the static agents do not achieve adequate low blood concentrations to treat infective endocarditis effectively. A bacteriostatic antibiotic such as linezolid can attain sufficient bloodstream concentrations resulting in higher cure rates for IE [12]. Daptomycin, a rapidly bactericidal agent, is inferior to vancomycin in left-sided IE [13]. For an individual antibiotic to be effective, the importance of its pharmacokinetic-pharmacodynamic properties and attaining adequate drug levels at the infection site is substantial than static versus cidal properties used in predicting clinical efficacy. An intact immune system is critical for the efficacy of bacteriostatic agents, and bactericidal agents are preferred in immunosuppressed patients. Broad-spectrum agents cover many susceptible pathogens, whereas narrow-spectrum agents cover a limited number of pathogens. Broad-spectrum agents are used empirically in the therapy of lung and abdominal infections. Narrow-spectrum agents are used in a limited number of indications.

2. Bacteriostatic antibiotics

These include folate inhibitors (sulfonamides and trimethoprim) in **Table 1** (2A I), tetracyclines in **Table 2** (2A II), glycylcyclines in **Table 3** (2A III), macrolides in **Table 4** (2A IV), lincosamides in **Table 5** (2A V), oxazolidinones in **Table 6** (2A VI) and fusidic acid in **Table 7** (2A VII).

Dapsone can substitute sulfamethoxazole in the TMP-SMX combination for PCJ pneumonia in patients with allergies to sulfonamide antibiotics [89]. TMP-SMX is the drug of choice for Q-fever in pregnancy. An essential fact to remember is that TMP-SMX does not cover *pseudomonas* and should be avoided in streptococcal infections due to a higher incidence of resistance [90]. Iclaprim is a DHFR inhibitor with bactericidal activity against *methicillin-sensitive Staphylococcus aureus* (MSSA), *Methicillin-resistant* (MRSA), *beta-hemolytic Streptococcal spp,* and *Enterococcus*

Origin	Sulfonamides are sulfanilamide derivatives identical to para-aminobenzoic acid (PABA) required for folic acid synthesis in most bacteria. Trimethoprim is a synthetic derivative from trimethoxybenzyl-pyrimidine [14].
Mechanism of action	Sulfonamides antagonize PABA inclusion into dihydropteroate by its greater affinity for tetrahydropteroic acid synthetase in microorganisms resulting in decreased dihydrofolic acid, a substrate for dihydrofolate reductase (DHFR) [15, 16]. Trimethoprim is a potent bacterial inhibitor of DFR, preventing the formation of tetrahyrofolic acid needed for purine and deoxyribonucleic acid [14]. Thus, sulfonamides and trimethoprim together stop two consecutive steps essential in the folic acid synthesis. A combination of both is synergistic and bactericidal in trimethoprim and the sulfa ratio of 1:20 [17].
Routes	Sulfonamides are available in oral, intravenous (IV), topical, and ophthalmic formulations. Trimethoprim is available in oral and intravenous formulations.
Indication	Sulfonamides: Nocardiosis, Toxoplasmosis, Plasmodium falciparum malaria, Nongonococcal urethritis, Trimethoprim: Acute urinary tract infection (UTI), Recurrent UTI Trimethoprim and sulfamethoxazole (TMP-SMX): Above indications plus UTI, Skin and soft tissue infections (SSTI) due to *Staphylococcus aureus, Pneumocystis jiroveci* (PCJ) pneumonia, and prophylaxis, Melioidosis, Whipple disease, Alternative in Listeria meningitis
Resistance	Sulfonamides: Point mutations in folP gene modifying dihydropteroate synthetase resulting in decreased affinity for sulfonamide [18]. PABA binding site alteration due to F28L/T and P64S mutations [19]. Integrons sul1, sul2, and sul3 coding drug resistance enzymes [20]. Trimethoprim: Plasmid-mediated resistant DHFR enzyme
Pharmaco-kinetics	Sulfonamides: Well distributed throughout the body, and protein binding predicts the blood and tissue levels. It is metabolized in the liver (CYP2C9 & CYP3A4 hepatic enzyme system) and excreted via renal excretion. Chronic kidney disease results in decreased renal clearance [21]. It can interact with multiple other drugs resulting in increased serum levels and toxicity especially antiseizure medications.
Toxicity	Skin: Rashes, Steven-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN) [22, 23]. Blood: Anemia, agranulocytosis, thrombocytopenia, methemoglobinemia [24]. Renal: Hyperkalemia, Acute renal failure, Interstitial nephritis, Lactic acidosis [24–26]. Gastrointestinal (GI): Pseudomembranous colitis, Pancreatitis, and Fulminant liver failure [27–29]. Others: aseptic meningitis

Table 1.
2AI folate inhibitors: Sulfonamides & trimethoprim.

faecalis. It undergoes hepatic clearance, and dose adjustment is needed in hepatic impairment. Tissue penetration is excellent in the lungs. It is effective without a sulfa moiety so that it can be used in patients with sulfa allergy. The side effects include nausea, headache, fatigue, and QT interval prolongation. Currently, it is under trials for SSTI and nosocomial pneumonia [91, 92].

Doxycycline is the drug of choice in bioterrorism caused by *Bacillus anthracis*, *Yersinia pestis*, *Francisella tularensis*, *Coxiella burnetti*, and *Brucella spp* [93]. In the medical intensive care unit (MICU), tetracyclines are the drug of choice in acute sepsis due to cholera, ehrlichiosis, *stenotrophomonas* infections, rickettsial disease, anaplasmosis, and PID.

In sepsis, tigecycline is used in MDR infections as a last resort, and the federal drug authority (FDA) has placed a boxed warning about this death risk. It can also be used effectively at a higher dosage in MDR hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

Origin	Tetracycline is derived from catalytic dehalogenation of chlortetracycline obtained from *Streptomyces rimosus* [30]. Doxycycline and Minocycline are semisynthetic derivatives of oxytetracycline.
Mechanism of action	Reversibly binds 30S ribosomal subunit of the bacteria and inhibits protein synthesis. In protozoa, it additionally binds to 70S ribosome and stops protein synthesis [30, 31].
Routes	Orally via capsules, tablets, syrups, and IV formulations.
Indication	Community-acquired bacterial pneumonia (CABP), MSSA &MRSA SSTI, Stenotrophomonas infections, *Helicobacter pylori* infection, Nongonococcal urethritis, Lyme disease, Rickettsial infections, Nocardiosis, Falciparum malaria, Cholera, Anaplasmosis, and Ehrlichiosis. Q fever, Brucellosis, Melioidosis, Acne vulgarism, the second line in syphilis, and a part of the combination regimen in pelvic inflammatory disease (PID).
Resistance	It is mediated mainly by active efflux pumps and ribosomal protection proteins. Other minor mechanisms include antibiotic enzymatic lysis, a decline in-wall permeability, and binding site alterations [32].
Pharmac-okinetics	Unlike tetracycline, food does not substantially alter doxycycline and minocycline absorption, and both have excellent bioavailability [33]. Lipid solubility determines the tissue and fluid levels of which minocycline > doxycycline > tetracycline. At higher doses, doxycycline reaches adequate levels in the cerebrospinal fluid (CSF) [34]. The clearance mechanism is via both renal (tetracycline) and hepatic (doxycycline and minocycline).
Toxicity/ Adverse effects	GI: pill-induced esophagitis, heartburn, epigastric pain, nausea, vomiting, acid reflux disorder [35]. Hepatotoxicity from IV tetracycline [36]. Skin: photosensitive rash and hyperpigmentation of body parts [37]. Nephrogenic diabetes insipidus: by demeclocycline [38]. Central Nervous System(CNS): Vestibular symptoms, Pseudotumor cerebri Teeth, and Bone: tooth staining, enamel hypoplasia, and diminished bone growth in premature infants exposed to tetracycline [39]. Hypersensitivity reactions: facial swelling, drug-induced lupus, anaphylaxis, urticaria [40]. Tetracyclines are teratogenic and reach the fetus via the placenta.

Table 2.
2A II tetracyclines.

Origin	Tigecycline is a semisynthetic derivative of minocycline developed against resistant organisms [41].
Mechanism of action	Its reversal binding to 30S ribosomes is stronger by five times, and ribosomal protection proteins do not affect it [42, 43].
Routes	Due to poor oral absorption, it is available in IV formulations.
Indication	Complicated SSTI, Complicated intraabdominal infections (cIAIs), CABP, Used as salvage therapy in critically ill patients when no other alternatives exist for multidrug-resistant infections (MDR).
Resistance	It is due to increased efflux pumps such as AcrAB and MexAB-OprM after detecting the drug [44]. *Pseudomona*s is intrinsically resistant due to MexXY efflux pump presence [45].
Pharmac-okinetics	Adequate tissue distribution was observed with a half-life of 37 to 67 hours and a plasma protein binding of about 80% [46]. No dose adjustment is required in renal impairment and mild to moderate hepatic impairment. Dose adjustment is needed for severe hepatic impairment. It is not removed by hemodialysis [47]. It is excreted by the liver and minimally by the kidney.
Toxicity/Adverse effects	GI: nausea, vomiting, transaminase elevation, acute pancreatitis. Others: infection, phlebitis, headache, dizziness, skin rash [47]. It is associated with increased mortality compared to other antibiotics used for the same indication. 13 clinical trials have validated this pooled analysis [48].

Table 3.
2A III glycylcyclines.

Origin	Erythromycin was obtained from *Streptomyces erythreus* present in the soil. Azithromycin and Clarithromycin are semisynthetic derivatives from erythromycin, which improve stability in gastric acid [49].
Mechanism of action	Macrolides bind to 23S ribosomal ribonucleic acid (rRNA), a subunit of the 50S subunit of the bacterial ribosome, and stop the RNA-based synthesis of proteins [50]. Bactericidal activity is seen against , *Hemophilus influenzae,* and *Streptococcus pneumoniae*.
Routes	It is available as oral liquid, tablet, capsule, IV, ophthalmic and topical preparations.
Indication	Erythromycin: used as an alternative to penicillin (PCN) in allergic patients. Treatment and preexposure prophylaxis in pertussis. Azithromycin: CABP, Pertussis, Trachoma, Chancroid, Babesiosis, *Mycobacterium avium complex* (MAC) infections, alternative for Lyme disease, sinusitis, pharyngitis, and acute otitis media. Clarithromycin: *Helicobacter pylori* infection, Nontubercular mycobacterial infection, *Campylobacter* enteritis, *MAC* infections
Resistance	50S ribosomal protein mutations or 23S rRNA receptor alterations confer resistance to macrolides (M), lincosamides (L), and streptogramin B (SB) (MLSB phenotype). *Erm* (erythromycin ribosome methylation) genes present on transposons or plasmids mediate this effect [51, 52].
Pharmac-okinetics	Erythromycin is metabolized by hepatic CYP3A cytochrome subclass of cytochrome 450 system. It is incompatible with other IV preparations [53, 54]. It follows total body water distribution [55] and persists in tissues longer than in blood. Oral azithromycin bioavailability is around 37% [56]. It is well distributed in tissues with levels > than in blood by 10 to 100 fold. It is excreted primarily unchanged via hepatic clearance into the feces. No dose adjustments are required for renal and hepatic impairment. Clarithromycin oral bioavailability is 55%, has excellent tissue distribution, and undergoes mainly hepatic clearance with 30% clearance vis the kidneys [50]. Dose adjustment is needed for renal failure only [57].
Toxicity/Adverse effects	Erythromycin: GI side effects (nausea, vomiting, and abdominal pain), Thrombophlebitis, Allergic reactions, Ototoxicity, Torsades de pointes. Clarithromycin and Azithromycin: GI side effects as above, Acute mania, Torsades de pointes, reversible cholestatic hepatitis [58–60].

Table 4.
2A IV macrolides.

Origin	Lincomycin is derived from *Streptomyces lincolnensis* present in the soil. Clindamycin is semisynthetically by chemically modifying lincomycin resulting in increased potency and bioavailability [61].
Mechanism of action	It binds to 50S ribosomal sites and inhibits protein synthesis, and competes with macrolides for the same site.
Routes	Available in IV, oral capsules and liquid solution, topical gel, foam or solution, and vaginal cream or suppository.
Indication	Gram-positive or anaerobic SSTI, acne vulgaris, part of the combination regimen against toxoplasmosis, falciparum malaria, and *Pneumocystis jiroveci* pneumonia.
Resistance	MLSB phenotype regulated by the ermA or ermC genes [62]. rRNA mutations, including the receptor site, 23S rRNA nucleotide methylation, and adenylation of clindamycin [51, 63–65].
Pharmac-okinetics	90% oral bioavailability with good tissue levels except in CSF [61, 66]. It is metabolized by the liver, and excretion occurs via feces and urine [67]. Dosing adjustment is needed in severe renal and hepatic impairment
Toxicity/Adverse effects	Cutaneous drug reactions in patients with (human leukocyte antigen)HLA-B*51:01 genotype including maculopapular eruptions, erythema multiforme, urticaria, drug rash with eosinophilia, and systemic symptoms (DRESS), SJS, TEN [68]. GI: diarrhea, pseudomembranous colitis by *Clostridioides difficile,* reversible transaminitis [69]. Others: agranulocytosis, thrombocytopenia, and neutropenia which are transient.

Table 5.
2A V lincosamides.

Two other newer tetracycline derivatives have been released Eravacycline, a fluorocycline, and Omadacycline, an aminomethylcycline., while omadacycline has been approved for SSTI and CABP. In contrast, Eravacycline has been approved for cIAI [94, 95]. Similar to tigecycline, neither of these agents cover pseudomonas.

Origin	Linezolid and Tedizolid are derived from 5-(halomethyl)-3-aryl-2-oxazolidinones (organic synthesis) by chemical modification. Unique structure with no cross-resistance seen.
Mechanism of action	Halts bacterial protein synthesis by binding to the V-domain of 23S RNA, a part of the 50S ribosomal unit [70]. Efficacy is proportional to the drug level area under the curve AUC/MIC ratio.
Routes	Available as oral tablets and IV formulations.
Indication	Linezolid: MSSA/MRSA nosocomial pneumonia, CABP, Gram-positive complicated and uncomplicated SSTI, *Vancomycin-resistant Enterococcus* (VRE) infections, Nocardiosis. Tedizolid: Gram-positive SSTI.
Resistance	It is <1% and due to 23S rRNA domain V region receptor site mutation, cfr (chloramphenicol-florfenicol resistance) ribosomal RNA methyltransferase, and optrA causing adenylation [71–73].
Pharmac-okinetics	Linezolid: oral bioavailability is 100%, excellent tissue distribution, and 31% plasma protein-bound [74]. It is oxidized and renally excreted. No dosage adjustment is needed. Tedizolid: oral bioavailability is 91% with adequate tissue distribution and 80% plasma protein-bound. It undergoes hepatic clearance with 20% excreted renally. No dosage adjustment is needed [75, 76].
Toxicity/Adverse effects	Blood: Thrombocytopenia, pancytopenia, pure red cell aplasia, and reversible myelosuppression [77]. Mitochondrial toxicity: lactic acidosis, peripheral and optic neuropathy [78–80]. Others: Serotonin syndrome with serotonergic medications, tooth and tongue discoloration, and hypoglycemia [78, 81, 82].

Table 6.
2A VI oxazolidinones.

Origin	It was derived from the fungus *Fusidium coccineum.*
Mechanism of action	It inhibits protein synthesis by preventing the translocation, elongation phase, and blocking the elongation factor G (EF-G) effect on the ribosome, making the bacteria susceptible to phagocytosis due to reduced surface proteins [83, 84]. It is active against MSSA, MRSA, *Coagulase-negative staphylococci*, *Clostridium spp, Peptostreptococcus,* and most anaerobes except for *Fusoabcterium spp*.
Routes	Available in oral, eye, topical, and IV formulations.
Indication	As a part of a combination regimen against staphylococcal SSTI and bone infections, especially with rifampin or beta-lactams.
Resistance	Chromosomal or plasmid-mediated mutations in the gene encoding the EF-G (fusA, fusB, fusC, and fusE).
Pharmac-okinetics	Newer film-coated tablets have better oral bioavailability, highly plasma protein-bound with adequate intracellular and tissue penetration [85, 86]. It undergoes hepatic metabolism and needs dose adjustment with hepatic impairment [87].
Toxicity/Adverse effects	Nausea, diarrhea, vomiting, and elevated bilirubin due to bile transport blockade. When used along with statin, the risk of rhabdomyolysis is observed after 20 to 30 days after therapy initiation [88].

Table 7.
2A VII fusidane (fusidic acid).

No dosing modification is needed for renal or hepatic impairment. They are teratogenic, and the anticoagulant dose needs adjustment when used concomitantly. A slightly increased mortality was observed in the CABP trial of omadacycline [94].

Azithromycin is an excellent choice for treating CABP caused by atypical organisms such as *Mycoplasma pneumoniae*, *Legionella* spp., *Chlamydia pneumoniae,* and *Coxiella burnetti.* An important fact is to remember the numerous interactions this class has with other medications, and also, it can prolong the QT interval resulting in ventricular tachyarrythmias.

When used in the therapy for staphylococcal infections, it is prudent always to perform a "D" test to identify any chance of inducible resistance. It is recommended not to use clindamycin as an empirical regimen against streptococcal infections due to a higher risk of resistance. Clindamycin can suppress the cyclosporine effect and can cause neuromuscular blockade.

Linezolid is an alternative for vancomycin in MRSA/MSSA pneumonia and is used in combination regimens for nosocomial pneumonia. It is an alternative in Nocardiosis and a part of combination regimens in the therapy of *Mycobacterium tuberculosis*, *Mycobacterium avium complex,* and *Mycobacterium abscessus complex*.

3. Bactericidal antibiotics

These include glycopeptides in **Table 8** (3A I), lipoglycopeptides in **Table 9** (3A II), lipopeptides in **Table 10** (3A III), aminoglycosides in **Table 11** (3A IV), quinolones in **Table 12** (3A V), penicillin in **Table 13** (3A VI), cephalosporins in **Table 14** (3A VII), beta-lactamase and beta-lactamase inhibitor combinations in **Table 15** (3A VIII), monobactams in **Table 16** (3A IX), carbapenems in **Table 17** (3A X), polymixins in **Table 18** (3A XI), epoxide in **Table 19** (3A XII), pleuromutilin in **Table 20** (3A XIII), rifamycins in **Table 21** (3A XIV) and metronidazole in **Table 22** (3A XV).

An increased risk of renal failure is observed when vancomycin is administered along with aminoglycosides and piperacillin-tazobactam [218, 219]. If a VRE strain susceptibility reveals sensitivity to teicoplanin, it should be avoided due to resistance emergence during therapy. When teicoplanin is used for IE, bone, and joint infections as a monotherapy, the recommendation is to keep serum levels close to 20 μg/mL and, if needed >30 μg/mL [220]. A higher AUC/MIC ratio is related to better clinical outcomes and decreased mortality with vancomycin therapy [221].

The lipoglycopeptides have a longer half-life and are currently undergoing trials for bacteremia, joint infections, osteomyelitis.

Retrospective data indicate higher cure rates and lower mortality when a higher dose (> 8 mg/kg/day) of daptomycin is used [222]. In the therapeutic failure of vancomycin therapy, a suggestion is to use a higher dose of daptomycin or combine it with a beta-lactam or aminoglycoside or TMP-SMX to increase its bactericidal activity. In VRE endocarditis with bacteremia, daptomycin with beta-lactam is an ideal combination to prevent the emergence of resistance [223, 224]. Due to lack of CNS penetration, it should not be used in the therapy for meningitis [225]. Daptomycin is inactivated by the pulmonary surfactant and is rendered ineffective in bronchoalveolar pneumonia but is adequate in hematogenous pneumonia [226]. In patients with chronic kidney disease and on dialysis, more frequent monitoring of CPK is ideal. CPK monitoring is a must if the patient is on statins for hyperlipidemia. It needs to be stopped if the CPK levels are >1000 units/L with clinical features of myopathy or > 2000 (ten times the upper limit) with no myopathy features [123].

Origin	Vancomycin was derived from *Amycolatopsis orientalis*. Teicoplannin was isolated from *Actinoplanes teichomyceticus*. Teicoplanin has not been approved in the United States as it did not offer any advantage over vancomycin.
Mechanism of action	Cell wall synthesis is stopped by inhibition of transpeptidation and disaccharide subunits incorporation into peptidoglycan.
Routes	Vancomycin is available in oral, IV, intrathecal, intraventricular, intraperitoneal, and intraocular formulations. Teicoplanin is available in oral, intramuscular, and IV formulations.
Indication	Vancomycin: Gram-positive and MRSA SSTI, MRSA bacteremia, MRSA native and prosthetic valve IE, Vancomycin sensitive Enterococcal IE, *Corynebacterium jeikeium* and *striatum* infections, MRSA meningitis, and ventriculitis, MRSA pneumonia, joint infections, and osteomyelitis. Pseudomembranous colitis by *Clostridioides difficile*, Febrile neutropenia, Pre-procedure surgical prophylaxis. Teicoplanin: MRSA bacteremia, Gram-positive and MRSA SSTI, Alternative for IE due to *Streptococci viridans* and *Enterococci*, Pseudomembranous colitis by Clostridioides difficile, Pre-procedure surgical prophylaxis.
Resistance	Vancomycin: mecA and mecC encode for a low-affinity penicillin-binding protein PBP2a and PBP2c. Some MRSA strains acquire the VanA gene from enterococci species. Enterococci with VanA, VanB, VanC, VanD, VanE, VanG, VanL, VanM and VanN genes encode a ligase assembling the last two amino acids or peptidoglycan precursors, resulting in a peptidoglycan precursor with less affinity for glycopeptides. Teicoplanin: All *Vancomycin intermediate Staphylococcus aureus* (VISA) strains are cross-resistant [96]. Enterococci containing the above Van genes render them resistant to it.
Pharmac-okinetics	Vancomycin: Oral intake results in minimal absorption. When given IV, efficacy is best indicated by 24 hour AUC/MIC ratio ≥ 400 associated with lower clinical failure [97]. Adequate CSF levels are seen in infection [98]. It is renally excreted with no tubular secretion or absorption, and creatinine clearance inversely affects its serum level. In obese patients, the dosing should be based on actual body weight instead of ideal weight due to increased distribution volume [99]. Therapy needs to be monitored with trough levels (correlate with AUC/MIC ratio) to prevent toxicity. Dose adjustment is needed with renal failure. Teicoplanin: Poor oral absorption, 90% bound to plasma protein, and highly bound in tissues. It reaches adequate concentrations in all tissues except for vitreous and CSF, even with infection. It undergoes renal clearance, and dosing adjustments are needed in renal failure. Trough levels ≥28 μg/mL are associated with hepatotoxicity. Monitoring not needed if dose used is <12 mg/kg/day. It has a long half-life of 83 to 168 hours [100].
Toxicity/Adverse effects	Frequently seen when the trough levels are ≥15 μg/mL with a treatment duration of >7 days [101]. Infusion-related reactions: red man syndrome, hypotension, and cardiac arrest. Others: Nephrotoxicity, Ototoxicity, Neutropenia, Thrombocytopenia, and DRESS [102–104]. Teicoplanin: Nephrotoxicity, fever, maculopapular rash, red man syndrome.

Table 8.
3A I glycopeptides.

Streptogramins are another class of lipopeptides rarely used currently. They are made up of two macrocyclic lactone peptolide components. They are labeled as streptogramin A, and streptogramin B. Quinupristin-Dalfopristin is a 30: 70 ratio IV formulation available for therapy. These components are bacteriostatic as dalfopristin ends protein synthesis by binding to 50S ribosomal unit and quinupristin prevents peptide elongation. Dalfopristin binding increases the affinity to quinupristin due to structural change resulting in synergistic bactericidal activity. It is currently used as an alternative for MSSA or streptococcal SSTI. It needs a central line for administration as it is an irritant and can cause thrombophlebitis [227].

Origin	Telavancin is a vancomycin derivative post alkylation [105]. Dalbavancin is a semisynthetic derivation from teicoplanin like glycopeptide, a fermentation product of Nonomuraea spp. Oritavancin is a semisynthetic derivation from lipoglycopeptide chloroeremomycin.
Mechanism of action	Telavancin: binds to peptidoglycan precursors, inhibits transglycosylation, and inhibits cell wall synthesis. It also disrupts cell wall homeostasis [106]. Dalbavancin: binds to peptidoglycan precursors with higher affinity and inhibits cell wall synthesis. Oritavancin: Binds to peptidoglycan precursors, stops transglycosylation, transpeptidation and inhibits cell wall synthesis. It disrupts the cell wall membrane [107].
Routes	Telavancin: available in IV formulations Dalbavancin: available in IV formulations Oritavancin: available in IV formulations
Indication	Telavancin: Acute gram-positive bacterial SSTI Dalbavancin: Acute gram-positive bacterial SSTI Oritavancin: Acute gram-positive bacterial SSTI in adults only
Resistance	Telavancin: VRE containing VanA gene are resistant to it [108]. Dalbavancin: is bacteriostatic against VISA strains, no activity against VanA but is active against VanB and VanC possessing bacterial strains. Oritavancin: VanZ gene and mutations in vanSB sensor gene ofthevanBcluster confer cross-resistance to teicoplanin and oritavancin [109].
Pharmac-okinetics	Telavancin: Tissue distribution is similar to vancomycin, 90% plasma protein bound, undergoes renal clearance and dose adjustment needed in renal failure [105]. It is recommended to avoid use in severe acute renal failure. Dalbavancin: High volume tissue distribution, plasma protein binding of 93%, and a half-life of 8 to 9 days. It undergoes primarily renal clearance with the remaining via feces. It requires dose modification in renal failure [110]. The best predictor of its activity is the 24-hour AUC/MIC. Oritavancin: High volume tissue distribution, plasma protein binding of 85–90%, and a half-life of 10 days. It gets intracellularly retained in the liver, kidneys, lungs, and lymphoid tissue, from where it is released slowly. No dosage adjustment is done for mild to moderate liver or renal impairment.
Toxicity/Adverse effects	Telavancin: prolongs the QTc interval, nephrotoxicity, nausea, vomiting, chills, and creatinine rise. It is teratogenic. Dalbavancin: pruritis, vomiting, nausea, infusion reactions, skin, and hypersensitive reactions. Oritavancin: nausea, headache, vomiting, diarrhea, mild transaminitis, hypersensitive reactions. Drug interactions can be seen as it inhibits cytochrome P450 enzymes.

Table 9.
3A II lipoglycopeptides.

Origin	Daptomycin is a lipopeptide antibiotic isolated from *Streptomyces roseosporus*.
Mechanism of action	It is an antimicrobial peptide of cation origin attaching to the cell wall in the presence of calcium, disrupting the cell wall structure by displacing the cell wall proteins and formation of an oligomer in the cell wall. This action is unalterable, causing impaired cell wall function and leakage of ions leading to cell death [111–113].
Routes	Available in only IV formulations
Indication	Acute SSTI by MSSA, MRSA, *Enterococcus faecalis*, streptococcal species (as an alternative in glycopeptide therapy failure or intolerance or higher MRSA vancomycin MIC. Acute MSSA, MRSA bacteremia, and right-sided endocarditis [114].
Resistance	Cell wall changes with increased fluidity, net positive charge, and lack of depolarization or permeability decreased phosphatidylglycerol, leading to daptomycin resistance. Multiple genes are involved in this, including mprF, yycFG, vraSR, dlt, rpoB, rpoC, pgsA, and cls [115–118].

Pharmac-okinetics	It has a long half of 7.3 to 9.6 hrs with a small distribution volume and is highly bound to plasma proteins (90% - 93%) [119, 120]. It gets excreted via the renal system unchanged. Dose adjustment is needed in acute renal failure and dialysis patients. It has poor penetration into CSF [121]. It is inactivated by the pulmonary surfactant leading to ineffectiveness against bronchioalveolar pneumonia. It exerts a dose-dependent postantibiotic effect longer than vancomycin [122].
Toxicity/Adverse effects	Higher doses (>8 mg/kg/day) results in elevation of serum creatinine phosphokinase (CPK) levels with no muscle cell lysis or fibrosis [123]. CPK level monitoring during therapy is a must. Peripheral neuropathy with paraesthesia and dysesthesia. Acute eosinophilic pneumonia (after ten days of therapy)

Table 10.
3A III lipopeptides.

Origin	Aminoglycoside with the name ending in mycin is derived from S*treptomyces* [124]. Aminoglycoside with the name ending in micin is derived from *Micromonospora spp*. Fermentation products*:* Neomycin, Gentamicin, Kanamycin Semisynthetic derivatives: Amikacin, Netilmicin
Mechanism of action	Cationic aminoglycosides bind to the anionic lipopolysaccharides and disrupt their structure resulting in cell wall leaks and altered permeability. Once in the cytosol, it binds reversibly to ribosomal decoder acceptance site on 16S reverse transfer RNA portion of messenger RNA (mRNA), a 30S subunit of prokaryotic ribosomes. This decreases the mRNA translocation and translation stopping protein synthesis [125–128]. They demonstrate the postantibiotic effect, synergistic behavior with other antibiotics, and concentration-dependent effect.
Routes	Available in IV and oral formulations.
Indication	Empirical therapy of aerobic gram-negative bacilli (GNB) including *Pseudomonas spp*. As a part of a combination therapy for HAP, *Enterococcal* bacteremia, and IE due to *enterococcus* and *streptococcus spp*. Acute urinary tract infection and cystic fibrosis exacerbations. Preoperative prophylaxis in gastrointestinal and genitourinary procedures.
Resistance	Altered cell wall membrane with diminished interaction, active efflux pumps resulting in lesser concentration in the cytosol [129, 130]. Decreased ribosomal binding due to mutation or methylation of the binding site [131]. Inactivation of the aminoglycosides by phosphorylation, adenylation, and nucleotidation [132]. Induce biofilm formation [133].
Pharmac-okinetics	Plasma protein binding is low, highly soluble in water, with distribution resembling extracellular fluid compartments [134, 135]. Appropriate concentrations are attained in all body fluids except for CSF and vitreous humor [136–138]. They undergo renal clearance unchanged with minimal excretion via feces [139]. Dose adjustment is needed in renal failure.
Toxicity/Adverse effects	Nephrotoxicity Ototoxicity includes both cochlear and vestibular Neuromuscular blockade

Table 11.
3A IV aminoglycosides.

Due to the lack of active intrinsic electron transport chain and cell membrane potential difference, the anaerobic bacteria are resistant to aminoglycosides. *Enterococci* are intrinsically resistant to aminoglycosides [228]. Once-daily dosing is effective as traditional multiple doses, decreases the risk of ototoxicity and nephrotoxicity, is straightforward, and is economical towards resources and time [229]. This dosing pattern does not decline neuromuscular function in sick intubated patients but needs evaluation in cystic fibrosis, meningitis, and osteomyelitis caused by aerobic gram-negative bacilli [230–232]. The once-daily dose should be used

Origin	Initially derived as a byproduct of chloroquine synthesis, the newer quinolones are semisynthetic with chemical modifications to increase their efficacy and absorption.
Mechanism of action	Inhibit deoxyribonucleic acid (DNA) synthesis by inhibiting DNA gyrase and topoisomerase IV. It also leads to hydroxy radicals, damaging the bacterial cellular molecules causing bacterial cell death [140, 141].
Routes	Available as oral, IV, and eye drop formulations
Indication	Acute cystitis, Acute uncomplicated, and cUTI. Acute Bacterial prostatitis, Sexually transmitted disease, PID, *Chlamydiae trachomatis*, *Hemophilus ducreyi*. Acute bacterial gastroenteritis due to *Shigella spp*, *Campylobacter jejuni*, Cholera, Typhoid, *Nontyphoidal Salmonellae* gastroenteritis in specific patients. Acute intraabdominal infections, Spontaneous bacterial peritonitis (SBP). Acute CABP, Acute bronchitis, Aspiration pneumonia, Lung abscess, HAP, *stenotrophomonas* infections. Acute osteomyelitis, Acute native and prosthetic joint infections, SSTI. MDR pulmonary tuberculosis, Nontuberculous mycobacterial infections, GNB susceptible organisms causing meningitis, Prophylaxis in neutropenic patients.
Resistance	Chromosomal gene mutations alter DNA gyrase, and topoisomerase IV decreases cell membrane permeability. Plasmid-mediated genes enabling acetylation and efflux pumps decreasing efficacy.
Pharmac-okinetics	Excellent oral bioavailability and food can alter absorption [142]. Plasma protein binding is low except for delafloxacin and gemifloxacin. Tissue distribution is excellent, with above serum levels seen in bile, prostate, kidney, lung, and stool [143]. Levofloxacin and moxifloxacin attain adequate CSF penetration [144]. Levofloxacin, ofloxacin, ciprofloxacin undergo renal clearance, whereas moxifloxacin undergoes hepatic metabolism. Dose adjustment is needed in renal insufficiency [145].
Toxicity/Adverse effects	GI: vomiting, nausea, abdominal discomfort, diarrhea, *Clostridioides difficile* associated diarrhea [146]. CNS: headache, dizziness, mood changes, peripheral neuropathy [147, 148]. Skin: allergy and skin reactions such as maculopapular rash, phototoxicity [149, 150]. Others: hypoglycemia, prolongs QT interval, increased risk of aortic aneurysm and dissection, retinal detachment, tendinitis with arthropathy [151–155].

Table 12.
3A V quinolones.

Origin	PCN was isolated from *Penicillium chrysogenum* in 1928 by Alexander Fleming [156]. Chemical modifications created numerous semisynthetic PCNs. Natural PCNs: PCN V, PCN G. Penicillinase resistant PCN: Methicillin. Nafcillin, Oxacillin. Aminopenicillins: Amoxicillin, Ampicillin. Carboxypenicillins: Ticarcillin and Carbenicillin. Ureidopenicillins: Piperacillin, Azlocillin and Mezlocillin.
Mechanism of action	PCNs bind to multiple PBP simultaneously, stopping the cell wall synthesis and creating hydroxy radicals that permanently damage the cell. PCNs do not affect dormant bacteria [141, 157].
Routes	Oral, IV, and intramuscular (IM) formulations are available.
Indication	IV PCN G is the antibiotic of choice for PCN susceptible strains causing pneumococcal and meningococcal meningitis, streptococcal IE, and neurosyphilis. Benzathine PCN is used in syphilis treatment and for rheumatic fever prophylaxis. Oral PCN V or G or Benzathine PCN are used to stop outbreaks of streptococcal infection. Intrapartum prophylaxis with PCN is used at membrane rupture or at labor to prevent S*treptococcal agalactiae* infections in colonized patients. PCNase resistant PCNs are the agent of choice for MSSA infections and an alternative to treat streptococcal infections. AminoPCNs treat UTI, Upper and lower airway infections, Gastroenteritis, IE, Meningitis by susceptible non-beta- lactamase organisms. IV ampicillin is the treatment of choice for *Enterococcus faecalis* IE and other infections. Amoxicillin is a part of the combination regimen against *Helicobacter pylori.* Oral amoxicillin or ampicillin are used as prophylaxis in asplenic

	or agammaglobulinemia patients to prevent infections by capsulated organisms. Ampicillin-sulbactam is the drug of choice for aspiration pneumonia. Piperacillin-tazobactam is an antipseudomonal and is also used for necrotizing fasciitis, susceptible GNB infections.
Resistance	Presence of beta-lactamase [158]. Alteration of cell membrane permeability with a decreased intracellular entry (absence of porin) [159]. Presence of efflux pumps [159]. Synthesis of PBP with decreased affinity for the beta-lactam [160].
Pharmac-okinetics	PCNs vary in their oral absorption and plasma protein binding. The tissue distribution is more than adequate in most tissues. The primary route of excretion is via the renal system, whereas some undergo biliary excretion too.
Toxicity/Adverse effects	Hypersensitivity reactions: rash, anaphylaxis, exfoliative dermatitis, allergic vasculitis, SJS, and TEN [161]. GI: nausea, vomiting, diarrhea, Clostridioides difficile associated diarrhea, liver function test abnormality with oxacillin in patients with HLA-B 5701 [162, 163]. Hematological: neutropenia [164]. Renal: Nephrotoxicity, allergic interstitial nephritis [165]. CNS: Myoclonic seizures.

Table 13.
3A VI penicillin (beta-lactams).

Origin	Semisynthetic derivatives of Cephalosporin C isolated from *Acremonium chrysogenum* [166]. First-generation: cefazolin, cephalexin, and cefadroxil. Second generation: cefprozil and cefuroxime, cephamycin: cefoxitin Third generation: cefdinir, cefditoren, cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftriaxone. Fourth generation: Cefepime, Cefpirome. Fifth-generation: Ceftaroline, ceftobiprole. Siderophore cephalosporins: Cefiderocol.
Mechanism of action	They bind to PBPs and stop transpeptidation and block the cell wall synthesis resulting in a bactericidal effect with a postantibiotic effect [167]. MRSA active cephalosporins bind to PBP2A, whereas the other cephalosporins bind to PBP1A&B in gram negatives [168]. Cephalosporins active against gram-positive organisms bind to PBP 2&3 (186). Cefiderocol binds to iron and enters the bacteria via siderophores into the periplasmic space and binds to PBP in addition to being a poor substrate for efflux pumps [169].
Routes	First, second and third generations are available in oral and parenteral (IV/IM) formulations. The fourth and fifth-generation are available in IV formulations. Fifth-generation are available in IV formulations. Siderophore cephalosporins: available in IV formulations.
Indication	First-generation: oral therapy for MSSA and *Streptococcal* SSTI outpatient, susceptible *Streptococcal* SSTI, MSSA IE, the prophylactic antibiotic of choice for prosthesis implantation and surgical procedures with a high risk of infection except for intraabdominal procedures. Second generation: as a part of a combination regimen for PID (cefoxitin), nontuberculous mycobacterial infection (cefoxitin), cefuroxime for acute otitis media, pharyngitis, maxillary sinusitis, and an alternative for Lyme disease [170, 171]. Third generation: treatment of susceptible GNB bacilli induced SSTI, Prosthetic joint infection (PJI), CABP, cUTI, and peritonitis [172]. Empirical therapy for CABP, acute bronchitis, and meningitis. IM single dose for Neisseria gonorrhea and chancroid [173]. Lyme disease and an alternative for PCN allergic patients with syphilis, typhoid fever, and shigellosis [174, 175]. Monotherapy for *Streptococcal* IE [176]. Ceftazidime is the drug of choice for susceptible *Pseudomonas spp* infections, including CNS [177]. Fourth generation: antibiotic of choice for infections caused by AmpC (Class C beta-lactamases) inducible resistant organisms [178]. Febrile neutropenia monotherapy or a part of a combination regimen [179]. Empirical therapy in severe CABP, HAP by *Pseudomonas spp* or resistant *Enterobacteriaceae* [180]. It is an alternative for susceptible GNB meningitis, bacteremia, SSTI, PJI and cUTI. Fifth-generation: Ceftaroline used for MRSA pneumonia, CABP, SSTI, HAP, and in combination with daptomycin for daptomycin resistant MRSA infections [181–183]. Ceftobiprole also is an alternative for *Pseduomonal spp* infections. Siderophore cephalosporins:

	approved for use in cUTI by *Enterobacterales & P. aeruginosa,* HAP, and VAP by the *Enterobacterales, P. aeruginosa, and Acinetobacter baumannii complex* [169].
Resistance	Beta-lactamase hydrolyzes the antibiotic. Cell wall membrane changes alter the entry of antibiotics through the lipopolysaccharide layer. Efflux pumps removing the antibiotic from the periplasmic space. PBP changes to alter antibiotic binding.
Pharmac-okinetics	The first three generations are water-soluble and come in oral and parenteral formulations, whereas the fourth and fifth-generation are parenteral only. Distribution is dependent on their lipid solubility and plasma protein binding. They reveal higher serum concentrations and lower tissue levels. The third and fourth generations attain adequate CNS concentrations. Most of them undergo renal clearance except for ceftriaxone and cefoperazone, which undergo biliary excretion. Probenecid inhibits tubular secretion of cephalosporins and increases their half-life. Renal failure will need a dose adjustment. Ceftriaxone dose is adjusted with simultaneous renal and hepatic impairment [184]. Cefiderocol is excreted renally and needs renal dose adjustment [185].
Toxicity/Adverse effects	Hypersensitivity reactions: immunoglobulin E (IgE)-mediated reactions occur in <1 in 100,000 patients; fever, rash, eosinophilia, serum sickness, and anaphylaxis are seen. Cross-reaction frequency is ≤1%. Hematology: eosinophilia, neutropenia (prolonged use), anemia, thrombocytopenia, hypoprothrombinemia, impaired platelet aggregation, hemolytic anemia (ceftriaxone). Nephrology: allergic interstitial nephritis GI: nausea, vomiting, diarrhea, *Clostridioides difficile* infection, biliary pseudolithiasis (ceftriaxone), transaminitis. CNS: seizures, encephalopathy Others: fever, disulfiram-like reaction, phlebitis.

Table 14.
3A VII cephalosporins.

Combinations	Augmentin = Amoxicillin + Clauvulinic acid in an 2:1, 4:1,7:1 ratio (isolated from *Streptomyces clavuligerus* [186]. Unasyn = Ampicillin + Sulbactam in an 2:1 ratio Sulperazone = Cefoperazone + Sulbactam in an 1:1 ratio Zosyn = Piperacillin + Tazobactam in an 8:1 ratio Zerbaxa = Ceftolazone + Tazobactam in a 2:1 ratio Avycaz, Zavicefta = Ceftazidime + Avibactam in a 4:1 ratio Vabomere = Meropenem + Vaborbactam in a 1:1 ratio
Mechanism of action	Clavulanic acid: is potent and inhibits class A beta-lactamase and some extended-spectrum beta-lactamases (ESBL). Sulbactam: is a broad-spectrum inhibitor than clavulanic acid but less potent (inhibits class A beta-lactamases). Tazobactam: spectrum is similar to sulbactam but is more potent. Avibactam: inhibits class A beta-lactamases, including ESBL, *Klebsiella pneumoniae* carbapenemase (KPC), class C, and some class D beta-lactamases. It does not stop Metall0beta-lactamases (MBL). Vaborbactam: inhibits class A beta-lactamases including ESBL, KPC, class C beta-lactamases with no effect on MBL and class D beta-lactamases.
Routes	Augmentin: available orally and IV formulations. Unasyn: available in IV formulations Sulperazone: available in IV formulations Zosyn: available in IV formulations Zerbaxa: available in IV formulations Avycaz, Zavicefta: available in IV formulations Vabomere: available in IV formulations
Indication	Augmentin: acute otitis media, acute sinusitis, outpatient CABP by susceptible organisms with a higher dose, diabetic foot infection, SSTI, human or animal bites. Unasyn: as a part of a combination regimen against MDR *Acinetobacter baumannii* infection, SSTI, cIAIs, and obstetric and gynecological infections. Sulperazone: treatment of *A. baumannii* infection Zosyn: treatment of pneumonia, SSTI, cIAIs, febrile neutropenia, and polymicrobial infections [187]. Zerbaxa: indicated in cUTI, cIAIs, and Carbapenemase resistant *Pseudomonas aeruginosa* infections. Avycaz, Zavicefta: indicated in cUTI, cIAIs, HAP, and KPC *Enterobacteriaceae* infections. Vabomere: indicated in KPC *Enterobacteriaceae* infections and cUTI.
Resistance	Augmentin: plasmid-mediated beta-lactamase TEM-1 and OXA-1 (Oxacillin beta-lactamases) [188]. Unasyn: cephalosporinase, ESBL, and carbapenemase production by resistant strains. Sulperazone: cephalosporinase, ESBL, and carbapenemase

	production by resistant strains. Zosyn: ESBL and carbapenemase production by resistant strains. Zerbaxa: carbapenemase production KPC, OXA, ESBL, and MBL by resistant strains. Avycaz, Zavicefta: porin mutations, efflux pumps, and MBL. Vabomere: coproduction of KPC and class B or D beta-lactamases, porin mutations, and efflux pumps [189].
Pharmacokinetics	Augmentin: well absorbed orally and undergoes renal clearance with dosing adjustment needed in renal impairment. It does not penetrate CSF but reaches therapeutic levels in the peritoneum, bile, tonsils, and middle ear. Unasyn: renally cleared and dose adjustment needed in renal insufficiency. Levels in peritoneal and intestinal fluids are the same as in serum with minimal CSF penetration. Sulperazone: available in IV formulations Zosyn: renally cleared and will need a dose adjustment and minimal CSF penetration. Zerbaxa: renally cleared and will need a dose adjustment. Avycaz, Zavicefta: gets excreted renally unchanged, and dosage adjustment is a must when creat clearance is <50 mL/min. Vabomere: the majority of the drug undergoes renal clearance so that it will need dose adjustment with renal insufficiency.
Toxicity/Adverse effects	Augmentin: skin reactions, delayed hypersensitivity, diarrhea, and nausea. Unasyn: occasional transaminitis and similar reactions as seen with ampicillin Sulperazone: occasional transaminitis and similar reactions as seen with ampicillin. Zosyn: platelet dysfunction, immune thrombocytopenia, allergic reactions, renal failure, Clostridioides difficile infection [190, 191]. Zerbaxa: headache, nausea, diarrhea, *Clostridioides difficile* infection Avycaz, Zavicefta: anxiety, nausea, vomiting, and constipation. Vabomere: phlebitis, headache, diarrhea, and infusion site reactions.

Table 15.
3A VIII beta-lactamase inhibitors and beta-lactam combinations.

Origin	It is a semisynthetic derivation of a biochemical substance isolated from *Chromobacterium violaceum*.
Mechanism of action	It avidly binds to PBP3 of aerobic GNB, inhibiting cell wall synthesis resulting in death [192]. It remains active against all class B beta-lactamases and the majority of class A and D beta-lactamases. It is destroyed by KPC, ESBLs, and AmpC beta-lactamases if present in a larger quantity.
Routes	Available in IV formulations.
Indication	As an alternative in susceptible aerobic GNB infections in patients with beta-lactam allergy. As a part of a combination regimen against MBL producing GNB infections.
Resistance	It is via efflux pumps and alterations to the PBP3 binding site [193].
Pharmacokinetics	Orally it is absorbed poorly with 56% plasma protein binding after IV administration. Excellent tissue distribution with CSF penetration. Excretion is renally, and dose adjustment is needed in renal impairment and severe hepatic impairment.
Toxicity/Adverse effects	Nausea, vomiting, diarrhea, rash, phlebitis [194]. Crossreaction with other beta-lactams is rare even in patients with anaphylaxis to other beta-lactams.

Table 16.
3A IX monobactams.

cautiously in IE patients [176]. Inhaled aminoglycosides used in conjunction with a beta-lactam reveal better clinical outcomes [233]. For endophthalmitis and intracranial infections, they need to be administered locally (direct intravitreal injection, intraventricular administration). Aminoglycoside combination regimens diminish the emergence of resistant strains to the companion antibiotic and aminoglycoside. The synergistic antibiotic effect is observed when aminoglycoside is combined with an anti-cell wall antibiotic (beta-lactam). This combination is effective in the therapy of MSSA, enterococci, *pseudomonas spp,* and *Streptococcal viridans* infections but not in MRSA infections.

Origin	They are semisynthetic derivatives from thienamycin, an antibiotic isolated from *Streptomyces cattleya*. The human renal enzyme dehydropeptidase breaks down imipenem and is combined with cilastatin which inhibits this enzyme.
Mechanism of action	They gain entry into the periplasmic space via porins located on the cell wall and avidly bind to the PBPs 1a, 1b, 2, 4, and also to PBP3 minimally. This stops the cell wall synthesis and leads to the death of the bacteria. They are inactive against organisms producing MBL or class B beta-lactamases such as *Stenotrophomonas maltophilia* and *Elizabethkingia meningoseptica*. Ertapenem has minimal activity against *Pseudomonas* and *Acinetobacter* spp. Imipenem is partially active against *Enerococcus faecalis* [195].
Routes	IV formulations: Imipenem. Meropenem, Ertapenem, Doripenem. Oral formulations: Tebipenem in Japan.
Indication	Treatment of bacterial meningitis, *Pseudomonas spp*, and ESBL bacterial infections. An alternative choice for infections caused by AmpC organisms. Treatment of infections such as bacteremia, cUTI, cIAI, HAP, SSTI, nocardiosis, and actinomycosis.
Resistance	Beta-lactamase synthesis breaks down carbapenem such as KPC, OXA, and MBL. Decreased cell wall entry due to porin mutations or lack of porins. Efflux pumps. Alterations in PBPs site resulting in less avid binding of the carbapenem.
Pharmac-okinetics	Poor oral absorption except for Tebipenem. Plasma protein binding, if higher, leads to a longer half-life (Ertapenem) and once-daily dosing. Tissue distribution and penetration are excellent, including CSF [195]. Excretion is via the renal route, and dose adjustments are needed in renal impairment. Only imipenem undergoes destruction by dehydropeptidase.
Toxicity/Adverse effects	Phlebitis, nausea, vomiting, headache, diarrhea, rash, and *Clostridioides difficile* infection. Seizures, especially with imipenem. Interact with valproic acid and lead to subtherapeutic valproate levels [196]. Potential crossreactivity exists between PCN and cephalosporins; a negative PCN skin test makes it safer to administer a carbapenem [197].

Table 17.
3A X carbapenems.

Origin	Polymixin B is semisynthetically derived from a biochemical product from *Bacillus polymyxa*. Polymixin E (Colistin) is semisynthetically derived from a biochemical product from *Bacillus colistinus*. It is commercially available in an inactive prodrug methanesulfonate (CMS) which is converted to colistin invivo.
Mechanism of action	It is a surface-active agent with both lipophilic and lipophobic subunits which infiltrate the outer cell membrane of GNB. Then they interact with the phospholipids electrostatically, resulting in cell membrane destruction. They bind avidly to lipid A portion of lipopolysaccharide and stop its endotoxin effect [198].
Routes	Polymixin B: available in oral, IV/IM, and topical formulations. Polymixin E: available in oral, IV/IM, inhalation, and topical formulations.
Indication	Polymixin B favored over CMS in all infections except in UTI. Oral preparations are used for intestinal decontamination. Administered intraventricularly for GNB meningitis. Inhaled CMS for infections in Cystic fibrosis. Parenteral administration for severe systemic infections caused by MDR GNB, including VAP.
Resistance	Resistance is mediated via the plasmid-mediated MCR-1, MCR-2, and MCR-3, which alter the lipopolysaccharide structure and prevent polymixin binding [199]. Cross-resistance between the polymyxins is complete [200].
Pharmac-okinetics	They are poorly absorbed, and post IV administration, the distribution to the biliary tract, CSF, joint and pleural fluid is low. CMS undergoes renal clearance, so the dose needs to be adjusted in renal impairment. Both colistin and polymyxin undergo nonrenal clearance (Unknown exact mechanism) after extensive tubular reabsorption with no need for renal dose adjustment [201].

Toxicity/Adverse effects	Dose-related nephrotoxicity is frequent with colistin than polymyxin B seen as renal impairment often reversible on stopping the medication. Dose-related neurotoxicity manifesting as neuromuscular blockade resulting in muscular weakness, apnea, and respiratory failure. This effect can be augmented on concurrent administration with aminoglycosides. Peripheral neuropathy of extremities and perioral paraesthesia [202].

Table 18.
3A XI polymixins.

Origin	It was isolated from the soil bacteria *Streptomyces fradiae*.
Mechanism of action	It inhibits phosphoenolpyruvate synthetase, an enzyme needed to synthesize N-acetylmuramic acid, an essential component of cell wall formation, thus inhibiting cell wall formation. Its bactericidal effect is broad, covering resistant gram-negative and gram-positive microorganisms [203, 204].
Routes	Available in IV and oral formulations. Only oral formulation is currently approved.
Indication	The oral form has been approved for uncomplicated UTI due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*. IV formulation has been used in a combination regimen against deep-seated infections due to MDR organisms.
Resistance	Modification of phosphoenolpyruvate synthetase enzyme, porin mutations, and some carbapenemases such as OXA. No cross-resistance to other antimicrobial classes.
Pharmac-okinetics	It undergoes renal clearance with dose adjustment needed in renal impairment. Higher doses are associated with bradycardia [205].
Toxicity/Adverse effects	Hypernatremia, hypokalemia, hypocalcemia, and phlebitis.

Table 19.
3A XII epoxide (fosfomycin).

Origin	It is isolated from the fungus *Pleurotus mutilus.*
Mechanism of action	It inhibits protein synthesis by binding to 23SrRNA part of the 50S ribosome subunit. Its activity against gram-positive organisms is potent invitro (MSSA/MRSA/*Streptococcal spp*). Its spectrum of bactericidal effects is broad, covering both gram-positive and negative respiratory pathogens.
Routes	Available in both oral and IV formulations.
Indication	It is approved for CABP therapy in patients >18 years old by both IV and oral formulations.
Resistance	Mutations in the 23S rRNA and methylation of the target site preventing Lefamulin from 23S rRNA binding [206].
Pharmac-okinetics	It undergoes hepatic clearance by cytochrome CYP3A and can lead to interactions. Dose adjustment is needed in hepatic impairment and none in renal failure.
Toxicity/Adverse effects	Infusion site reactions, phlebitis, headache, nausea, diarrhea, and QT prolongation [207].

Table 20.
3A XIII pleuromutilin (lefamulin).

Plazomicin is a semisynthetic aminoglycoside derived from sisomicin. It is potent against MDR GNB, especially the ones with carbapenemase. It has been approved currently for the treatment of complicated UTI (cUTI) by aerobic

Origin	Rifampin was semisynthetically obtained from rifamycin SV isolated from *Amycolatopsis mediterranei.* Similarly, Rifabutin, Rifapentine, and Rifaximin are semisynthetic modifications.
Mechanism of action	Rifamycins bind avidly to DNA-dependent RNA polymerase and block RNA synthesis.
Routes	Rifampin: available in oral and IV formulations. Rifabutin, Rifapentine, Rifaximin: available in oral formulations.
Indication	Rifampin: Antitubercular therapy for active tuberculosis. Treatment of Nontubercular mycobacterial infections due to *Mycobacterium leprae* (*M. leprae*), *Mycobacterium avium-intracellulare* (MAC), *Mycobacterium kansasii*. Combination therapy for synergistic antistaphylococcal effect and antibiofilm effect in PJI, chronic osteomyelitis, and SSTI. Therapy for resistant *Streptococcus pneumoniae* strains causing CNS infections and *Enterococcal* hip and knee PJI. Therapy for severe *legionella* infection along with a macrolide. As a part of combination therapy of *Rhodococcus equi* infections in immunosuppressed patients. As a part of combination therapy of MDR GNB infections. Brucellosis and complicated Bartonella infection antimicrobial therapy. Chemoprophylaxis in Meningococcal meningitis and Active *Hemophilus influenzae* infection close contacts. Rifabutin: As an alternative to rifampin in the treatment of tuberculosis and MAC infection. Rifapentine: As a part of the short regimen for latent tuberculosis therapy, Rifaximin: Hepatic encephalopathy treatment, Alternative for travelers diarrhea and recurrent Clostridioides difficile infection. It is an alternative for GI invasive pathogens *Salmonella*, *Shigella*, *Campylobacter,* and *Escherichia coli*.
Resistance	*rpoB* gene mutations result in decreased binding of rifamycins to RNA polymerase [208]. Decreased cellular uptake of rifampin. Mutations in the *arr* gene lead to ribosylation of rifamycins and decreased binding [209].
Pharmac-okinetics	Rifampin: excellent oral bioavailability with broad tissue and fluid distribution, including brain [210]. It undergoes hepatic clearance, enterohepatic circulation with biliary excretion, and minimal renal excretion. Dosage adjustment is needed in hepatic impairment. It induces hepatic enzyme CYP3A resulting in drug interactions, especially with protease inhibitors. Rifabutin: is more lipid-soluble with a long half-life and extensive tissue distribution, including CSF. Its metabolites post hepatic metabolism undergo renal clearance, so dose adjustment is needed with hepatic and renal impairment. Hepatic enzyme induction is minimum. Protease inhibitors increase their levels. Rifapentine: Food increases its bioavailability, and it is more potent with a longer half-life. Intracellular concentrations are higher than rifampin with minimal CSF penetration. It undergoes hepatic clearance with induction of hepatic enzymes CYP3A4 and protease inhibitors decrease its absorption [211]. Rifaximin: Oral absorption is minimal, and 97% of the drug gets excreted in stools. It can induce cytochrome P450 3A4, but it is not seen as the systemic levels are minimal [212]. No dosage adjustment is required.
Toxicity/Adverse effects	Rifampin: type 1 hypersensitivity reactions, flu-like syndrome, hemolysis, thrombocytopenia, acute interstitial nephritis with tubular necrosis, mild transaminitis with increased risk of hepatotoxicity with isoniazid [213], and red-orange discoloration of body fluids. Rifabutin: polyarthralgia, leukopenia, and uveitis [214]. Rifapentine:flu-like syndrome, hyperuricemia, hemolysis, and renal failure. Rifaximin: neutropenia.

Table 21.
3A XIV rifamycins.

gram-negative bacilli. It is synergistic with other beta-lactams, especially zosyn cefepime and doripenem [234]. The main side effects are tinnitus, headache, dizziness, and mild to moderate drowsiness.

Delafloxacin, a newer quinolone, has MRSA activity and can be used in native and prosthetic joint infections as an oral pill.

Origin	It is a semisynthetic derivative of azomycin isolated from a *streptomyces* bacterium. Tinidazole, Secnidazole and Ornidazole are the other semisynthetic derivatives.
Mechanism of action	It enters the cell passively and then gets an electron transferred to its nitro group, creating a free radical which is cytotoxic and interacts with DNA (prodrug to an active drug). This change enhances the drug gradient in the cell by increased uptake. The active drug oxidizes DNA damaging it and block DNA synthesis [215].
Routes	Available in oral capsules, tablets, topical gels, creams, lotion, vaginal gel, suspension, and IV formulations.
Indication	Treatment of parasitic infections such as trichomoniasis, symptomatic GI *Dientamoeba fragilis* infection, Giardiasis, mild to moderate *Clostridioides difficile* infection, anaerobic infections of CNS, lung, abdomen, Skin, gynecologic, oral, dental, bone, and joint. As a part of a combination regimen against *Helicobacter pylori.* As an alternative agent recommended for surgical prophylaxis in intraabdominal, head, and neck cancer, urology surgery for patients intolerant or allergic to beta-lactams [216]. Prophylaxis perioperatively in obstetric and gynecologic procedures [217].
Resistance	Decreased uptake of the antibiotic. Active drug efflux pumps. Reduced activation of the prodrug (↓nitroreductase enzymes). Inactivation of the antibiotic (nim-encoded nitroimidazole reductase). Altered DNA repair [215].
Pharmac-okinetics	Oral bioavailability is close to 100%, with a more considerable volume of distribution attaining excellent concentrations in tissue, body fluids, abscess, and CSF [10]. It undergoes hepatic clearance and enterohepatic circulation with some amount being excreted renally with no change. Dosage adjustment is needed in hepatic impairment.
Toxicity/Adverse effects	Common ones include nausea, metallic taste, dry mouth, diarrhea, vaginal candida infection, CNS side effects on prolonged therapy (aseptic meningitis, encephalopathy, ataxia, seizure). Rare serious events include ototoxicity, Stevens-Johnson syndrome, pancreatitis [10].

Table 22.
3A XV metronidazole.

PCN skin tests are inaccurate in predicting skin reactions. In PCN or cephalosporin allergy patients, the clinical decision to use a different cephalosporin is decided by the severity of the reaction and the cephalosporin to be used. In patients with no severe reactions, a cephalosporin with a different side chain can be used. It is recommended not to use a cephalosporin in case of a severe reaction [235]. Cephalosporins are not active against atypical organisms responsible for CABP. An initial study disclosed increased mortality with cefepime than other cephalosporins compared to a beta-lactam plus beta-lactamase inhibitor (BLI), which was not observed in a more extensive meta-analysis [236, 237]. Cefepime is not recommended to be used in ESBL infections [238]. Siderophore cephalosporins Cefiderocol are active against all beta-lactamases and carbapenemase enzymes [239]. It is also active against the GNB lactose-non fermenters by its affinity for the PBP3.

Zosyn should not be used to treat ESBL infections with bacteremia due to higher mortality observed in trials compared to meropenem [240, 241].

Most *Burkholderia cepacia, Stenotrophomas maltophilia*, *Acinetobacter baumannii* strains are resistant to aztreonam.

Lactose-non fermenters such as *Stenotrophomonas maltophilia, B. cepacia,* and *Elizabethkingia meningoseptica* are intrinsically resistant to all carbapenems due to intrinsic MBL synthesis. Similarly, *Enterobacteriaceae* containing KPC (*Klebsiella pneumoniae*), OXA (*A. baumannii*), or acquired MBL are resistant to carbapenems. They are an ideal choice for polymicrobial infections as they also cover MSSA. *Pseudomonas aeruginosa* resistance to carbapenems is primarily due to porin

mutations and efflux pumps than the carbapenemase. Porin mutations affect the imipenem, whereas the efflux pumps affect the meropenem and doripenem [242, 243]. The duration of therapy for lactose-non fermenters causing VAP is controversial, as a shorter duration of seven days is associated with an increased recurrence rate [244].

Compared to other antimicrobial classes, polymixins have been associated with poorer outcomes, but this appears to be a poor application of prior suboptimal dose adjustments based on the newer pharmacokinetics and pharmacodynamics data [245, 246]. Polymixin combination regimens should be used as a last resort in the absence of any alternative antimicrobial regimen.

Extreme consideration should be given to the possible drug interactions when rifamycins are used clinically due to their ability to induce the hepatic cytochrome system.

4. Antibiotics in ICU

Antimicrobial prescription in the intensive care unit has three essential ideals to be followed: the correct time when to initiate the antimicrobial, what dose to be used, and how long the antimicrobial should be used. Initiate empirical regimen as early as possible once the infection is suspected to prevent poor clinical outcomes [247]. Trials reveal a positive association between earlier antimicrobial use and mortality in sepsis and septic shock [248]. 2016 surviving sepsis guidelines recommend administering appropriate antimicrobial therapy within one hour of sepsis and septic shock recognition based on the moderate quality of evidence [249]. The empirical regimen should be based on the clinical presentation and associated risk factors. The dose used should be based on the antimicrobial pharmacokinetics, and antibiotics are labeled as either time-dependent (beta-lactams), concentration-dependent (aminoglycosides and daptomycin), and concentration-dependent with time dependence (fluoroquinolones, linezolid) [250].

For time-dependent antimicrobials, the best way to achieve efficacy is a continuous infusion to keep the drug levels above the MIC for a longer time [251]. For concentration-dependent antimicrobials, once-daily higher doses are adequate as they demonstrate postantibiotic effect with reduced adverse events [252]. It is prudent to increase the antimicrobial dosage in patients with augmented renal clearance (burns, trauma, febrile neutropenia) to increase the antimicrobial dosage to achieve the target drug levels [253]. De-escalation of antibiotics is done via three different methods. First, once empirical therapy is initiated, follow the pending culture results, and on day three, when the antimicrobials have reached adequate therapeutic levels, the regimen can be de-escalated to a narrower spectrum based on the patient's culture results and clinical diagnosis. Second, in patients with negative culture results, which is a common finding in ICU patients, the de-escalation process is unclear. For example, in patients treated for HAP who are clinically improving with negative sputum cultures for MRSA and *P. aeruginosa*, antibiotics covering these organisms can be stopped as per guidelines [254]. The third mechanism uses the empirical regimen for the shortest duration possible for a better clinical outcome [255]. This recommendation is based on expert opinion than clinical data.

Recent guidelines based on multiple trials conducted on the VAP antimicrobial therapy duration suggest using the treatment for seven days than 14 days [256]. However, they also recommend following the improvement in clinical, imaging, and laboratory parameters to decide the duration of therapy judiciously. Seven days of VAP therapy was associated with an increased recurrence of infections among lactose-non fermenter GNB such as Pseudomonas and Acinetobacter spp. [244].

Similarly, in MRSA and MSSA pneumonia, the duration is decided by the clinical picture, and most often, it is more than seven days and closer to 14 days.

Antibiotic use in the intensive care unit (ICU) usually follows two different thought processes. One way is to use a single or limited number of antimicrobials as workhorse agents as empirical therapy for infections which carries an inherent risk of resistance emergence via selective pressure (antibiotic homogeneity). This was initiated to control resistance. Another way is to select the antibiotics based on clinical presentation and comorbid risk factors associated with decreased resistance (antibiotic heterogeneity). This is a newer initiation in managing resistance. It is recommended to use antibiotic heterogeneity as much as possible to prevent antimicrobial resistance emergence [257]. Antibiotic stewardship is a must in this modern era for better clinical outcomes, prevent antibiotic adverse events and resistance using local data, reduce the costs by selecting the correct antibiotic dose duration and route. An ideal stewardship team should include an infectious disease consultant, clinical microbiologist, infectious disease trained clinical pharmacist. The current guidelines recommend two strategies to attain this objective. First, reduce the future antibiotic use by auditing institutional antimicrobial usage with feedback to the prescribers. Second, it is ideal to restrict certain antimicrobials to prevent inappropriate usage and decrease institutions' economic burden. Measures taken to enhance the ICU staff education boosts the stewardship process and increases its acceptance among health care workers.

5. Conclusion

Antibiotic resources are finite and need to be managed judiciously with principles based on antimicrobial stewardship. Management of sick patients in ICU will need timely appropriate antimicrobial adjustments based on new laboratory results and clinical parameters. It seems reasonable to utilize a stewardship team to support the intensivist in the ICU for better outcomes. It seems appropriate to extend the stewardship program to progressive care units or step-down units where antimicrobial utilization is greater than the floors. Education of the ICU staff and positive feedback to antibiotic prescribers can change prescription behavior from antibiotic homogeneity to antibiotic heterogeneity to prevent the emergence of MDR organisms.

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Acronyms and abbreviations

MIC	Minimum inhibitory concentration
MBC	Minimum bactericidal concentration
CLSI	Clinical and Laboratory Standards Institute
EUCAST	European Committee on Antimicrobial Susceptibility Testing
IE	Infective endocarditis
PABA	Para-aminobenzoic acid
DHFR	Dihydrofolate reductase
IV	Intravenous
UTI	Urinary tract infection
TMP-SMX	Trimethoprim and sulfamethoxazole
SSTI	Skin and soft tissue infections
PCJ	Pneumocystis jiroveci
foiP	Dihydrofolate reductase encoding gene
SJS	Steven-Johnson syndrome
TEN	Toxic epidermal necrolysis
GI	Gastrointestinal
MSSA	Methicillin-sensitive *S. aureus*
MRSA	Methicillin-resistant *S. aureus*
CABP	Community-acquired bacterial pneumonia
PID	Pelvic inflammatory disease
CSF	Cerebrospinal fluid
CNS	Central Nervous System
MICU	Medical intensive care unit
cIAIs	Complicated intraabdominal infections
MDR	Multidrug-resistant
FDA	Federal drug authority
HAP	Hospital-acquired pneumonia
VAP	Ventilator-associated pneumonia
rRNA	ribosomal ribonucleic acid
PCN	Penicillin
MAC	*M. avium* complex
MLSB	Macrolide Lincosamide and streptogramin B
Erm	Erythromycin ribosome methylation
HLA	Human leukocyte antigen
DRESS	Drug rash with eosinophilia and systemic symptoms
AUC	Area under the curve
VRE	Vancomycin-resistant Enterococcus
optrA	Adenylation coding gene
EF-G	Elongation factor G
fusA	Elongation factor G coding gene
PBP	Penicillin-binding protein
mecA&C	Methicillin resistance encoding gene
Van	Vancomycin resistance encoding gene
VISA	Vancomycin intermediate *S. aureus*
CPK	Creatinine phosphokinase
mRNA	messenger RNA
GNB	Gram-negative bacillus
cUTI	Complicated UTI
DNA	Deoxyribonucleic acid
SBP	Spontaneous bacterial peritonitis

IM	Intramuscular
PJI	Prosthetic joint infection
IgE	Immunoglobulin E
BLI	Beta-lactamase inhibitor
ESBL	Extended-spectrum beta-lactamases
KPC	*K. pneumoniae* carbapenemase
MBL	Metallo-beta-lactamase
OXA	Oxacillin beta-lactamases
AmpC	Class C beta-lactamses
CMS	Methanesulfonate
MCR	Lipopolysaccharide encoding gene
rpo	RNA polymerase rifamycin binding target encoding gene
arr	Methytransferase encoding gene

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