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ANTIBACTERIAL AGENTS: BACTERIOSTATIC AND BACTERICIDAL

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ABSTRACT

Bacteria are microorganisms which called prokaryotic that have a few micrometres in length. Bacteria are live in the soil, water, acidic hot springs, radioactive waste, and the deep portions of earth's crust and among microorganism bacteria are the first life forms appeared on the earth. Penicillins block a bacterial enzyme called transpeptidase enzyme which is used for the secretion of bacterial cell wall. Probenecid accelerates the amount of penicillins in blood serum levels by preventing the excretion of penicillin through kidneys. Ceftriaxone is not given in hyperbilirubinemic neonates because ceftriaxone displaces bilirubin from albumin, and enhancing the free bilirubin accumulations and accelerates the risk of jaundice in neonates. Ceftriaxone has the ability to react with calcium-containing solution and also have the ability to form precipitate in lungs and kidneys of infants less than twenty eight days old and this side effect may be life-threatening; so ceftriaxone is given with products which containing calcium such as ringer lactate in infants less than twenty days old and all population. Vancomycin is given for the management of severe infections caused by vulnerable strains of methicillin-resistant (beta-lactam-resistant) staphylococci.

KEY WORDS : Antibacterial agents; Bacteriostatic; Bactericidal

Introduction

In the world infectious disease are the leading cause of millions death; however the development of antimicrobials to destroy them were gone to accelerate the emergence of antibiotics resistance [1]. The simple one-celled organism called bacteria was first distinguished in the 1670s by van Leeuwenhoek. At the end of nineteenth century; the consideration of bacteria and disease has been advanced. The development of infectious disease by bacteria encourage the researchers not only to response certain difficult questions about infectious diseases, but also they determine a medications that able to kill, hinder, or lower the growth of such disease-causing bacteria. These challenges made the scientists for radical finding to destroy bacteria called antibacterial agent example penicillium discovered in 1928 by Sir Alexander Fleming [3, 4]. Microorganisms, like bacteria, viruses and fungi, are available in all environments. Prevention of these microorganisms is critical for inhibiting the transmission of infectious disease, happened from contaminated food or water caused by blocking the breakdown of substances. Antibiotics and biocides are used frequently to define chemicals and other factors used to kill or hinder the development of detrimental microorganism [6, 7]. Antimicrobial medicines have causes a melodramatic alters the management of infectious diseases and a destiny of mankind. Modern medication is eminently dependent on antibiotics that capable multiple process enclosing abdominal surgeries, bone marrow and organ transplants, managing immune compromised patients and cancer patients and for ordinary hip and knee replacements [8]. Antibiotic classified as beneath

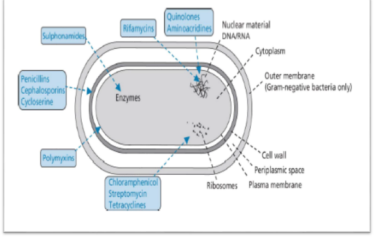

Figure 1 schematic illustration of mechanisms of action of antibacterial agents

Penicillins

Penicillins are a class of antibacterial medicines that attempt a broad relegate of bacteria. They belong to β-lactams antibiotic category. The fundamental structure of the penicillins is a nucleus involving of a thiazolidine ring, the β-lactam ring, and a side chain [9].

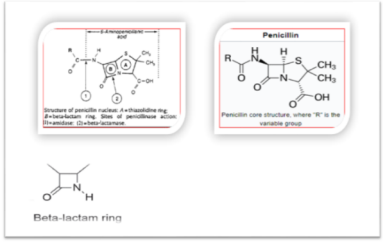

Figure 2 chemical structures of penicillins

Mechanism of action: Penicillins inhibit bacteria from propagating by suppressing bacteria from formation the walls that enclose them. The peptidoglycan wall is incessantly remaking amid duplication and excrescency. Penicillin has the ability to blocks cross-linking of peptidoglycan in the bacterial cell wall. The enzyme called DD-transpeptidase which is group of penicillin-binding proteins is used to catalyst for the reaction of blockage of cross-linking of bacterial cell wall called peptidoglycan. Penicillin has 4 membered beta lactam rings that can be irreversibly bind to DD-transpeptidase to inactivate bacterial cell wall. The bacteria, thereupon, are incapable to construct their cell walls even while distinctive proteins persist to compartmentalize the wall [10]

Classification: Penicillin classified into 5 groups based on their antimicrobial activity [11]: (1) Natural penicillins (penicillinase sensitive), instances: penicillin G, penicillin V potassium: Spectrum of activity: Natural penicillin are highly active against non β-lactamase generating gram-positive bacteria, anaerobes, and selected gram-negative cocci, such as Neisseria. Active against: G+ve aside from penicillinase generating staphylococci G –ve cocci (N. menigitidis, N. gonorrhea), Spirochetes (T. pallidum, Borrelia), although, natural penicillin has little activity against gram-negative, rods, and they are highly vulnerable to hydrolysis by beta lactamases. Clinical use: Pencillin G is medicine of choice for pneumonia or meningitis by Streptococcus pneumonia, Pharyngitis by streptococcus pyrogenes, infectious endocarditis by

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streptococcus viridians. (2) Penicillinase-resistant penicillins (antistaphylococcal), instances: cloxacillin, dicloxacillin, methicillin, nafcillin, oxacillin, and isoxazolyl penicillins: Spectrum of activity: Are semi-synthetic antibiotics resistant to staphylococcal penicillinase (consequently effective against streptococci and most community-acquired penicillinase- generating staphylococci): Clinical use: Nafcillin and oxacillin medicines of choice for treating, MSSA, infections, cloxacillin and dicloxacillin used to treat localized skin infections: (3) Aminopenicillins (wide spectrum penicillins), instances: ampicillin and amoxicillin; Antimicrobial of activity: Semisynthetic penicillins are mostly active against gram negative bacteria when compared with the natural penicillin and penicillinase-resistant penicillins beyond streptococcus involving pneumococcus strains. Ampicillin and amoxicillin are also most effective against multiple strains of haemophilus influenza, Escheria coli, streptococcus faecalis and salmonella. Clinical use: Aminopenicillins such as ampicillin and amoxicillin are mainly used for many infectious diseases such as chest infections (e.g. bronchitis, pneumonia), otitis media, urinary tract infections, biliary infections and also amoxicillin preventing of bacterial endocarditis. (4) Extended-spectrum penicillins (carboxypenicillins), carbenicillin and ticarcillin; Spectrum of activity: Sensitive to destroyed by β-lactamases is ordinarily little effective against g (+) infections than the other penicillins: (5) Extended-spectrum penicillins (antipseudomonal) (acyl ureidopenicillins), azlocillin, mezlocillin, and piperacillin. The carboxypenicillins and ureidopenicillins are also appertained to as antipseudomonal penicillins: Spectrum of activity: Carboxypenicillins are mostly active against certain isolates of P. aeruginosa and some proteus spp. that are resistant to ampicillin and its congeners, sensitive to destroyed by β-lactamases are ordinarily little effective against g(+) infections than other penicillins

Contraindications: Penicillins are not given in individuals who have previous history of severe allergic reaction or penicillin and its derivatives; and also in individuals who have SJS after administering penicillin or a penicillin derivative, and in individuals who drank alcohol chronically [12].

Adverse drug reaction: Allergic reactions: urticaria, pruritus, angioedema. Penicillins are the most ubiquitous cause of drug allergy (1-10% of the patients who have experience an allergic reaction). Anaphylaxis: laryngealedema, bronchoconstriction, severe hypotension in 0.2% of patients. The penicillins can also cause acute interstitial nephritis, a disease described by inflammation of the tubules and interstitium of the kidneys. Acute interstitial nephritis can also available with hematuria, fever, and rash [13].

Drug interactions: If concurrent administration of penicillin and oral contraceptives; penicillin interrupt the enterohepatic cycling of ethinylestradiol by lowering the bacterial strains of the small intestine, which is responsible for the hydrolysis of the conjugated hormone. The prevention of hydrolysis can lead to an accelerated fecal loss of the hormone, resulting in reducing circulating levels of ethinylestradiol. Penicillin + Aminoglycosides: Aminoglycosides such alike gentamicin and penicillins such like ampicillin are frequently given for severe infections in hospitalized patients owing to penicillin mediated cell damage, facilitate entry (intracellular uptake) of the aminoglycosides in to the cell, which causes the subsequent bactericidal effect against the enterococci. Probenecid accelerates the amount of penicillin in serum levels by suppressing excretion of penicillins through kidneys. Concomitant administration of ampicillin and allopurinol may be accelerating the occurrence of medicine related skin rash. If penicillin given with BCG; Penicillin lower the effect of BCG live vaccine and typhoid live vaccine [14].

Other cell wall synthesis inhibitors (carbapenems such as imipenem, meropenem, and aztreonam), ticaracillin-clavulnate and piperaciin-tazobactam); Carbapenems like imipenem, meropenem, aztreonam), these groups of drugs are inhibit beta lactamase. Carbapenems is expressed as the 4:5 fused ring lactam of penicillin with a double bond between carbon-2 and carbon-3, but in carbapenem carbon on at carbon-1 substituted by sulfur [15].

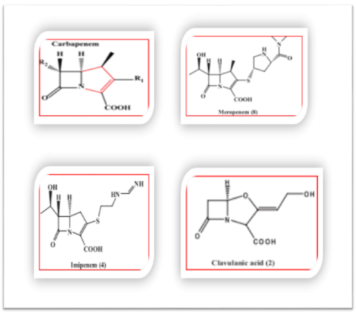


Figure 3 chemical structures of carbapenems

Mechanism of action: carbapenems function by suppressing the secretion of the bacterial cell wall and they bind with great affection to penicillin binding proteins of gram-positive and gram-negative bacteria.

Antibacterial Activity: The antimicrobial activities of carbapenems are excellent against gram-positive, gram-negative, and anaerobic. From carbapenem group, doripenem is the most active against P. aeruginosa and has limited spectrum of activity against aerobic gram-negative rods (involving P. aeruginosa) [16]. Ticarcillin and clavulanate; ampicillin and sulbactam; amoxicillin and clavulanate; piperacillin and tazobactam; they have no antimicrobial activity, but they combine with other penicillins and irreversibly blocks beta lactamase enzymes that destroy penicillin.

Clinical use: Used for intra-abdominal interactions, otitis externa, skin infections, UTI, liver abscess

Adverse drug reaction: Disturbances in LFTs, headache, phlebitis, seizures, rash, GI disturbance's, swelling and pain at injection site

Drug interactions: Meropenem serum level perhaps accelerated with probenecid administration

Cephalosporin

The fundamental structure involves a beta lactam ring fused to 6 member sulphur containing dihydrothiazine ring.

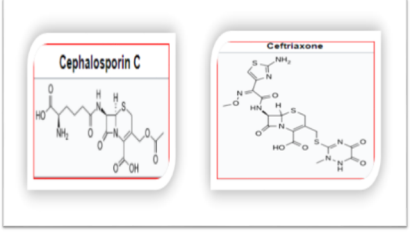


Figure 4 chemical structures of cephalosporins

Based on their spectrum of activity against gram-positive and gram-negative bacteria as well as their temporal discovery cephalosporins are grouped into five classes. Spectrum of activity: From 1st generation to 3rd generation is accelerating activity against G-ve & anaerobes, accelerating resistance to destroy beta-lactamase, accelerating capability to achieve CSF. Cephalosporins are categorized as parenteral and oral based on its route of administration [17]. (1) First-generation: Cefazolin, cephalothin, cephapirin, and cephradine are prepared as parenteral route of administration. Cefadroxil, Cephalexin, and Cephradine are prepared as oral route of administration. Spectrum of activity: The antibacterial activity of first-generation cephalosporins against

most gram-positive cocci as well as gram-negative bacteria, e.g., Escherichia coli (E. coli), Proteus mirabilis, and Klebsiella pneumoniae are well. Clinical use: First-generation cephalosporins may be used for treatment of skin and soft tissue infections, urinary tract infections, throat caused by streptococcus, ear infections such as otitis media, pneumonia and also certain first-generation cephalosporins are used for prophylactic antibiotics during surgery including the chest, abdomen, or pelvis. First-generation cephalosporins have greater activity against Gram-positive bacteria, though they also act against gram-negative bacteria. (2) Second-generation: Cefamandole, cefonicid and cefuroxime are administrated via parenteral. Cefaclor, cefprozil, cefuroxime, and loracarbe are prepared as oral administration. Antimicrobial of activity: The antibacterial activities of second-generation cephalosporins are highly active against haemophilus influenzae, Moraxella catarrhalis, and Bacteroides spp and also act on some group of gram-positive and gram-negative bacteria. When compared with first-generation cephalosporins, second-generation cephalosporins have little activity against some gram-positive bacteria. The frequent usage of second-generation cephalosporins used for treatment of respiratory infections, such as bronchitis or pneumonia and other infections occasionally managed with first-generation cephalosporins involve ear infections, sinus infections, urinary tract infections, gonorrhea, meningitis, sepsis. (3)Third-generation: Cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, and moxalactam are administered via parenteral route of administration. Cefixime, cefdinir, cefditoren, cefpodoxime and ceftibuten are administered via oral route of administration: Antimicrobial of activity: The antibacterial activity of third-generation cephalosporins are little activity against most gram-positive organisms; but have accelerated activity against Enterobacteriaceae, Neisseria spp., and H. influenza. When compared third-generation cephalosporins with first and second generation cephalosporins; the third-generation cephalosporins are highly active against gram-negative bacteria. Third-generation cephalosporins are also greater active against bacteria those perhaps resistant to the previous generations of cephalosporins, but their activity against gram-positive bacteria, involving streptococcus and staphylococcus species less active than 1st and 2nd generations. Ceftazidime is the only third-generation cephalosporin, which frequently used for treatment of pseudomonas infections, enclosing hot tub folliculitis. Third-generation cephalosporins perhaps also are used to treatment of skin and soft tissue infections, pneumonia, urinary infections, gonorrhea, meningitis, Lyme disease, sepsis. (4) Fourth-generation: Cefepime and Cefpirome are the two groups of fourth generation cephalosporins currently available. Spectrum of activity: When compare fourth-generation cephalosporins with third-generation cephalosporins they have comparable antimicrobial activity but fourth-generation cephalosporins are highly activity against gram-negative bacteria with antimicrobial resistance, like beta-lactamase. Fourth-generation cephalosporins are work against on both gram-positive and gram-negative bacteria and also ordinarily used for treatment of most severe infections or for those with weakened immune systems. Cefepime can be used for treatment of skin and soft tissue infections, pneumonia, urinary tract infections, abdominal infections, meningitis, and sepsis. **(*5)** Fifth-generation: Fifth-generation cephalosporins are highly active against MRSA. Ceftaroline and Ceftobiprole are new groups of fifth-generation cephalosporins. *indicate"new".

Mechanism of action: Cephalosporins prevent the bacteria cell wall that is strengthening by cross-linking peptidoglycan units through penicillin-binding proteins (PBP, peptidoglycan transpeptidase). The presence of beta-lactam rings on cephalosporins binds to the penicillin-binding protein to prevent the normal activity of bacteria and incapable to secrete a cell wall, the bacteria die. They function by inhibiting the secretion of the bacterial cell wall [18]

Contraindications: Ceftriaxone is not given in hyperbilirubinemic neonates because ceftriaxone displaces bilirubin from albumin, and enhancing the free bilirubin accumulations and accelerates the risk of jaundice in neonates. Ceftriaxone has the ability to react with calcium-containing solution and also have the ability to form precipitate in lungs and kidneys of infants less than twenty eight days old and this side effect may be life-threatening; so ceftriaxone is given with products which containing calcium such as ringer lactate in infants less than twenty days old and all population [19].

Adverse drug reaction: Hypersensitivity reaction (rash, hives, and swelling, anaphylaxis): Ubiquitous-nausea, vomiting and diarrhea, bronchospasm, and urticaria, drug-induce immune hemolytic anemia, vitamin K deficiency, cross-reactivity with penicillin allergy, nephrotoxic, disulfrum-like reaction.

Drug interactions: Concurrent administration of certain first-generation cephalosporins with some medication such as furosemide, aminoglycosides or other nephrotoxic agents accelerates the risk of nephrotoxicity. Concomitant administration of certain third-generation medications and anticoagulant medications are increases the risk of bleeding due to elevated prothrombin times, which is reversible with vitamin K. Ceftriaxone + NS, Cephalosporins+ Probenecid, Cephalosporins+alcohol [20]

Aminoglycosides

Gentamicin, tobramycin, neomycin, streptomycin, amikacin and etc

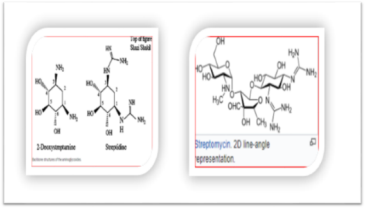


Figure 5 chemical structures of aminoglycosides

Mechanism of action: Aminoglycosides inhibit protein production by binding to 30s and 50s ribosomal subunits [21]

Spectrum of Activity: Aminoglycosides are highly active against aerobic and facultative gram-negative bacilli (Enterobacteriaceae to Pseudomonas spp. and acinetobacter spp.) and aerobic gram-positive bacteria. Clinical use: Urinary Tract Infections, pneumonia, meningitis, bacterial endocarditis, sepsis. Gentamicin: the aminoglycoside routinely prescribed during pregnancy and streptomycin for tuberculosis

Adverse drug reaction: Aminoglycosides most often cause renal impairment in the elderly. Severe adverse reactions are linked to aminoglycoside use involving hearing loss (ototoxicity) and kidney damage (nephrotoxicity) [22].

Drug interaction: Concomitant administration of aminoglycosides and some beta-lactams reveals synergistic activity against several gram-positive and gram-negative bacteria and is also used for management of severe infections, which kill microorganism instantaneously (example, for management of endocarditis caused by Enterococcus species with a combination of penicillin groups such as benzathine penicillin etc and gentamicin).

Quinolones and flouroquinolones

The synthetic antibacterial agents called 6-fluoroquinolones (AKA 4-quinolones or quinolones are derived from, nalidixic acid and oxolinic acid. In structure of these synthetic antibacterial there carboxylic acid at position 3which is highly required for antimicrobial activity, correspondently also like a keto group are available at its position. The activity against pseudomonas are delivered by substitution of a piperazinyl ring at position 7and the availability of a fluorine atom at position 6 lengthens its activity of the molecule to certain but not all gram-positive bacteria. Synthetic antibacterial agents have no activity against streptococcus because it is resistant strains [23]

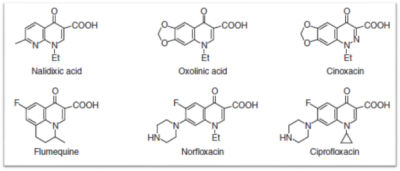


Figure 6 chemical structures of quinolones

Fluoroquinolones have bactericidal broad spectrum activity, has reasonable oral bioavailability, and usually it has reasonable tolerability sequenced in expansive clinical use of the recent clinical management.

Antimicrobial activity: Fluoroquinolones are highly active against enterobacteriaceae, on few gram-negative bacteria and P. aeruginosa, also it have activity against staphylococci, mycobacteria, chlamydia, mycoplasma and urea plasma. Fluoroquinolones has little or no activity against streptococci (especially group D streptococci), enterococci, and anaerobic bacteria [24].

Mechanism of action: These inhibit bacterial DNA duplication/ block the enzyme DNA gyrase.

Antimicrobial Activity: Recent fluoroquinolones have high activity against aerobic gram-negative bacilli, specifically members of the family enterobacteriaceae, M. catarrhalis, and haemophilus and against gram-negative cocci such as neisseria species. The only available quinolones with sufficient potency against P. aeruginosa are ciprofloxacin and levofloxacin.

Clinical use: Fluoroquinolones are used for the treatment of urinary tract infections caused by multi medication resistance bacteria, instances, Pseudomonas and for bacterial diarrhea caused by shigella, salmonella, E coli, or campylobacter. Quinolones also recommended for infections of soft tissues, bones, and joints and in intraabdominal and respiratory tract infections.

Adverse drug reaction: Fluoroquinolones are well tolerated. The common side effects of fluoroquinolones are nausea, vomiting, and diarrhea. Sometimes, headache, dizziness, insomnia, skin rash, or abnormal liver function tests advance. Damage expanding cartilage and cause an arthropathy. Flouroquinolones should be avoided during pregnancy and breastfeeding. Quinolones can also cause arrhythmias by prolongation of the QT interval [25].

Drug interaction: If fluoroquinolones and antacids are concomitantly administrated; antacids highly lower the absorption of fluoroquinolones because antacids form chelation with fluoroquinolones due calcium content in both medications. If fluoroquinolones concurrently given with probenecid, probenecid decreases the renal clearance of fluoroquinolones. Concomitant administration of fluoroquinolones and corticosteroids may accelerate the risk of tendon injury. Fluoroquinolones increases the serum level of theophylline if given together [26].

Vancomycin Vancomycin is a tricyclic glycopeptide antibiotic with bactericidal activity

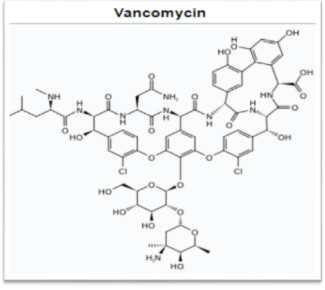


Figure 7 chemical structure of vancomycin

Mechanism of action: Vancomycin inhibits bacterial cell wall secretion by preventing elongation of peptidoglycan & cross linking and vancomycin blocks transpeptidation by binding to D-alanyl-D-alanine residues of the bacterial cell wall [27].

Antimicrobial activity: Vancomycin has the ability to displace activity against most strains of aerobic gram-positive microorganisms (diphtheroids enterococci (e.g., enterococcus faecalis) staphylococci, involving staphylococcus aureus and staphylococcus epidermidis (enclosing heterogeneous methicillin-resistant strains) streptococcus bovis, viridans group streptococci.

Clinical use: Vancomycin is used for the management of severe infections caused by vulnerable strains of MRSA. Vancomycin is also given for individuals who are allergic to penicillin, for patients who cannot take or who have failed to answer to other medicines, involving the penicillins or cephalosporins, and for infections caused by vancomycin-vulnerable organisms that are resistant to other antimicrobial medicines. Vancomycin is used as primary treatment when MRSA strains are suspected, but after vulnerability data are avail, treatment vancomycin is started.

Contraindicated: Vancomycin is not given for individuals who had obvious hypersensitivity to this antibiotic and solutions containing dextrose perhaps such as corn or corn products [28].

Adverse drug reaction: Vancomycin causes ototoxicity tinnitus, high-tone hearing loss, and deafness in farthest in stances. Intravenous infusion of vancomycin can sequence in chills, fever, and a maculopapular skin rash frequently enclosing the head and upper thorax (red man syndrome) is not known to cause fetal affliction, during pregnancy even it is category C. It irritates the tissues surrounding the injection site [29]

Drug interaction: If vancomycin and an aminoglycoside are administered together, they act synergistically in vitro against multiple strains of staphylococcus aureus, streptococcus bovis, enterococci, and the viridans group streptococci. Coincidentally administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing and anaphylactoid reactions [30]

Polymyxin B and colistin

Cyclic cationic polypeptide detergents are groups of Polymyxins. The two parenteral polymyxins that have been used are polymyxin B and polymyxin E (colistin). There are two preparation of colistin called colistin sulphate which administered orally or topically and colistimethate sodium which prepared for intramuscular, intravenous or the nebulised form administration [31].

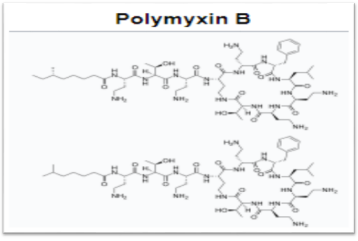


Figure 8 chemical structure of polymyxin B

Mechanism of action: polymyxin B interact strongly with phospholipids and rupture the structure of cell membranes especially, polymyxins attach to LPS and phospholipids in the exterior cell membrane of gram-negative bacteria. They competitively displace divalent cations from the phosphate groups of membrane lipids, which lead to the destabilization of the exterior cell membrane, the leakage of intracellular contents, and bacterial cell death [32]

Antimicrobial Activity: Polymyxins has the consequential activity against gram-negative aerobic pathogens, involving most

members of the enterobacteriaceae family, E. coli, enterobacter spp., klebsiella spp., citrobacter spp., salmonella spp., and shigella spp. Polymyxins has antimicrobial activity against on most gram-negative aerobic bacilli.

Clinical use: Used for MDR gram-(-) bacilli and for intestinal decontamination.

Adverse drug reaction: Muscle weakness and apnea (interference with neurotransmission at the neuromuscular junction), vertigo, and slurred speech. Polymyxins are nephrotoxic, and administration with aminoglycosides should be avoided if possible [33]

Drug interaction: When polymyxin administered coincidentally with vancomycin it accelerates risk of ototoxicity and nephrotoxicity Sulphonamides

Sulfonamides derived from sulfanilamide (p-amino benzene sulfonamide) are routinely appertained to as sulfa drugs. The sulfa drugs are still consequential as antimicrobial agents, whereas they have been displaced in multiplex systemic infections by the natural and semisynthetic antibiotics. The sulfonamide drugs were the first effective chemotherapeutic agents to be employed systemically for the precluding and heal of bacterial infections in humans [34].

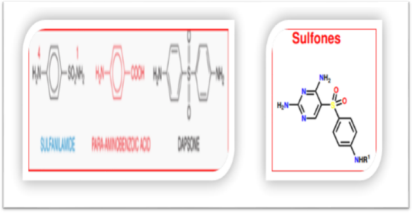


Figure 9 chemical structures of sulphonamides

Antibacterial spectrum: Sulphonamides hinder both G (+) and G (-) bacteria, nocardia, chlamydia trachomatis.

Certain enteric bacteria (E coli, klebsiella, salmonella, shigella, and enterobacter)

Mechanism of action: Sulphonamides act to prevent folate secretion at earliest stages. Competitively block dihydropteroate synthetase (DHPS) and inhibit folic acid synthesis. They interfere with the microbial synthesis of folic acid at separate steps in the biosynthetic pathway that ultimately leads to bacterial DNA synthesis inhibition [35].

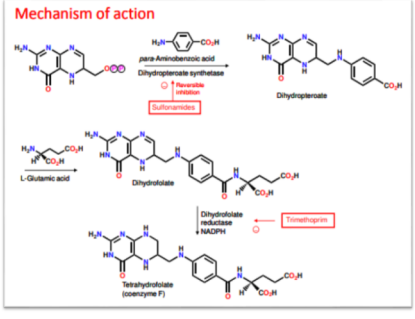


Figure 10 mechanisms of actions of sulphonamides

Clinical use: Sulphonamides used for treatment of uncomplicated urinary tract infections caused by E. coli, nocardiosis. Toxoplasmosis (combination of pyrimethamine and sulfadiazine is the treatment of choice). Sulfonamide (sulfadoxine) in combination with pyrimethamine (fansidar) is treatment of choice chloroquine-resistant malaria caused by P. falciparum and toxoplasmosis.

Contraindications: Sulfonamides can replace bilurubin from plasma proteins, with the pitfall of kernicterus in the neonate if used during the third trimester of pregnancy [36]

Adverse drug reaction: Sulphonamides causes hypersensitivity reactions. Mild reactions are frequent (rash, drug fever, and photosensitivity), SJS, hematologic effects (hemolytic anemia in patients with G-6-P deficiency), kernicterus: a disorder in newborns caused by deposition of bilirubin in the brain. The drugs should not be given to infants under the age of 2 months, pregnant women near term or breastfeeding mothers, renal damage from crystalluria. Adequate hydration and alkalinization of urine prevent the problem [37]

Drug interaction: If sulphonamides given with warfarin, hypoglycemic medicines such as sulfonylureas, phenytoin and methotrexate are compete together for plasma protein binding transiently accelerates the plasma levels of sulphonamide medicines [38]

Amphenicols

Synthetically generated chloramphenicol is isolated originally from the organism streptomyces venezuelae resulted in soil and compost [39]

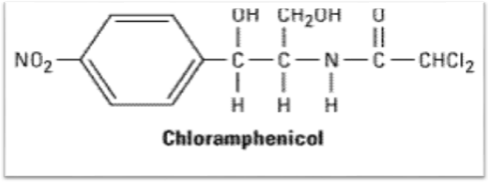


Figure 11 chemical structure of chloramphenicol

Mechanism of action: Chloramphenicol blocks protein secretion in bacteria binding to 50s ribosome, and to a least restrictions, in eukaryotic cells and also prevents protein secretion in vulnerable organisms by competing with messenger RNA for binding sites on the ribosome necessitated for the formation of peptide bonds. Chloramphenicol reversibly binds to the 50S subunit of the 70S ribosome, which precludes the devotedness of the amino acid-containing end of the aminoacyl-tRNA to its binding region, thereby blocking peptidyl transferase [40].

Clinical use: Chloramphenicol used for treatment of systemic infections such as bacterial meningitis caused by N. meningitis, S. Pneumonia), and also used for typhoid Fever, rickettsial diseases, brucellosis as alternative.

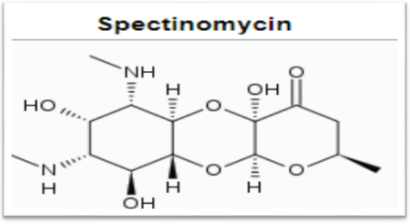
Adverse drug reaction: Chloramphenicol can cause hematologic problems such as (bone marrow suppression, hemolytic anemia), cardiac impairment (cardiovascular collapse), neurologic problems (optic neuritis, peripheral neuritis, encephalopathy, headache, mental confusion, depression), other hypersensitivity reaction, nausea, vomiting, diarrhea, pseudomembranous colitis, glossitis, stomatitis, ototoxicity (topical otic formulations), gray baby syndrome because newborn infants have no the ability to adequately conjugate CAF to form the glucuronide. Cross allergy perhaps happen with chemically related medicines such as thiazides, and hypoglycemics. Chloramphenicol cause nephrotoxicity because they perhaps precipitate in the urine at acidic pH, causing crystalluria and hematuria [41]

Drug interaction: If phenytoin with chloramphenicol concurrently administrated; phenytoin perhaps causes concentration of chloramphenicol in serum that reach toxic levels [42].

Spectinomycin

Spectinomycin belongs to the chemical group of aminoglycosides [43].

Figure 12 chemical structure of spectinomycin



Mechanism of action: Spectinomycin binds to the 30S subunit of the bacterial ribosome and ruptures protein secretion. One form of resistance has emerged in the 16S ribosomal RNA in Pasteurella multocida [44]

Clinical use: Spectinomycin is given intramuscular injection for treatment of gonorrhea, specifically in individuals who are allergic to penicillins.

Adverse drug reaction: Side effects of spectinomycin involve itching, chills, stomach ache, and red rash [45].

Drug interaction: Coincident administration of spectinomycin with lithium causes lithium toxicity.

Trimethoprim

An aminopyrimidine antibiotic whose structure involves of pyrimidine 2, 4-diamine and 1, 2, 3-trimethoxybenzene moieties is linked by a methylene bridge. A synthetic derivative of trimethoxybenzyl-pyrimidine called trimethoprim hast the ability to act as antibacterial and antiprotozoal properties. As a pyrimidine inhibitor of bacterial dihydrofolate reductase, trimethoprim binds strongly to the bacterial enzyme, inhibiting the generation of tetrahydrofolic acid from dihydrofolic acid. The antibacterial activity of trimethoprim is potentiated by sulfonamides (NCI04) [46]

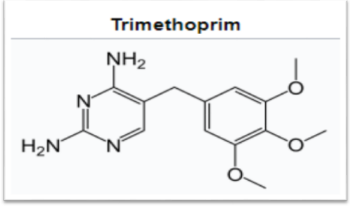


Figure 13 chemical structure of trimethoprim

Antibacterial Spectrum: Trimethoprim displays broad-spectrum activity, active against most g (+) and g (-), least activity against anaerobic bacteria

Mechanism of action: It damages the tetrahydrofolate synthesis pathway and the same mechanism of action with sulfonamides [47] Clinical use: In acute urinary tract infections (100 mg twice daily), for most community-acquired organisms tend to be vulnerable to the great concentrations that are resulted in the urine.

Contraindications: Trimethoprim is contraindicated in pregnant women near to the birth, nursing mothers, individuals with megaloblastic anemia owing to folate deficiency, in patients with possible folate deficiency, severe allergies, bronchial asthma or glucose-6-phosphate 4 dehydrogenase deficiencies, elderly patients. Trimethoprim also contraindicated in persons with AIDS; who have a greater risk for leucopenia and rash [48].

Adverse drug reaction: TMP: antifolate adverse effects (megaloblastic anemia, leukopenia, and granulocytopenia) particularly in pregnant patients and those having very meager diets. Nausea and vomiting, drug fever, renal damage [49]

Drug interaction: Other diaminopyrimidines-pyrimethamine, azathioprine, or methotrexate is potentiated by TMP, sequencing in severe leukopenia. Sulfonamides replace warfarin from binding albumin, thus escalating its serum level. SMX inhibits the clearance of phenytoin, extending its half-life [50].

Tetracycline

There is short acting TTC such as oxytetracycline, tetracycline HCL; intermediate acting demclocycline HCl; long acting such as doxycycline, minocycline and long- acting and third generation tigecycline are groups of tetracycline [51]. Doxycycline, tetracycline, and minocycline belong to tetracyclines group.

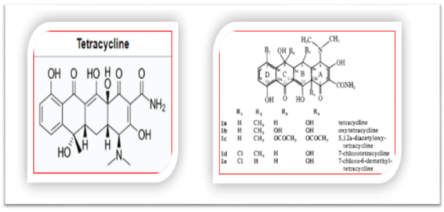


Figure 14 chemical structure of tetracycline

Mechanism of action: Tetracycline binds reversibly to the 30S bacterial ribosomal subunit, and inhibits the binding of amino-acyl-tRNA to the acceptor site on the mRNA complex. This used to suppress the incorporation of amino acids to the progressing peptide chain, thereby eventually blocking protein secretion [52].

Antimicrobial activity: Most tetracyclines except tigecycline are nearly having identical properties. Tigecycline has activity against gram positive, gram negative and anaerobic. Tetracycline is also active against multi drug resistant pathogens resistant to older tetracyclines like MRSA, VRE, resistant pneumococci and acinetobacter baumanii.

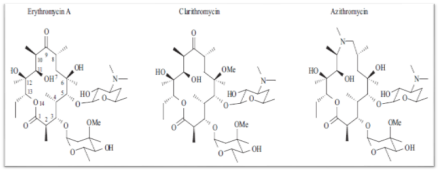
Clinical use: Tetracycline used for treatment of rickettsial diseases such as typhoid/typhus fever, anthrax, occasionally applicable in the treatmentment of protozoal infections such as E. histolytica, P. falciparum, acne, and for peptic ulcer disease in combination of tetracyclines, metronidazole and bismuth salicylate against H. Pylori in bismuth based quadruple therapy for H-pylor eradication.

Adverse drug reaction: Photosensitivity, hypersensitivity, perpetual enamel hypoplasia or discoloration of perpetual teeth and tooth enamel in fetuses and children, skeletal growth deterioration in immature infants or perhaps decelerate fetal skeletal advancement if taken during pregnancy, and gastrointestinal symptoms like esophageal ulcerations can happen after oral administration. They can sequence in hepatotoxicity specifically in pregnant females and escalate pre-existing renal failure by suppressing protein secretion, kidney toxicity, and change in intestinal flora perhaps sequence in superinfections (overgrowth of non-vulnerable organisms such as candida), diarrhea, pseudomembranous colitis caused by clostridium difficile, dizziness, vertigo

Drug interaction: Tetracyclines may be chelated by concurrently administered antacids and may be more poorly absorbed.

Macrolides: Linezolid is a member of the oxazolidinone group. Macrolide antibiotics are bacteriostatic in nature. Erythromycin, clarithromycin and azithromycin are macrolides belong to one of the most routinely used families of clinically consequential antibiotics used for treatment of infections caused by gram-positive bacteria such as staphylococcus aureus, streptococcus pneumoniae and streptococcus pyogenes. Chemically, macrolides are represented by a 14-, 15- or 16-membered lactone ring carrying one or more sugar moieties and additional substitutions linked to several atoms of the lactone ring [53]

Figure 15 chemical structures of macrolides



Spectrum of Activity: Macrolides has wide antimicrobial activity against gram-positive and gram-negative bacteria, involving actinomycetes and mycobacteria, treponemes, mycoplasma, chlamydiae, and rickettsiae. It is active against intracellular organisms involving salmonella, legionella, chlamydiae and C. burnetti.

Mechanism of action: Macrolides has four modes of prevention of protein secretion assigned below: 1) prevention of the advancement of the budding peptide chain during early rounds of translation; 2) elevation of peptidyl tRNA dissociation from the ribosome; 3) suppression of peptide bond conformation; and 4) interference with 50S subunit congregation. Entire of these mechanisms have certain correlation with the position of the macrolide attaching site on the ribosome [54].

Clinical use: Azithromycin and clarithromycin is used for treatment of acute bronchitis, sinusitis, otitis media, pharyngitis, soft tissue infections, CAP, uncomplicated enteric fever. Azithromycin recommended for acute non-gonococcal urethritis and M. avium complex infections in patients with AIDS. Clarithromycin is significant constituent of regimens used to exterminate H-pylori positive in peptic ulcer disease patients.

Adverse drug reaction: Macrolides cause fatal gastrointestinal disturbances which happened in horses. Hypersensitivity of macrolides uncommonly observed, cardiac toxicity [55]

Drug interaction: Clarithromycin is used in combination with other medicines for treatment of disseminated mycobacterium avium-intracellulare (MAC) in individuals who had AIDS and in treatment of helicobacter pylori in individuals who have peptic ulcer disease.

Lincomycin and Clindamycin

The lincosamide group of antibacterials originates from a natural product, lincomycin, and involves semisynthetic derivatives, clindamycin and pirlimycin. The most clinically applicable lincosamide, clindamycin, is often used to treatment of infections caused by streptococci and staphylococci. It is especially useful in treatment of connective tissue infections because of its approbatory skin and bone absorptivity and action against strains generating necrotizing toxins [56]

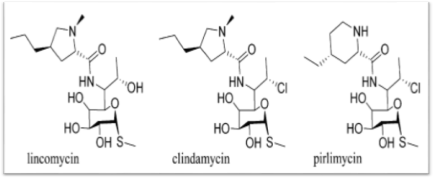


Figure 16 structures of the common lincosamide group antibiotics

Mechanism of Action: Lincosamide antibiotics have similar or overlapping 50S ribosomal binding sites as those for the macrolides and chloramphenicol, and they perhaps compete with these medicines for binding/ a molecular mechanism by which clindamycin prevents ribosomal protein biosynthesis in prokaryotic microorganisms is associated with the fact that clindamycin´s three dimensional structure closely resembles LPro- Met and the D-ribosyl ring of adenosine, which happen near alone at the 3´-ends of L-Pro-Met-tRNA and deacylated-tRNA for a brief interval following the formation of a peptide bond between L-Pro-tRNA and L-MettRNA [57].

Spectrum of Activity: Clindamycin is most potent than lincomycin but identical in potency to erythromycin against staphylococci, pneumococci, S. pyogenes, and streptococci of the viridans group when strains are sensitive to both. Clindamycin has been one of the most active antibiotics obtainable against B. fragilis. It is also effective against vulnerable community acquired MRSA.

Clinical use: Clindamycin used for treatment of penetrating wounds of the abdomen and the gut. In combination with aminoglycoside or cephalosporin, clindamycin plus primaquine is an effective discretion to co-trimoxazole for moderate to moderately severe PCP in AIDS patients and also used in combination with pyrimethamine for AIDS related toxoplasmosis of the brain.

Adverse drug reaction: Diarrhea (in 2% to 20% subjects), pseudomembranous colitis caused by the toxin from C. difficile, described by abdominal pain, diarrhea, fever, and mucus and blood in the stools. It perhaps lethal; discontinuation of the medicine, joined with administration of metronidazole orally or intravenously ordinarily is curative, skin rashes, SJS, impaired liver function [58]

Drug interaction: Coincident administration of lincosamide with neuromuscular blockers perhaps escalates respiratory depression and antagonizes the consequence of parasympathetic.

Conclusion

Bacteria also live in symbiotic and parasitic kinships with plants and animals. There are generally 40 million bacterial cells in a gram of soil and a million bacterial cells in a millilitre of fresh water. Antimicrobial agents and biocides are terms frequently used substitutable to delineate chemicals and other agents used to deliberately kill or block the expansion of injurious microbes. If sulphonamides given with warfarin, hypoglycemic medicines such as sulfonylureas, phenytoin and methotrexate are compete together for plasma protein binding transiently accelerates the plasma levels of sulphonamide medicines. Cotrimoxazole can competitively block dihydropteroate synthetase (DHPS) and inhibit folic acid synthesis. They interfere with the microbial synthesis of folic acid at separate steps in the biosynthetic pathway that ultimately leads to bacterial DNA synthesis inhibition.

Abbreviations

ADRs: Adverse drug reactions; CYP450: cytochrome P450; BCG: Bacillus Calmette Guerin; ; DNA: Dihydropteroate Synthetase; DI: Drug interaction; HCL: Hydrochloric acid; PH: Potenz Hydrogen; GIT: Gastrointestinal Tract; MAC: Mycobacterium avium-intracellulare; MRSA: methicillin-resistant Staphylococcus aureus; PCP: Pneumocystis Carinii Pneumonia; PBP: Penicillin-binding proteins; NS: Normal Saline; P-gp: Pglycoprotein; RNA: Ribonucleic acid; SJS: Stevens-Johnson syndrome; TMP: Trimethoprim; tRNA: Transfer Ribonucleic acid; UTIs: Urinary Tract infections; VRE: Vancomycin-resistant enterococci

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