I'm not a bot

Beta-lactam antibiotics have been a cornerstone in combating bacterial infections, offering solutions for many common and severe ailments. These drugs are valued for their broad-spectrum efficacy and relatively low toxicity compared to other antibiotic classes. However, antibiotic resistance poses challenges to their continued effectiveness. This article explores various aspects of beta-lactam antibiotics, including their mechanisms, types, and how bacteria develop resistance, providing insights into current medical practices and future considerations. Mechanism of Action Beta-lactam antibiotics target the bacterial cell wall, essential for maintaining cell integrity and shape. The cell wall is primarily composed of peptidoglycan, a polymer that provides mechanical strength. Beta-lactams interfere with the synthesis of this component by binding to penicillin-binding proteins (PBPs), enzymes involved in the final stages of peptidoglycan assembly. This binding inhibits the cross-linking of peptidoglycan strands, leading to a weakened cell wall. As the bacterial cell attempts to grow and divide, the compromised cell wall cannot withstand the internal osmotic pressure, resulting in cell lysis and death. This mechanism is particularly effective against actively dividing bacteria, as they are constantly remodeling their cell walls. The specificity of beta-lactams for bacterial cells, as opposed to human cells, accounts for their relatively low toxicity, making them a preferred choice in many clinical settings. The effectiveness of beta-lactam antibiotics is influenced by their ability to reach and bind to PBPs, which can vary among different bacterial species. Some bacteria possess multiple PBPs with varying affinities for beta-lactams, affecting the drug's efficacy. Additionally, the outer membrane of Gram-negative bacteria can act as a barrier, limiting the access of beta-lactams to their target sites. This necessitates the development of different beta-lactam compounds to overcome such barriers and enhance antibacterial activity. Types of Beta-Lactam Antibiotics Beta-lactam antibiotics encompass a diverse group of compounds, each with unique structural features and antibacterial spectra. These variations allow for targeted treatment of a wide range of bacterial infections. The primary classes include penicillins, cephalosporins, carbapenems, and monobactams, each offering distinct advantages and applications in clinical practice. Penicillins Penicillins are the earliest discovered beta-lactam antibiotics, with penicillin G being the first to be used clinically. They are primarily effective against Gram-positive bacteria, such as Streptococcus and Staphylococcus species. Over time, various derivatives have been developed to enhance their spectrum and stability, including amoxicillin and ampicillin, which are effective against some Gram-negative bacteria. Resistance to penicillins has emerged, often due to the production of beta-lactamase enzymes by bacteria, which hydrolyze the beta-lactam ring, rendering the antibiotic ineffective. To counteract this, beta-lactamase inhibitors like clavulanic acid are sometimes combined with penicillins to restore their efficacy. Cephalosporins Cephalosporins are a broad class of beta-lactam antibiotics developed over several generations, each with expanded activity against a wider range of bacteria. The first-generation cephalosporins, such as cephalexin, are effective primarily against Gram-positive bacteria. Subsequent generations, including cefuroxime and ceftriaxone, have increased efficacy against Gram-negative organisms and are often used to treat infections like pneumonia and urinary tract infections. The structural modifications in cephalosporins enhance their resistance to beta-lactamases, making them a valuable option in cases where penicillin resistance is a concern. However, the emergence of extended-spectrum beta-lactamases (ESBLs) poses a challenge, as these enzymes can degrade many cephalosporins, necessitating careful selection and use in clinical settings. Carbapenems Carbapenems, such as imipenem and meropenem, are among the most potent beta-lactam antibiotics, known for their broad-spectrum activity against both Gram-positive and Gram-negative bacteria, including many resistant strains. They are often reserved for severe or high-risk infections, such as those caused by multidrug-resistant organisms. Carbapenems are structurally unique, allowing them to evade many beta-lactamases, including ESBLs, which makes them effective against bacteria that are resistant to other beta-lactams. Despite their efficacy, the rise of carbapenem-resistant Enterobacteriaceae (CRE) has become a significant concern in healthcare settings, driven by the production of carbapenemase enzymes that inactivate these drugs. This resistance highlights the need for ongoing surveillance and the development of new therapeutic strategies. Monobactams Monobactams, with aztreonam being the only commercially available agent, are a unique class of beta-lactam antibiotics characterized by a single beta-lactam ring. They are specifically effective against aerobic Gram-negative bacteria, including Pseudomonas aeruginosa, making them useful in treating infections where Gram-negative pathogens are predominant. Monobactams are particularly valuable for patients with allergies to other beta-lactams, as they have a low cross-reactivity with penicillins and cephalosporins. While monobactams are resistant to some beta-lactamases, they are susceptible to others, such as metallo-beta-lactamases, which can limit their effectiveness. Their narrow spectrum of activity necessitates careful consideration of the infecting organism and susceptibility patterns when selecting monobactams for treatment. Resistance Mechanisms The emergence of resistance to beta-lactam antibiotics is a growing concern, driven by the adaptive capabilities of bacteria to survive in the presence of these drugs. One primary mechanism by which bacteria develop resistance is through the modification of target sites. Bacteria can alter or acquire mutations in the genes encoding penicillin-binding proteins (PBPs), reducing the binding affinity of beta-lactams. This alteration allows the bacteria to continue synthesizing their cell walls despite the presence of the antibiotic, thereby circumventing its intended effects. Additionally, the efflux pump systems in bacteria contribute significantly to resistance. These pumps actively expel antibiotics from the bacterial cell, decreasing the intracellular concentration of the drug and thus its efficacy. Efflux pumps can be specific to certain antibiotics or have broad-spectrum activity, impacting a wide range of drugs, including beta-lactams. The increased expression of efflux pumps is often a response to selective pressure from antibiotic exposure, highlighting the importance of judicious use of these medications. Another significant factor in resistance is the ability of bacteria to acquire resistance genes from other organisms through horizontal gene transfer. This process can occur via transformation, transduction, or conjugation, allowing bacteria to rapidly disseminate resistance traits within a population. The acquisition of mobile genetic elements, such as plasmids that carry beta-lactamase genes, can spread resistance across different bacterial species, exacerbating the challenge of controlling resistant infections. Class of broad-spectrum antibiotics β-Lactam antibioticDrug classCore structure of penicillins (top) and cephalosporins (bottom) the 2 most common groups of β-lactam antibiotics . β-lactam ring in red.Class identifiersUseBacterial infectionATC codeJ01CBiological targetPenicillin binding proteinExternal linksMeSHD047090Legal statusIn Wikidata β-Lactam antibiotics (beta-lactam antibiotics) are antibiotics that contain a β-lactam ring in their chemical structure. This includes penicillin derivatives (penams), cephalosporins and cephamycins (cephems), monobactams, carbapenems[1] and carbacephems.[2] Most β-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics. Until 2003, when measured by sales, more than half of all commercially available antibiotics in use were β-lactam compounds.[3] The first β-lactam antibiotic discovered, penicillin, was isolated from a strain of Penicillium rubens (named as Penicillium notatum at the time).[4][5] Bacteria often develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring. To overcome this resistance, β-lactam antibiotics can be given with β-lactamase inhibitors such as clavulanic acid.[6] β-Lactam antibiotics are indicated for the prevention and treatment of bacterial infections caused by susceptible organisms. At first, β-lactam antibiotics were mainly active only against gram-positive bacteria, yet the recent development of broad-spectrum β-lactam antibiotics active against various gram-negative organisms has increased their usefulness.[citation needed] In uninflamed (normal) brain meninges, the penetration of beta-lactam antibiotics is low, at 0.15 of AUCCSF/AUCS ratio (the ratio of area under curve of cerebrospinal fluid against area under curve of serum).[7] Common adverse drug reactions for the β-lactam antibiotics include diarrhea, nausea, rash, urticaria, superinfection (including candidiasis).[8] Infrequent adverse effects include fever, vomiting, erythema, dermatitis, angioedema, pseudomembranous colitis.[8] Pain and inflammation at the injection site is also common for parenterally administered β-lactam antibiotics.[citation needed] Immunologically mediated adverse reactions to any β-lactam antibiotic may occur in up to 10% of patients receiving that agent (a small fraction of which are truly IgE-mediated allergic reactions, see amoxicillin rash). Anaphylaxis will occur in approximately 0.01% of patients.[8][9] There is perhaps a 5–10% cross-sensitivity between penicillin-derivatives, cephalosporins, and carbapenems;[citation needed] but this figure has been challenged by various investigators.[who?][citation needed] Nevertheless, the risk of cross-reactivity is sufficient to warrant the contraindication of all β-lactam antibiotics in patients with a history of severe allergic reactions (urticaria, anaphylaxis, interstitial nephritis) to any β-lactam antibiotic. Rarely, allergic reactions have been triggered by exposure from kissing and sexual contact with a partner who is taking these antibiotics.[10] A Jarisch–Herxheimer reaction may occur after initial treatment of a spirochetal infection such as syphilis with a β-lactam antibiotic.[citation needed] Penicillin and most other β-lactam antibiotics act by inhibiting penicillin-binding proteins, which normally catalyze cross-linking of bacterial cell walls.[11] In the absence of β-lactam antibiotics (left), the cell wall plays an important role in bacterial reproduction. Bacteria attempting to grow and divide in the presence of β-lactam antibiotics (right) fail to do so, and instead shed their cell walls, forming osmotically fragile spheroplasts.[12] β-Lactam antibiotics are bactericidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity,[6] especially in gram-positive organisms, being the outermost and primary component of the wall. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by DD-transpeptidases, also known as penicillin binding proteins (PBPs). PBPs vary in their affinity for penicillin and other β-lactam antibiotics. The number of PBPs varies between bacterial species.[11] β-Lactam antibiotics are analogues of d-alanyl-d-alanine—the terminal amino acid residues on the precursor NAM/NAG-peptide subunits of the nascent peptidoglycan layer. The structural similarity between β-lactam antibiotics and d-alanyl-d-alanine facilitates their binding to the active site of PBPs. The β-lactam nucleus of the molecule irreversibly binds to (acylates) the Ser62 residue of the PBP active site. This irreversible inhibition of the PBPs prevents the final crosslinking (transpeptidation) of the nascent peptidoglycan layer, disrupting cell wall synthesis.[13] β-Lactam antibiotics block not only the division of bacteria, including cyanobacteria, but also the division of cyanelles, the photosynthetic organelles of the glaucophytes, and the division of chloroplasts of bryophytes. In contrast, they have no effect on the plastids of the highly developed vascular plants. This is supporting the endosymbiotic theory and indicates an evolution of plastid division in land plants.[14] Under normal circumstances, peptidoglycan precursors signal a reorganisation of the bacterial cell wall and, as a consequence, trigger the activation of autolytic cell wall hydrolases. Inhibition of cross-linkage by β-lactams causes a build-up of peptidoglycan precursors, which triggers the digestion of existing peptidoglycan by autolytic hydrolases without the production of new peptidoglycan. As a result, the bactericidal action of β-lactam antibiotics is further enhanced.[citation needed] Another possibility that has been proposed to account for much of the cytotoxicity of β-lactams focuses on the oxidation of the guanine nucleotide in the bacterial nucleotide pool.[15] The incorporation of oxidized guanine nucleotide into DNA could cause cytotoxicity. Bacterial cytotoxicity could arise from incomplete repair of closely spaced 8-oxo-2'-deoxyguanosine lesions in the DNA resulting in double-strand breaks.[15] See also: β-Lactam reactivity Two structural features of β-lactam antibiotics have been correlated with their antibiotic potency.[16] The first is known as "Woodward's parameter", h, and is the height (in angstroms) of the pyramid formed by the nitrogen atom of the β-lactam as the apex and the three adjacent carbon atoms as the base.[17] The second is called "Cohen's parameter", c, and is the distance between the carbon atom of the carboxylate and the oxygen atom of the β-lactam carbonyl.[18] This distance is thought to correspond to the distance between the carboxylate-binding site and the oxyanion hole of the PBP enzyme. The best antibiotics are those with higher h values (more reactive to hydrolysis) and lower c values (better binding to PBPs).[16] By definition, all β-lactam antibiotics have a β-lactam ring in their structure. The effectiveness of these antibiotics relies on their ability to reach the PBP intact and their ability to bind to the PBP. Hence, there are two main modes of bacterial resistance to β-lactams: enzymatic hydrolysis of the β-lactam ring and possession of altered penicillin-binding proteins.[citation needed] If the bacterium produces the enzyme β-lactamase or the enzyme penicillinase, the enzyme will hydrolyse the β-lactam ring of the antibiotic, rendering the antibiotic ineffective.[19] (An example of such an enzyme is New Delhi metallo-beta-lactamase 1, discovered in 2009.) The genes encoding these enzymes may be inherently present on the bacterial chromosome or may be acquired via plasmid transfer (plasmid-mediated resistance), and β-lactamase gene expression may be induced by exposure to β-lactams.[citation needed] Clavulanic acid Amoxicillin The production of a β-lactamase by a bacterium does not necessarily rule out all treatment options with β-lactam antibiotics. In some instances, β-lactam antibiotics may be co-administered with a β-lactamase inhibitor. For example, Augmentin (FGP) is made of amoxicillin (a β-lactam antibiotic) and clavulanic acid (a β-lactamase inhibitor). The clavulanic acid is designed to overwhelm all β-lactamase enzymes, and effectively serve as an antagonist so that the amoxicillin is not affected by the β-lactamase enzymes. Another β-lactam/β-lactamase inhibitor combination is piperacillin/tazobactam with a broad spectrum of antibacterial activity that includes gram-positive and -negative aerobic and anaerobic bacteria. The addition of tazobactam to piperacillin has enhanced its stability against a wide range of β-lactamase enzymes including some Extended-Spectrum β-lactamases.[20] Other β-lactamase inhibitors such as boronic acids are being studied in which they irreversibly bind to the active site of β-lactamases. This is a benefit over clavulanic acid and similar β-lactam competitors, because they cannot be hydrolysed, and therefore rendered useless. Extensive research is currently being done to develop tailored boronic acids to target different isozymes of beta-lactamases.[21] However, in all cases where infection with β-lactamase-producing bacteria is suspected, the choice of a suitable β-lactam antibiotic should be carefully considered prior to treatment. In particular, choosing appropriate β-lactam antibiotic therapy is of utmost importance against organisms which harbor some level of β-lactamase expression. In this case, failure to use the most appropriate β-lactam antibiotic therapy at the onset of treatment could result in selection for bacteria with higher levels of β-lactamase expression, thereby making further efforts with other β-lactam antibiotics more difficult.[22] In the context of medical pharmacology, penicillins, cephalosporins, and carbapenems, while all have the β-lactam ring that serves as the fundamental structure, also have an auxiliary ring that carries a carboxylate group that is positioned on the same side as the carbonyl group within the β-lactam ring, and, as such, this structural configuration is critical to their antimicrobial activity.[23] Bacterial resistance to these antibiotics primarily occurs through the production of β-lactamases, enzymes that hydrolyze the amide bond of the β-lactam ring, thereby eliminating the antimicrobial activity of these antibiotics. This resistance mechanism underscores the importance of the structural integrity of the β-lactam ring for the antibiotic's function.[24] The color change from colorless or light yellow to amber or even red in an aqueous solution of a β-lactam antibiotic can denote β-lactamase hydrolysis of amide bonds in the β-lactam ring.[25][26] This is often observed with a chromogenic β-lactamase substrate like ceftriaxone, merapenem, or nitrocefin,[27] that undergoes a distinctive color change from yellow to red as the amide bond in the β-lactam ring is hydrolyzed by β-lactamase.[27][28] This color change is a visual indicator of the presence and activity of β-lactamase enzymes, which are responsible for conferring resistance to β-lactam antibiotics in many bacterial species. The hydrolysis of the β-lactam ring by β-lactamase enzymes renders the antibiotic ineffective, thereby allowing the bacteria to survive in the presence of the antibiotic.[28] Some β-lactam antibiotics like ceftriaxone and meropenem are known to be relatively unstable in solution, especially when stored for extended periods, and degrade in an aqueous solution even without the presence of β-lactamase.[29] For ceftriaxone, the color of solutions can range from light yellow to amber, depending on the length of storage, concentration, and diluent used.[30][31] A study found that meropenem concentrations dropped to 90% of the initial concentration at 7.4 hours at 22°C and 5.7 hours at 33°C, indicating degradation over time.[29] As a response to the use of β-lactams to control bacterial infections, some bacteria have evolved penicillin binding proteins with novel structures. β-Lactam antibiotics cannot bind as effectively to these altered PBPs, and, as a result, the β-lactams are less effective at disrupting cell wall synthesis. Notable examples of this mode of resistance include methicillin-resistant Staphylococcus aureus (MRSA)[32] and penicillin-resistant Streptococcus pneumoniae. Altered PBPs do not necessarily rule out all treatment options with β-lactam antibiotics.[medical citation needed] See also: List of β-lactam antibiotics The β-lactam core structures. (A) A penam. (B) A carbapenam. (C) An oxapenam. (D) A penem. (E) A carbapenem. (F) A monobactam. (G) A cephem. (H) A carbacephem. (I) An oxacephem. β-Lactams are classified according to their core ring structures.[33] β-Lactams fused to saturated five-membered rings: β-Lactams containing thiazolidine rings are named penams. β-Lactams containing pyrrolidine rings are named carbapenams. β-Lactams fused to oxazolidine rings are named oxapenams or clavams. β-Lactams fused to unsaturated five-membered rings: β-Lactams containing 2,3-dihydrothiazole rings are named penems. β-Lactams containing 2,3-dihydro-1H-pyrrole rings are named carbapenems. β-Lactams fused to unsaturated six-membered rings: β-Lactams containing 3,6-dihydro-2H-1,3-thiazine rings are named cephems. β-Lactams containing 1,2,3,4-tetrahydropyridine rings are named carbacephems. β-Lactams containing 3,6-dihydro-2H-1,3-oxazine rings are named oxacephems. β-Lactams not fused to any other ring are named monobactams. By convention, the bicyclic β-lactams are numbered starting with the position occupied by sulfur in the penams and cephems, regardless of which atom it is in a given class. That is, position 1 is always adjacent to the β-carbon of β-lactam ring. The numbering continues clockwise from position one until the β-carbon of β-lactam is reached, at which point numbering continues counterclockwise around the lactam ring to number the remaining to carbons. For example, the nitrogen atom of all bicyclic β-lactams fused to five-membered rings is labelled position 4, as it is in penams, while in cephems, the nitrogen is position 5.[citation needed] The numbering of monobactams follows that of the IUPAC; the nitrogen atom is position 1, the carbonyl carbon is 2, the α-carbon is 3, and the β-carbon 4.[citation needed] To date, two distinct methods of biosynthesizing the β-lactam core of this family of antibiotics have been discovered. The first pathway discovered was that of the penams and cephems. This path begins with a nonribosomal peptide synthetase (NRPS), ACV synthetase (ACVS), which generates the linear tripeptide δ-(L-α-aminoadipyl)-L-cysteine-D-valine (ACV). ACV is oxidatively cyclized (two cyclizations by a single enzyme) to bicyclic intermediate isopenicillin N by isopenicillin N synthase (IPNS) to form the penam core structure.[34] Various transamidations lead to the different natural penicillins. This figure outlines the different methods of β-lactam closure among the various classes of β-lactam compounds. Penams and cephems are cyclized oxidatively (first row); clavams and carbapenems are closed by ATP-utilizing amidation (second and third row); and some monobactams may be closed by a third method (fourth row). The biosynthesis of cephems branch off at isopenicillin N by an oxidative ring expansion to the cephem core. As with the penams, the variety of cephalosporins and cephamycins come from different transamidations, as is the case for the penicillins.[citation needed] While the ring closure in penams and cephems is between positions 1 and 4 of the β-lactam and is oxidative, the clavams and carbapenems have their rings closed between positions 1 and 2 of the ring. β-lactam synthetases are responsible for these cyclizations, and the carboxylate of the open-ring substrates is activated by ATP.[35] In clavams, the β-lactam is formed prior to the second ring; in carbapenems, the β-lactam ring is closed second in sequence.[citation needed] The biosynthesis of the β-lactam ring of tabtoxin mirrors that of the clavams and carbapenems. The closure of the lactam ring in the other monobactams, such as sulfazecin and the nocardicins, may involve a third mechanism involving inversion of configuration at the β-carbon.[36] List of β-lactam antibiotics ATC code J01C Beta-lactam antibacterials, penicillins ATC code J01D Other beta-lactam antibacterials Bacteria Cell wall Discovery and development of cephalosporins History of penicillin Nitrocefin ^ Holten KB, Onusko EM (August 2000). "Appropriate prescribing of oral beta-lactam antibiotics". American Family Physician. 62 (3): 611–20. PMID 10950216. Archived from the original on June 6, 2011. Retrieved November 8, 2008. ^ Yao, JDC, Moellering, RC Jr. (2007). "Antibacterial agents". In Murray, PR, et al. (eds.). Manual of Clinical Microbiology (9th ed.). Washington D.C.: ASM Press. Cited in Non-Penicillin Beta Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination (Report). 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Retrieved from " Beta-lactam antibiotics are used in the management and treatment of bacterial infections. This activity will highlight the mechanism of action, adverse event profile, and other key factors (e.g., off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions) pertinent for members of an interprofessional healthcare team in the treatment of patients. Objectives: Identify the mechanism of action of beta-lactam antibiotics.Describe the possible adverse effects of beta-lactam antibiotics.Outline the appropriate monitoring of patients taking beta-lactam antibiotics.Summarize interprofessional team strategies for improving care coordination and communication to advance beta-lactam antibiotics and improve outcomes. Access free multiple choice questions on this topic. Beta-lactam antibiotics are one of the most commonly prescribed drug classes with numerous clinical indications. Their advent starting from the 30s of the twentieth century drastically changed the fight against bacterial infectious diseases. Nowadays, it has been calculated that the annual expenditure for these antibiotics amounts to approximately $15 billion USD, and it makes up 65% of the total antibiotics market.[1] Their use, however, clashes with the worrying phenomenon of antimicrobial resistance remains, which represents a global health issue.From a biochemical point of view, these drugs have a common feature, which is the 3-carbon and 1-nitrogen ring (beta-lactam ring) that is highly reactive. This class includes:Penicillins. These antibiotics (most of which end in the suffix -cillin) contain a nucleus of 6-animopenicillanic acid (lactam plus thiazolidine) ring and other ringside chains. The group includes natural penicillins, beta-lactamase-resistant agents, aminopenicillins, carboxypenicillins, and ureidopenicillins.Cephalosporins. They contain a 7-aminocephalosporanic acid nucleus and side-chain containing 3,6-dihydro-2 H-1,3- thiazane rings. Cephalosporins are traditionally divided into five classes or generations, although acceptance of this terminology is not universal. Carbapenems. Their defining structure is a carbapenem coupled to a beta-lactam ring that confers protection against most beta-lactamases, although resistance to these compounds is a significant issue and occurs mainly among gram-negative pathogens (e.g., Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii), which produce different classes of beta-lactamases termed as carbapenemase. Monobactams. The beta-lactam ring stands alone and not fused to another ring.Beta-lactamase inhibitors. They work primarily by inactivating serine beta-lactamases, which are enzymes that hydrolyze and inactivate the beta-lactam ring (especially in gram-negative bacteria). These agents include the first-generation beta-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam) and the newer avibactam and vaborbactam that are active against carbapenemase such as Klebsiella pneumoniae carbapenemase (KPC). Mechanism of Resistance Resistance to beta-lactams is an alarming and growing phenomenon and, in turn, a public health challenge. It concerns, above all, Streptococcus pneumoniae and individual gram-negative bacilli such as Pseudomonas aeruginosa. With emerging resistance for antibiotics, it makes sense to look into mechanisms of resistance as it can help decide which drugs to prescribe in different scenarios and ways to overcome the same. Although bacterial resistance to beta-lactams mostly expresses through the production of beta-lactamases, other mechanisms are involved. Following are the mechanisms of resistance[2]:Inactivation by the production of beta-lactamases Decreased penetration to the target site (e.g., the resistance of Pseudomonas aeruginosa Alteration of target site PBPs (e.g., penicillin resistance in pneumococci)Efflux from the periplasmic space through specific pumping mechanisms Indications For Beta-Lactam Antibiotics The indications for using the beta-lactam antibiotics are many and vary according to the subclass considered[3] Penicillins Natural penicillins [penicillin G (IV), penicillin V (PO)] are used to treat selected gram-positive and gram-negative infections:Penicillin susceptible Streptococcus pneumonia and meningitisStreptococcal pharyngitisEndocarditisSkin and soft tissue infectionsNeisseria meningitides infectionsSyphilis Beta-lactamase-resistant Agents These agents [oxacillin (IV), nafcillin (IV), dicloxacillin (PO)] are active against gram-positive organisms. Despite the occurrence of widespread resistance among staphylococci, they remain antibiotics of choice in managing methicillin-susceptible staphylococci (MSSA):Skin and soft tissue infections (MSSA)Serious infections due to MSSA Aminopenicillins These antibiotics have activity against gram-positive and gram-negative bacteria (e.g., many Enterobacteriaceae) anaerobic organisms. They are commonly used together with beta-lactamase inhibitors.Amoxicillin (PO), ampicillin (PO/IV):Upper respiratory tract infections (sinusitis, pharyngitis, otitis media)Enterococcus faecalis infectionsListeria infectionsAminopenicillins/beta-lactamase inhibitors: amoxicillin/clavulanate (PO), ampicillin-sulbactam (IV)Upper respiratory tract infections (sinusitis, otitis media)Intra-abdominal infections Ureidopenicillins Piperacillin (ureidopenicillin) has activity against aminopenicillin-resistant gram-negative bacilli (Pseudomonas aeruginosa). They are commonly combined with beta-lactamase inhibitors. Cephalosporins First-generation cephalosporins Cefazolin(IV), cephalexin (PO), cefadroxil (PO)Skin and soft tissue infections serious infections due to MSSA Perioperative surgical prophylaxis Second-generation cephalosporins Cefuroxime (IV/PO), cefoxitin (IV), cefotetan (IV), cefaclor (PO) cefprozil (PO)Upper respiratory tract infections (sinusitis, otitis media)Cefoxitin, cefotetan-gynecologic infections,perioperative surgical prophylaxis Third-generation cephalosporins Cefotaxime (IV), ceftriaxone (IV), cefpodoxime (PO), cefixime (PO), cefdinir (PO), cefditoren (PO), ceftibuten (PO)Community-acquired pneumonia, meningitisUrinary tract infectionsStreptococcal endocarditisGonorrheaSevere Lyme disease. Anti-pseudomonal Cephalosporins Ceftazidime (IV), ceftazidime/avibactam (IV), cefepime (IV) [Fourth-generation], ceftolozone/tazobactam (IV) [also been described as "fifth-generation"]Nosocomial infections-pneumoniaMeningitisComplicated Intra-abdominal Infections (cIAI) [ceftazolone plus beta-lactamase inhibitor]Complicated Urinary Tract Infections (cUTI) [ceftazolone plus beta-lactamase inhibitor] Anti-Methicillin-resistant Staphylococcus aureus (MRSA) cephalosporins Ceftaroline (IV), ceftobiprole (IV) [Also been described as "fifth-generation"] Community-acquired pneumoniaHospital-acquired pneumonia (excluding ventilator-acquired pneumonia)Skin and soft tissue infection Carbapenems Imipenem/cilastatin (IV), meropenem (IV), doripenem (IV)Nosocomial infections-pneumonia, intra-abdominal infections, urinary tract infectionsMeningitis (especially meropenem) Ertapenem (IV)Community-acquired infectionsNosocomial infections. Monobactams Aztreonam (IV). It is effective only against aerobic gram-negative organisms but shows no activity against gram-positive bacteria or anaerobes.Nosocomial infections, e.g., pneumoniaUrinary tract infections Because the emergence of antimicrobial resistance has become a progressively great concern, new beta-lactam and beta-lactamase inhibitor combinations (ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, aztreonam/avibactam), siderophore-conjugated cephalosporins (cefiderocol), and siderophore-conjugated monobactams have been developed and represent options for the management of complicated infections, especially in the intensive care unit.[4][5]Peptidoglycan or murein is a vital constituent of the bacterial cell wall that provides mechanical stability to it. It is an extremely conserved constituent of both the gram-positive and gram-negative envelopes. Nevertheless, peptidoglycan is a thick structure in gram-positive bacteria (≥10 layers), while it is thin (one or two layers) in gram-negative ones. Concerning its structure, peptidoglycan is composed of glycan chains made of N-acetylglucosamine and N-acetylmuramic acid disaccharide subunits; the N-acetylmuramic part is linked to highly conserved pentapeptide or tetrapeptide stems (l-alanine–d-isoglutamine–l-lysine–d-alanine–[d-alanine].The beta-lactam antibiotics inhibit the last step in peptidoglycan synthesis by acylating the transpeptidase involved in cross-linking peptides to form peptidoglycan. The targets for the actions of beta-lactam antibiotics are known as penicillin-binding proteins (PBPs). This binding, in turn, interrupts the terminal transpeptidation process and induces loss of viability and lysis, also through autolytic processes within the bacterial cell.[6] When administered orally, one must consider that food can affect oral absorption. Moreover, the absorption of some molecules such as cefuroxime and cefpodoxime becomes decreased by H2 blockers or nonabsorbable antacids. The administration of these agents can be through different routes.Penicillin V is preferable for oral administration, given 30 min before the meal or 2 hours after.Penicillin G is available in 2 parenteral preparations: benzathine and procaine.Penicillin G benzathine dosing is once monthly as it has a longer half-life.Penicillin G procaine is given once daily due to a shorter half-life.Neither should be administered intravenously to avoid serious toxicity.Penicillinase-resistant penicillins (oxacillin, cloxacillin, and dicloxacillin) are available in oral and parenteral preparations.Aminopenicillins: ampicillin and amoxicillin are available in both oral and parenteral preparations, though amoxicillin is preferred orally.Antipseudomonal penicillins: piperacillin is only available for parenteral administration.Most cephalosporins are absorbed readily after oral administration; the administration of others can be intramuscularly or intravenously. Because beta-lactam antibiotics demonstrate a time-dependent effect on bacterial eradication (the duration that the pathogen is exposed to the antibiotic is crucial for bacterial eradication), their continuous infusions may have advantages over standard intermittent bolus dosing. This therapeutic approach is particularly effective, especially when pathogens present higher minimum inhibitory concentrations (MIC).[7] Thus, the time free drug concentrations remain above the MIC (fT>MIC) becomes a better predictor of killing.Compared to other classes, beta-lactam agents are usually safe and well-tolerated.[8] The most frequent side effects are allergic reactions that vary from 0.7% to 10%. These reactions may occur with any dosage form of penicillin and are mostly maculopapular rashes, whereas reports of anaphylaxis appear in 0.004 to 0.015% of patients.[9] Apart from allergic reactions, beta-lactams can induce other side effects. In particular, these are:Penicillin G and piperacillin are also associated with impaired hemostasis due to defective platelet aggregation.An IV injection of benzathine penicillin G has correlations with cardiorespiratory arrest and death.Cephalosporins carry associations with rare instances of bone marrow depression, including granulocytopenia.Some cephalosporins are potentially nephrotoxic and correlate with renal tubular necrosis. Ceftriaxone can cause jaundice in neonates by displacing bilirubin from albumin.It can also lead to biliary pseudolithiasis due to its high affinity for biliary calcium.Cefepime correlates with encephalopathy and nonconvulsive status epilepticus at high doses or in patients with renal dysfunction.Imipenem is associated with seizures when given in high doses to patients with CNS lesions or renal insufficiency.[10]Penicillins are contraindicated in patients with previous anaphylactic reactions or serious skin reactions, for example, Stevens-Johnson syndrome and toxic epidermal necrosis.[8]Most of the available penicillins have a short half-life, less than an hour mostly. Administration of the parenteral agents is every four hours, usually when treating serious systemic infections with normal renal function. Piperacillin and ampicillin require dose adjustment when given in patients with renal insufficiency (GFR less than 10 ml/min). Other agents like nafcillin, oxacillin, cloxacillin, and dicloxacillin have the hepato-biliary mode of excretion and therefore require no modification in renal impairment.All penicillins achieve therapeutic levels in pleural, pericardial, peritoneal, synovial fluids, and urine. Of note, cerebrospinal fluid (CSF) penetration is poor in the absence of inflammation but achieves therapeutic levels in meningitis.[11]Penicillins are the most commonly used broad-spectrum antibiotics by many clinicians, including primary care providers, internists, infectious disease experts, and nurse practitioners. Within the subgroups of penicillins, there are differences between the antibiotics in pharmacokinetics, coverage, safety, and cost, which gives a fair amount of choice to make in selecting which drug to use.[12]Their use still requires the coordination of an interprofessional team. The clinicians above will be ordering/prescribing, but nursing will often administer (inpatient) or counsel on administration (outpatient). Pharmacists need to involve themselves via medication reconciliation, looking for interactions, and reinforcing administration instructions. Nurses will often be the first line of contact in the event of adverse events and are also well-positioned to evaluate therapeutic effectiveness. Pharmacists shall verify dosing and duration of therapy and contact the prescriber on encountering any discrepancy. All healthcare team members need to be mindful of anaphylactic reactions to beta-lactam agents and the potential for crossover allergies and communicate these to the team when present.Although beta-lactams use is very common, their effective prescription requires an interprofessional team approach for optimal patient outcomes. [Level 5]Review Questions1.Thakuria B, Lahon K. 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[PubMed: 31306394]12.Han ML, Liu X, Velkov T, Lin YW, Zhu Y, Creek DJ, Barlow CK, Yu HH, Zhou Z, Zhang J, Li J. Comparative Metabolomics Reveals Key Pathways Associated With the Synergistic Killing of Colistin and Sulbactam Combination Against Multidrug-Resistant Acinetobacter baumannii. Front Pharmacol. 2019;10:754. [PMC free article: PMC6620532] [PubMed: 31333468] Disclosure: Neelanjana Pandey declares no relevant financial relationships with ineligible companies. Disclosure: Marco Cascella declares no relevant financial relationships with ineligible companies. Beta-lactam antibiotics are those that contain 4-member, nitrogen-containing, beta-lactam ring at the core of their structure. This ring mimics the shape of the terminal D-Ala-D-Ala peptide sequence that serves as the substrate for cell wall transpeptidases. At present, there are four major beta-lactam subgroups.Molecular structure of common beta-lactam antibioticsBeta-lactam subgroupsExamplesPenicillinsPenicillin, Ampicillin, PiperacillinCephalosporinsCefazolin, Cefotaxime, Ceftriaxone, Ceftazidime, CefepimeMonobactamsAztreonamCarbapenemsImipenem, MeropenemThe beta-lactam ring is key to the mode of action of these drugs that target and inhibit cell wall synthesis by binding the enzymes involved in the synthesis. These enzymes are anchored in the cell membrane and as a group is referred to as penicillin-binding proteins (PBPs). Bacterial species may contain between 4-6 different types of PBPs. The PBPs involved in cell wall cross-linking (i.e.,transpeptidases) are often the most critical for survival.The 4-member ring of beta-lactam antibiotics gives these compounds a three-dimensional shape that mimics the D-Ala-D-Ala peptide terminus that serves as the natural substrate for transpeptidase activity during cell wall peptidoglycan synthesis. Tight binding of these beta-lactam drugs to the transpeptidase active site inhibits cell wall synthesis. Death results from osmotic instability caused by faulty cell wall synthesis, or the binding of the beta-lactam to PBP may trigger a series of events that lead to autolysis and death of the cell.Mechanism of action of beta-lactam antibioticsBeta-lactam agents are active against both gram-positive and gram-negative bacteria but effectiveness varies owing to structural differences in cell-wall structure (e.g., the outer membrane present in gram-negative but not gram-positive bacteria) and PBP content.Three pathways play an important role to confer resistance to beta-lactams. They are; enzymatic destruction of the antibiotics, altered antibiotic targets, or decreased uptake of the drug.Resistance pathwaySpecific mechanismExamplesEnzymatic destruction of antibioticsβ-lactamase enzymes destroy β-lactam ring so the antibiotic cannot bind to penicillin-binding protein (PBP) and interfere with cell wall synthesisStaphylococcal resistance to penicillin. Resistance of Enterobacteriaceae and Pseudomonas aeruginosa to several penicillins, cephalosporins, and aztreonam.Altered targetMutational changes in original PBPs or acquisition of different PBPs that do not bind β-lactams sufficiently to inhibit cell wall synthesisStaphylococcal resistance to methicillin and other available β-lactams. Penicillin and cephalosporin resistance in Streptococcus pneumoniae and viridans streptococci.Decreased uptakePorin channels (through which β-lactams cross the outer membrane to reach PBP of gram-negative bacteria) change in number or character so that β-lactam uptake is substantially diminished.Pseudomonas aeruginosa resistance to imipenem.Hydrolysis of penicillins & cephalosporin antibiotics by β-lactamaseDestruction of beta-lactams by beta-lactamase enzyme-producing bacteria is by far the most important method of resistance. Beta-lactamases open the beta-lactam ring and the altered structure of the drug can no longer bind to PBPs and is no longer to inhibit cell wall synthesis. But not all β-lactams are susceptible to hydrolysis by every β-lactamase. For example, staphylococcal beta-lactamase can readily hydrolyze penicillin and penicillin derivative but fails to hydrolyze many cephalosporins and imipenem.Do you know?Both gram-positive and gram-negative bacteria produce β-lactamase. β-lactamases produced by gram-positive bacteria are secreted into the surrounding environment but that of gram-negative bacteria remains in the periplasmic space.The organisms change or acquire a gene that code for altered PBPs. β-lactams lack sufficient affinity for the altered PBP, thus can not prevent their function (i.e. cell wall synthesis continues even in the presence of antibiotics. For example, methicillin-resistant Staphylococcus aureus (MRSA) developed resistance to methicillin and all other β-lactams using this mechanism.β-lactam resistance mechanisms of gram-positive and gram-negative bacteria.Image source (Bailey & Scott's Diagnostic Microbiology)Decreased uptake of the drug contributes significantly to β-lactam resistance in gram-negative bacteria. This happens because of the changes in the number, or characteristics of the outer membrane porins (through which β-lactams reach to inner peptidoglycan layer of gram-negative bacteria). E.g. Pseudomonas aeruginosa resistance to imipenem.Protecting beta-lactam ring from beta-lactamases by molecular alterations of beta-lactam rig. For example, methicillin and oxacillin which are close molecular derivatives of penicillin are resistant to staphylococcal β-lactamase.Combining beta-lactamase inhibitors and beta-lactam with antimicrobial activity. Beta-lactam combination compromised of a β-lactam with antimicrobial activity (e.g., ampicillin, amoxicillin, piperacillin) and a β-lactam without antimicrobial activity but is capable of binding and inhibiting β-lactamases (e.g., sulbactam, clavulanate, tazobactam). The β-lactamase inhibitor avidly and irreversibly binds to the β-lactamase and renders the enzyme incapable of hydrolysis, thus allowing another β-lactam (β-lactamase susceptible beta-lactam) to exert its antimicrobial effect. Examples of these beta-lactam combinations includeampicillin/sulbactamamoxicillin/clavulanate and,piperacillin/tazobactam.Such combinations are only effective against organisms that produce β-lactamases that are bound by the inhibitor; they have little effect on the resistance that is mediated by altered PBPs.Challenging the bacteria with antimicrobial having a different mechanism of action. For example use of vancomycin (non-beta-lactam agent) for MRSA.link to Martin Lewis Agar: Principle, Composition, and Useslink to Hematopoiesis: Stages, Sites, and Its Regulation You are here: Urology Textbook > Drugs in Urology > Beta-lactam antibiotics β-lactam antibiotics contain a four-membered lactam ring (three C and 1 N) and a variable chemical residue. Mechanism of Action β-lactam antibiotics inhibit the peptidoglycan synthesis of the bacterial wall: they bind to so-called penicillin-binding proteins (peptidoglycan synthetases) and thereby inhibit the polymerization of the peptidoglycan and covalent cross-linking of the bacterial wall. The bacteria-specific mechanism of action leads to a good tolerance. Classification of Urologically Significant β-Lactam Antibiotics: Penicillins: Cephalosporins: Cephalosporins are β-lactam antibiotics, which are grouped into four generations according to their antibiotic spectrum of activity. The first generation has mainly gram-positive activity. The second and third generations have more gram-negative activity with decreased activity against gram-positive bacteria. The fourth generation of cephalosporins has a broad spectrum of activity. The following list provides an overview of the generations of cephalosporins with significant substances for urologists: First generation: cefazolin Second generation: cefaclor, cefuroxime Third generation: cefotaxime, ceftriaxone, ceftazidime for parenteral application. Cefpodoxime and ceftibuten for oral formulations. Fourth generation: cefepime, ceftolozan (combined with tazobactam) Carbapenems: Carbapenems are reserve antibiotics with a broad spectrum of activity. Imipenem, meropenem, ertapenem, doripenem Monobactams: Monobactams are effective in the gram-negative range and are an option in patients with an allergy to β lactams. β-Lactamase Inhibitors: β-lactamase inhibitors are combined with β-lactam antibiotics to extend the spectrum of activity. Index: 1–9 A B C D E F G H I J K L M N O P Q R S T U V W X Y Z Simon und Stille 1997 SIMON, C. ; STILLE, W.: Antibiotika-Therapie in Klinik und Praxis. 9. Auflage. Stuttgart New York : Schattauer, 1997 Deutsche Version: Beta-Lactam Antibiotika Urology-Textbook.com – Choose the Ad-Free, Professional Resource This website is designed for physicians and medical professionals. It presents diseases of the genital organs through detailed text and images. Some content may not be suitable for children or sensitive readers. Many illustrations are available exclusively to Steady members. Are you a physician and interested in supporting this project? Join Steady to unlock full access to all images and enjoy an ad-free experience. Try it free for 7 days—no obligation. You are here: Urology Textbook > Drugs in Urology > Beta-lactam antibiotics β-lactam antibiotics contain a four-membered lactam ring (three C and 1 N) and a variable chemical residue. Mechanism of Action β-lactam antibiotics inhibit the peptidoglycan synthesis of the bacterial wall: they bind to so-called penicillin-binding proteins (peptidoglycan synthetases) and thereby inhibit the polymerization of the peptidoglycan and covalent cross-linking of the bacterial wall. The bacteria-specific mechanism of action leads to a good tolerance. Classification of Urologically Significant β-Lactam Antibiotics: Penicillins: Cephalosporins: Cephalosporins are β-lactam antibiotics, which are grouped into four generations according to their antibiotic spectrum of activity. The first generation has mainly gram-positive activity. 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Index: 1–9 A B C D E F G H I J K L M N O P Q R S T U V W X Y Z Simon und Stille 1997 SIMON, C. ; STILLE, W.: Antibiotika-Therapie in Klinik und Praxis. 9. Auflage. Stuttgart New York : Schattauer, 1997 Deutsche Version: Beta-Lactam Antibiotika Urology-Textbook.com – Choose the Ad-Free, Professional Resource This website is designed for physicians and medical professionals. It presents diseases of the genital organs through detailed text and images. Some content may not be suitable for children or sensitive readers. Many illustrations are available exclusively to Steady members. Are you a physician and interested in supporting this project? Join Steady to unlock full access to all images and enjoy an ad-free experience. Try it free for 7 days—no obligation. Share — copy and redistribute the material in any medium or format for any purpose, even commercially. Adapt — remix, transform, and build upon the material for any purpose, even commercially. 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MeSH Heading beta-Lactams Tree Number(s) D02.065.589.099 D02.886.108 D03.633.100.300 Unique IDD047090 RDF Unique Identifier Scope NoteFour-membered cyclic AMIDES, best known for the PENICILLINS based on a bicyclo-thiazolidine, as well as the CEPHALOSPORINS based on a bicyclo-thiazine, and including monocyclic MONOBACTAMS. The BETA-LACTAMASES hydrolyze the beta lactam ring, accounting for BETA-LACTAM RESISTANCE of infective bacteria. Entry Term(s) 4-Thia-1-Azabicyclo(3.2.0)Heptanes 4-Thia-1-Azabicyclo(4.2.0)Octanes beta-Lactam Pharm Action Anti-Bacterial Agents Registry Numbers 0 Previous Indexing Lactams (1974-2004) Public MeSH Note2005; see LACTAMS 1996-2004 History Note2005; use LACTAMS 1996-2004 Date Established 2005/01/01 Date of Entry 2004/07/07 Revision Date 2020/05/27 Beta-lactam antibiotics are used in the management and treatment of bacterial infections. This activity will highlight the mechanism of action, adverse event profile, and other key factors (e.g., off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions) pertinent for members of an interprofessional healthcare team in the treatment of patients. β-Lactams are the most widely used class of antibiotics. Since the discovery of benzylpenicillin in the 1920s, thousands of new penicillin derivatives and related β-lactam classes of cephalosporins, cephamycins, monobactams, and carbapenems have been discovered. Each new class of β-lactam has been developed either to increase the spectrum of activity to include additional bacterial species or to address specific resistance mechanisms that have arisen in the targeted bacterial population. Resistance to β-lactams is primarily because of bacterially produced β-lactamase enzymes that hydrolyze the β-lactam ring, thereby inactivating the drug. The newest effort to circumvent resistance is the development of novel broad-spectrum β-lactamase inhibitors that work against many problematic β-lactamases, including cephalosporinases and serine-based carbapenemases, which severely limit therapeutic options. This work provides a comprehensive overview of β-lactam antibiotics that are currently in use, as well as a look ahead to several new compounds that are in the development pipeline. The most widely used antibiotics are the β-lactams (e.g., penicillin). Efforts to develop broad-spectrum inhibitors of bacterially produced β-lactamase enzymes may curb resistance to this important class of antibiotics. When Alexander Fleming was searching for an antistaphylococcal bacteriophage in his laboratory in the 1920s, he deliberately left plates out on the bench to capture airborne agents that might also serve to kill staphylococci (Fleming 1929). His success was greater than he must have hoped for. His initial publication on benzylpenicillin described a substance that was unstable in aqueous solution but that might serve as an antiseptic or as a selective agent for isolation of Gram-negative bacteria that were present in mixed cultures of staphylococci and streptococci. As the potential utility of penicillin G as a parenteral therapeutic agent became more obvious, Fleming, Abraham, Florey, and a consortium of scientists from England and the United States were able to optimize the isolation and identification of benzylpenicillin to assist in the treatment of Allied soldiers in World War II (Macfarlane 1979). These activities set the stage for the launch of the most successful class of antibiotics in history. β-Lactam antibiotics are currently the most used class of antibacterial agents in the infectious disease armamentarium. As shown in Figure 1, β-lactams account for 65% of all prescriptions for injectable antibiotics in the United States. Of the β-lactams, cephalosporins comprise nearly half of the prescriptions (Table 1). The β-lactams are well tolerated, efficacious, and widely prescribed. Their major toxicity is related to an allergic response in a small percentage of patients who react to related side chain determinants; notably, these reactions are most common with penicillins and cephalosporins with minimal reactivity caused by monobactams (Saxon et al. 1984; Moss et al. 1991). The bactericidal mechanism of killing by β-lactams is perceived to be a major advantage in the treatment of serious infections. When these agents were threatened by the rapid emergence of β-lactamases, β-lactamase-stable agents were developed, as well as potent β-lactamase inhibitors (BLIs). In this introductory description of the β-lactams, the most commonly available β-lactams and BLIs will be presented, with a brief summary of their general characteristics. Occasional agents have been included for their historical or scientific importance. Note that resistance mechanisms will be discussed in detail in other articles in this collection. Proportion of prescriptions in the United States for injectable antibiotics by class for years 2004–2014. The percentage of standard units for each injectable antibiotic prescribed in the United States from 2004 to 2014 is shown as follows: β-lactams, 65.24%; glycopeptides, 9%; fluoroquinolones, 8%; macrolides/ketolides, 6%; aminoglycosides, 5%; polymyxins, 1%; trimethoprim/sulfamethoxazole, 0.5%; tetracyclines (excluding tigecycline), 0.4%; all other antibiotics (including daptomycin, linezolid, and tigecycline), 4.21%. (Data from the IMS MDART Quarterly Database on file at AstraZeneca.) Usage of parenteral β-lactams by class from 2004–2104 in the United States Class of β-lactam Percentage of prescriptionsa Narrow spectrum penicillins 3.12 Broad spectrum penicillinsb 36.54 Cephalosporins 47.49 Monobactams 1.66 Carbapenems 11.20 β-Lactam antibiotics are bactericidal agents that interrupt bacterial cell-wall formation as a result of covalent binding to essential penicillin-binding proteins (PBPs), enzymes that are involved in the terminal steps of peptidoglycan cross-linking in both Gram-negative and Gram-positive bacteria. Every bacterial species has its own distinctive set of PBPs that can range from three to eight enzymes

per species (Georgopapadakou and Liu 1980). The inhibition of bacterial peptidoglycan transpeptidation by penicillin was described mechanistically in a classical paper by Tipper and Strominger (1965), who noted a structural similarity of penicillin G to the terminal d-Ala-d-Ala dipeptide of the nascent peptidoglycan in the dividing bacterial cell. This mechanism is now known to involve binding of penicillin, or another β-lactam, to an active site serine found in all functional PBPs (Georgopapadakou et al. 1977). The resulting inactive acyl enzyme may then slowly hydrolyze the antibiotic to form a microbiologically inactive entity (Frère and Joris 1985). In addition to these functionalities, recent work has shown the binding of selected β-lactams, such as ceftaroline, to an allosteric site in PBP2a from Staphylococcus aureus, resulting in an increased sensitization of the organism to the antibiotic (Otero et al. 2013; Gonzales et al. 2015). PBPs may be divided into classes according to molecular mass (Goffin and Ghuysen 1998; Massova and Mobashery 1998), with low-molecular-mass PBPs serving mainly as monofunctional d-Ala-d-Ala carboxypeptidases. High-molecular-mass PBPs have been divided into two subclasses, one of which (class A) includes bifunctional enzymes with both a transpeptidase and a transglycosylase domain, and the second of which (class B) encompasses d-Ala-d-Ala-dependent transpeptidases. At least one PBP is deemed to be essential in each species, with a unique specificity for β-lactam binding that varies among each species and each β-lactam class (Curtis et al. 1979; Georgopapadakou and Liu 1980). In Gram-negative bacteria, essential PBPs include the high-molecular-weight PBPs 1a and 1b that are involved in cell lysis, PBP2, the inhibition of which results in a cessation of cell division and the formation of spherical cells, and PBP3 for which inhibition arrests cell division, resulting in filamentation. Cell death may occur as a result of inhibiting one or more of these PBPs (Spratt 1977, 1983). The roles of PBPs in Gram-positive bacteria and Mycobacterium tuberculosis are discussed in detail in Fisher and Mobashery (2016). Penicillin G (benzylpenicillin) was the first β-lactam to be used clinically, most frequently to treat streptococcal infections for which it had high potency (Rammelkamp and Keefer 1943; Hirsh and Dowling 1946). Another naturally occurring penicillin, penicillin V (phenoxymethylpenicillin), in an oral formulation is still used therapeutically and prophylactically for mild to moderate infections caused by susceptible Streptococcus spp., including use in pediatric patients (Pottegard et al. 2015). However, the selection of penicillin-resistant penicillinase-producing staphylococci in patients treated with penicillin G led to decreased use of this agent, and prompted the search for more penicillins with greater stability to the staphylococcal β-lactamases (Kirby 1944, 1945; Medeiros 1984). A list of historically important and clinically useful penicillins is provided in Table 2. Among the penicillinase-stable penicillins of clinical significance are methicillin, oxacillin, cloxacillin, and nafcillin, with the latter suggested as the β-lactam of choice for skin infections, catheter infections, and bacteremia caused by methicillin-susceptible S. aureus (Bamberger and Boyd 2005). All were used primarily for staphylococcal infections until the emergence of methicillin-resistant S. aureus (MRSA) in 1979–1980 (Hemmer et al. 1979; Saroglou et al. 1980). Penicillins of current and historical utility Penicillins with improved activity against Gram-negative pathogens included the orally bioavailable ampicillin and amoxicillin, both of which were introduced in the 1970s. These agents were initially used for the treatment of infections caused by Enterobacteriaceae and did not effectively inhibit the growth of Pseudomonas aeruginosa, which became more of a concern during the late 1970s. Carbenicillin was the first antipseudomonal penicillin to be introduced, but lacked stability to β-lactamase hydrolysis and was less potent than piperacillin or ticarcillin, later antipseudomonal penicillins. These latter drugs were considered to be potent broad-spectrum penicillins that included penicillin-susceptible staphylococci, enteric bacteria, anaerobes, and P. aeruginosa in their spectrum of activity. They were used extensively to treat serious nosocomial infections, especially when combined with a β-lactamase inhibitor (see below). Two parenteral penicillins with unusual chemical structures, mecillinam and temocillin (Table 2), were introduced to treat infections caused by enteric bacteria before the global emergence of extended-spectrum β-lactamases (ESBLs) in the late 1980s. Mecillinam (also known as amdinocillin), with a 6-β-amidino side chain, is a narrow-spectrum β-lactam that binds exclusively to PBP2 in enteric bacteria (Curtis et al. 1979). Because of this specificity, it shows synergy in vitro in combination with other β-lactams that bind to PBPs 1a/1b and/or PBP3 in Gram-negative bacteria (Hanberger et al. 1991), thus decreasing the possibility that a point mutation in a single PBP would lead to resistance (Hickman et al. 2014). Temocillin, the 6-α-methoxypenicillin analog of ticarcillin, had greater stability than ticarcillin to hydrolysis by serine β-lactamases, but lost antibacterial activity against Gram-positive bacteria, anaerobic Gram-negative pathogens, and some enteric bacteria that included the important pathogens Enterobacter spp. and Serratia marcescens (Martinez-Beltran et al. 1985). Mecillinam and temocillin are currently enjoying a resurgence in interest owing to their stability to many ESBLs (Livermore et al. 2006; Rodriguez-Villalobos et al. 2006), often resulting in greater than 90% susceptibility when tested against many contemporary ESBL-producing Enterobacteriaceae (Giske 2015; Zykov et al. 2016). Because increasing numbers of β-lactamases have compromised the use of penicillins as single agents (Bush 2013), there is currently limited therapeutic use of the penicillins as monotherapy. Ampicillin, amoxicillin, piperacillin, and ticarcillin have continued to be useful, primarily as a result of their combination with an appropriate β-lactamase inhibitor (see below). However, even ampicillin, amoxicillin, penicillin G, and penicillin V are still active as monotherapy against Group A streptococci, and Treponema pallidum, two of the few bacterial species that do not produce β-lactamases (Schaar et al. 2014). During the 1950s, the discovery of the naturally occurring penicillinase-stable cephalosporin C opened a new pathway to the development of hundreds of novel cephalosporins (Newton and Abraham 1956; Abraham 1987) to treat infections caused by the major penicillinase-producing pathogen of medical interest at that time, S. aureus. Dozens of cephalosporins were introduced into clinical practice (Abraham 1987), either as parenteral or oral agents. The molecules exhibited antibacterial activity with MICs often ≤4 μg/mL against not only staphylococci, but also Streptococcus pneumoniae and non-β-lactamase-producing enteric bacteria. The parenteral agents were generally eightfold more potent than the oral agents that were used in some cases to replace oral penicillins in penicillin-allergic patients. The early cephalosporins, for example, those in the cephalosporin I subclass (Bryskier et al. 1994) introduced before 1980, were labile to hydrolysis by many β-lactamases that emerged following their introduction into clinical practice, so that only a few of the early molecules remain in use (see Table 3), primarily to treat mild to moderate skin infections caused by methicillin-susceptible S. aureus (MSSA) (Giordano et al. 2006). Cefazolin with high biliary concentrations is still used for surgical prophylaxis and for treatment of abdominal infections (Sudo et al. 2014) and is effective as empiric therapy in 80% of Japanese children with their first upper urinary tract infection (Abe et al. 2016). Cephalosporins of current clinical utility or of historical interest When the TEM-1 penicillinase began to appear on transmissible plasmids in Neisseria gonorrhoeae (Ashford et al. 1976) and Haemophilus influenzae (Gunn et al. 1974; Khan et al. 1974), it was quickly recognized that the penicillins and cephalosporins in medical use were becoming ineffective, not only in treating those TEM-1-producing organisms, but also for the enteric bacteria and P. aeruginosa that could all acquire this enzyme. Another surge of synthetic activity in the pharmaceutical industry provided both oral and parenteral cephalosporins with stability to this common enzyme. These agents tended to have decreased potency against the staphylococci, but gained antibacterial activity against Gram-negative pathogens. Cefuroxime, dosed parenterally or orally as the axetil ester, was the only member of the cephalosporin II class (Bryskier et al. 1994) with both oral and systemic dosage forms, but its stability to β-lactamase hydrolysis was diminished compared to later oral cephalosporins (Jacoby and Carreras 1990). As seen with cefuroxime, acceptable oral bioavailability of cefpodoxime required esterification through addition of a proxetil group to attain sufficient absorption for efficacy (Bryskier and Belfiglio 1999). Of the oral agents approved after 1983 in Table 3, cefdinir was generally more stable to hydrolysis, not only to the original TEM enzyme, but also to the AmpC cephalosporinases that are produced at a basal level in many enteric bacteria and P. aeruginosa (Payne and Amyes 1993; Labia and Morand 1994). Among the parenteral agents introduced in the 1980s were the cephamycin cefoxitin, and cephalosporins in the cephalosporin III and cephalosporin IV subclasses (Bryskier et al. 1994), which continue to serve as important antibiotics for the treatment of serious infections caused by Gram-negative pathogens. The novel oxacephem moxalactam, or latamoxef, which had similar antimicrobial activity to the cephalosporin III/IV subclasses, has exquisite stability to hydrolysis by β-lactamases (Sato et al. 2015), but was not a highly successful antibiotic owing, in part, to a relatively high frequency of bleeding in patients treated with this drug (Brown et al. 1986). The cephamycin cefoxitin is notable for its characteristic 7-methoxy side chain that confers stability to the TEM-type β-lactamases, including ESBLs. It has useful antibacterial activity against MSSA and enteric bacteria that do not produce high levels of AmpC cephalosporinases (Jacoby and Han 1996). Cefotaxime, cefoperazone, ceftriaxone, and ceftazidime, designated as subclass cephalosporin III, and cefepime in the cephalosporin IV subclass, are also known as expanded-spectrum cephalosporins with increased hydrolytic stability to the common penicillinases, SHV-1 and TEM-1 β-lactamase (Martinez-Martinez et al. 1996). These agents have diminished activity against staphylococci and enterococci compared to earlier cephalosporins, but have more potent activity against Gram-negative organisms. Cefepime tends to have lower MICs against enteric bacteria than the other expanded-spectrum cephalosporins, attributed to greater penetration through the OmpF outer-membrane porin protein (Nikaido et al. 1990; Bellido et al. 1991). Cefotaxime and ceftriaxone are often used to treat susceptible streptococcal infections; all can be used to treat serious infections caused by enteric bacteria if the organisms test susceptible. Notably, ceftazidime and cefepime have maintained their observed activity against P. aeruginosa, with recent susceptibility rates exceeding 80% (Sader et al. 2015). A liability of the expanded-spectrum cephalosporins, however, began to emerge only a few years after the introduction of cefotaxime, when the ESBLs were identified with the ability to hydrolyze all of the β-lactams, with the exception of the carbapenems. These enzymes, in addition to both serine and metallo-carbapenemases, have severely compromised the activity of almost all penicillins and cephalosporins, necessitating the development of combination therapy with other β-lactams, β-lactamase inhibitors, or antibiotics from other classes. Ceftolozane, recently approved in combination with tazobactam for the treatment of complicated urinary tract infections and complicated intraabdominal infections, shows potent antipseudomonal activity, and includes activity against enteric bacteria that produce some ESBLs (Zhanel et al. 2014), particularly CTX-M-producing isolates (Estabrook et al. 2014). Another recent addition to the cephalosporin family is the siderophore-substituted cephalosporin S-649266 with a catechol in the 3-position, thus allowing the molecule to enter the cells via an iron transport mechanism (Kohira et al. 2015). In addition to increased penetrability, the cephalosporin is stable to hydrolysis by many carbapenemases, resulting in activity against many β-lactam-resistant enteric bacteria (Kohira et al. 2015). In the mid-1990s, reports began to emerge describing cephalosporins with MICs