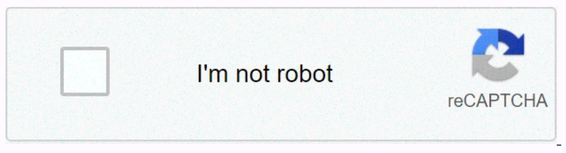
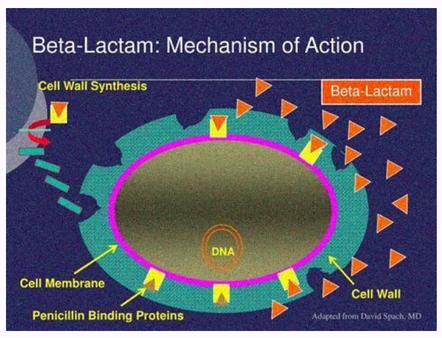


I am not robot!

Mechanism of action for beta lactam antibiotics

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 beta-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] Medical use 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 cerebrosopinal fluid against area under curve of serum).[7] Adverse effects Adverse drug reactions 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] Allergy/hypersensitivity 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. Mechanism of action Inhibition of cell wall synthesis 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 Ser403 residue of the PBP active site.



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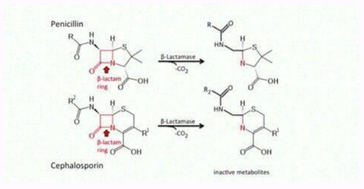

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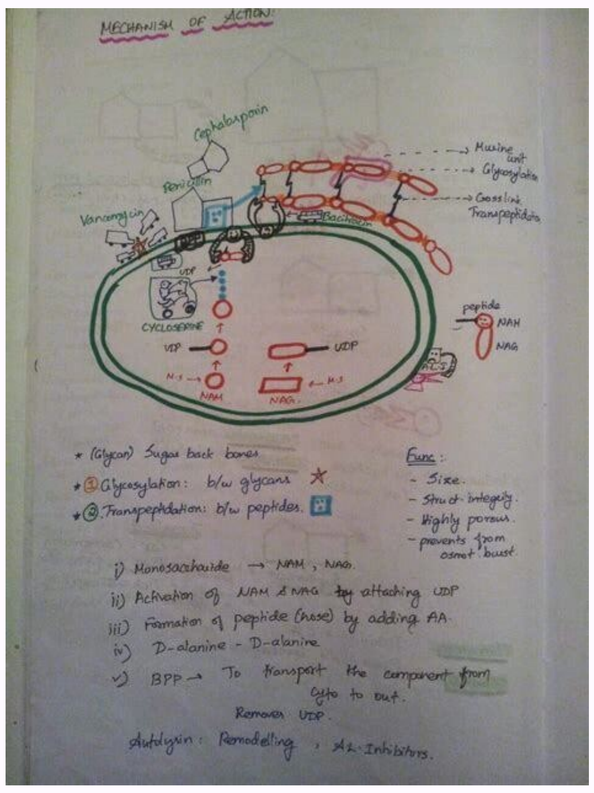

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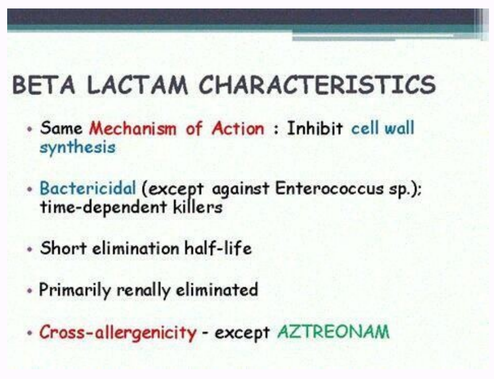

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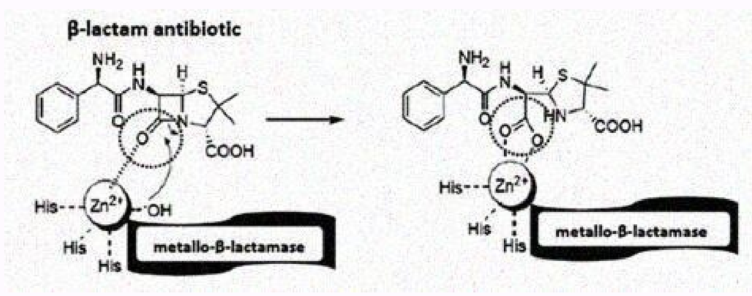

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The addition of tazobactam to piperacillin has enhanced its stability against a wide range of β-lactamase enzymes including some Extended-Spectrum β-lactamases.[20] Other β-lactamase inhibitors such as boronic acids are being studied in which they irreversibly bind to the active site of β-lactamases. This is a benefit over clavulanic acid and similar beta-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] Possession of altered penicillin-binding proteins 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)[23] and penicillin-resistant Streptococcus pneumoniae. Altered PBPs do not necessarily rule out all treatment options with β-lactam antibiotics. Nomenclature 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.[24] 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. 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. Biosynthesis 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.[25] 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.
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 by two-electron processes 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.[26] 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.[27] See also 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 References ^ 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 2011-06-06. Retrieved 2008-11-08. ^ Yao, JDC; Moellering, RC Jr. (2007). "Antibacterial agents". In Murray, PR; et al. (eds.).
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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. The Beta Lactam Antibiotics as an Empirical Therapy in a Developing Country: An Update on Their Current Status and Recommendations to Counter the Resistance against Them.
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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.