e-ISSN:2582-7219

INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH IN SCIENCE, ENGINEERING AND TECHNOLOGY

Volume 6, Issue 4, April 2023

INTERNATIONAL STANDARD SERIAL NUMBER INDIA

Impact Factor: 7.54

International Journal Of Multidisciplinary Research In Science, Engineering and Technology (IJMRSET)

| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54| Monthly Peer Reviewed & Referred Journal |

| Volume 6, Issue 4, April 2023 |

| DOI:10.15680/IJMRSET.2023.0604033 |

Antimicrobial Activity of Penicillin

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ABSTRACT: Penicillin kills bacteria through binding of the beta-lactam ring to DD-transpeptidase, inhibiting its cross-linking activity and preventing new cell wall formation. Without a cell wall, a bacterial cell is vulnerable to outside water and molecular pressures, which causes the cell to quickly die.

KEYWORDS- Penicillin, cell-wall, bacteria, beta –lactam ring, transpeptidase

I. INTRODUCTION

In 1929, Alexander Fleming isolated penicillin from a strain of Penicillium notatum (84). By 1941, benzylpenicillin could be produced in sufficient quantity to treat several infected patients. Clinical trials with the agent, conducted by Florey and colleagues, were successful and during World War II, benzylpenicillin was used to treat patients with streptococcal, gonococcal, and treponemal infections. Shortages of the agent continued until the late 1940s when production of large amounts of drug became possible by a deep-fermentation procedure (85). Since then, many synthetic penicillins have been developed, but resistance to the agents has increased. Despite the emergence of resistance to penicillins and the development of other classes of anti-infective agents, the penicillins remain one of the most important anti-infective classes of drugs well into the nineties. In fact, penicillin G is still the drug of choice for many types of infections, including syphilis and certain types of endocarditis.

CLASS

Chemical Structure (Figure 1)

The basic chemical structure of all penicillins consists of a beta-lactam ring, a thiazolidine ring, and a side chain (6-aminopenicillanic acid). The antibacterial activity of the penicillins lies within the beta-lactam ring. Any alteration in this ring structure forms penicilloic acid and the antibacterial activity of the compound is lost. The side chain varies with each penicillin compound and generally determines the spectrum of activity, as well as the pharmacokinetic properties of the compound. There are several natural penicillins (penicillin dihydro F, X, and K), of which benzylpenicillin (penicillin G) is the most active and is the only natural penicillin used clinically (164).

Structure-Activity Relationships

Manipulations of the side chain have produced compounds that are stable against certain bacteria, such as Staphylococcus aureus, which produce beta-lactamase enzymes (penicillinase). The side chain sterically inhibits the beta-lactamase hydrolysis of the beta-lactam ring. Other penicillin compounds have side chains, which are stable against beta-lactamases produced by gram-negative rods. Side chain changes can also increase the bacterial permeability of the compound and can result in increased oral absorption from the intestinal tract by rendering oral agents more stable to gastric acid breakdown (167, 186).

ANTIMICROBIAL ACTIVITY

Classification of Penicillins and Spectrum of Activity

The penicillin compounds can be divided into categories based upon their spectrum of activity (Table 1). Minimum inhibitory concentration (MIC) data for 50% and 90% of specific organisms are located in Tables 2 and 3 (10, 70, 150, 228, 245, 255, 257, 261). For gram-negative organisms and anaerobes, resistance in up to 15% of strains is possible; therefore MIC90s must be interpreted cautiously.

Natural Penicillins

Penicillin G is a natural penicillin that is produced directly from fermentation of Penicillium crysogenum. Penicillin V is a derivative of penicillin G and because of similarities in spectrum of activity, is considered a natural penicillin. The natural penicillins have activity against non-beta-lactamase producing gram-positive cocci, including viridans streptococci, group A streptococci, Streptococcus pneumoniae, and anaerobic streptococcus (Peptostreptococcus, Peptococcus sp.). Enterococcus sp. is most susceptible to the natural penicillins. Other potential organisms with susceptibility include non-penicillinase producing strains of Staphylococcus aureus and coagulase-

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| DOI:10.15680/IJMRSET.2023.0604033 |

negative Staphylococcus, however because of the high likelihood of resistance, it is inappropriate to use natural penicillins as empiric treatment for a suspected Staphylococcal infection unless the organism's susceptibility is known. [1,2,3]The natural penicillins have activity against Clostridium sp. (excluding Clostridium difficile) and Actinomyces sp. Activity against gram-negative cocci is limited and includes Neisseria meningitidis, non-penicillinase producing Neisseria gonorrheae, and Pasteurella multocida. Similar to staphylococcal infection, natural penicillins should not be used for treatment of gonorrhea due to the increased potential of a resistant organism and subsequent treatment failure. The anaerobic coverage of penicillin V is less than that of penicillin G. Natural penicillins also have excellent activity against the spirochete, Treponema pallidum, the causative organism of syphilis.

Penicillinase-Resistant Penicillins

The agents in this group are also known as the antistaphylococcal penicillins. The addition of an isoxazolyl side chain to the penicillin compound protects the beta-lactam ring from acid hydrolysis by penicillinases produced by Staphylococcus sp. (150). Methicillin, the first agent synthesized in this group, is rarely used currently due to a higher incidence of occurrence of interstitial nephritis and is no longer commercially available in the United States. Nafcillin and oxacillin are the agents commonly used parenterally, while dicloxacillin is available for oral use. These agents have activity against Staphylococcus sp (including penicillinase-producing strains). Strains of methicillin-resistant Staphylococcus aureus(MRSA) and methicillin-resistant Staphylococcus epidermidis (MRSE) exist and can be the prevalent Staphylococcal organism in certain areas, such as certain hospitals or wards within the hospital. These organisms are not sensitive to the penicillinase-resistant penicillins.

While less active against streptococcal sp. as compared to the natural penicillins, based on MIC data, use of the penicillinase-resistant penicillins is acceptable (i.e. the MICs are low enough relative to achievable serum concentrations) for use against these organisms. Clinically, in serious, life-threatening infections where a gram-positive organism is suspected, combinations of penicillin G plus a penicillinase-resistant penicillin can be utilized to achieve maximal streptococcal and staphylococcal coverage. A notable exception to the gram-positive coverage of this class of penicillins is the Enterococci. These organisms are not susceptible to this class of penicillins. Anaerobic activity ranges from minimal to none and gram-negative activity is virtually nonexistent.

Aminopenicillins

Because of the need for improved coverage against gram-negative organisms, further manipulation of the side chain was conducted. By adding an amino group to the basic penicillin compound, the aminopenicillins were developed. The spectrum of activity against gram-positive organisms is similar to that of the natural penicillins. These agents retain activity against streptococcal sp. and have slightly greater activity against Enterococcus (ampicillin) and Listeria monocytogenes versus the natural penicillins. The added side chain does not, however, inhibit hydrolysis by Staphylococcal penicillinases or gram-negative beta-lactamases. The enhanced spectrum of these drugs includes activity against gram-negative bacilli, including H. influenzae, E. coli, Proteus mirabilis, Salmonella sp., and Shigella sp. (13, 83). These drugs were developed in the 1960s and were, at that time, very effective against these organisms. Presently, however, many strains of these gram-negative organisms are resistant to ampicillin. Combinations of an aminopenicillin plus a beta-lactamase inhibitor, such as clavulanic acid or sulbactam, are useful for treatment of infections caused by beta-lactamase producing organisms.

Carboxypenicillins

A carboxyl group substitution in place of the amino group yields penicillin compounds that have a greater gram-negative spectrum of action, including activity against Pseudomonas aeruginosa, most likely due to increased bacterial penetration through the cell wall. Carbenicillin and ticarcillin are the two drugs in this class. Their spectrum of activity includes that of ampicillin, while also encompassing Enterobacter, Providencia, Morganella, indole-positive Proteus, and Pseudomonas aeruginosa, with ticarcillin having slightly greater activity against Pseudomonas aeruginosa versus carbenicillin (19). Coverage against Klebsiella and Serratia are less predictable and, unlike ampicillin, these compounds have little activity against Enterococcus. These agents are not effective against beta-lactamase producing organisms unless combined with a beta-lactamase inhibitor (e.g. ticarcillin plus clavulanic acid).

Ureidopenicillins and Piperazine Penicillin

In order to increase gram-negative coverage and particularly coverage against Pseudomonas aeruginosa, a ureido group addition to the penicillin structure produces the compounds azlocillin and mezlocillin. A ureido group plus a piperazine side chain produces piperacillin. The gram-negative coverage of this class of penicillins includes that of the carboxypenicillins, plus coverage against Klebsiella, Serratia, Enterobacter, Enterococcus, and increased anaerobic

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coverage (228). The activity against Streptococci is slightly less that of the natural penicillins and ampicillin. Of the drugs in this class, piperacillin has the most activity against Pseudomonas aeruginosa (52, 255). As with the carboxypenicillins, drugs in this class are susceptible to inactivation by bacterial beta-lactamase production, unless combined with a beta-lactamase inhibitor (e.g. piperacillin plus tazobactam).

Pharmacodynamic Effects

When choosing an antimicrobial agent and designing appropriate dosing regimens for the drug, it is important to consider spectrum of activity, but also incorporate known pharmacodynamic principles about the drug. In this manner, efficacy can potentially be maximized while toxicity can be minimized. Some excellent reviews on these concepts have been published (71, 76). Such pharmacodynamic variables that are important to consider for the penicillins includes concentration-independent bactericidal activity, the post-antibiotic effect (PAE), and the duration of the dosing interval the drug's serum concentrations spend above the level of the organism's MIC (Time > MIC).

Bactericidal Effects

All beta-lactam drugs (including the penicillins) exert relatively concentration-independent bactericidal activity, meaning that the concentration of drug does not appreciably affect its ability to exert an antibacterial effect (25, 209). This assumes, however, that a level that exceeds the organism's MIC is attained. Theoretically, the bactericidal rate at 2 times above the MIC or 4 times above the MIC would be the same. However, once the drug concentration falls below the level of the MIC and the PAE has ceased, the kill rate diminishes. Time > MIC is therefore the important determinant of outcome for these drugs.

A paradoxical phenomenon of decreased effect with higher drug concentrations, known as the "Eagle effect", has been described with some strains of streptococci and staphylococci (111). This effect, however, does not appear to be clinically significant, as there is very limited data to support decreased bactericidal activity in vivo due to high serum concentrations.

Another factor that may influence bactericidal activity is bacterial inoculum size. Generally, the more dense the bacterial population (i.e. the older the infection), it is more likely that there will be resistant variants of the organism present. This may be the case with nosocomial gram-negative pneumonias or other serious infections. Treatment with a penicillin as monotherapy may result in a relapse after completion of therapy when the resistant sub-variants are no longer suppressed and begin to regrow. This scenario is not unique to the penicillins, and in fact may occur with other antibiotics when used as monotherapy.[4,5,6]

The bactericidal activity of the penicillins does not appear to be affected by changes in pH or oxygen tension. The location of the organism is important, however, as in vitro efficacy may not correspond to in vivo efficacy. Penicillins and other beta-lactams do not penetrate well into phagocytes (104), thus limiting their ability to kill intracellular pathogens. In addition, penicillins only exert their bactericidal effect on bacteria that are actively replicating.

Synergistic Bactericidal Activity

Combinations of a beta-lactam plus another agent, such as an aminoglycoside, kill some organisms most effectively. In these cases, antibacterial synergy occurs. Synergy is defined as an effect, such as bactericidal activity, that is significantly greater with the combination than the sum of the two agents when used alone. The mechanism of this effect with penicillins and aminoglycosides may be due to cell wall disruption by the penicillin, facilitating increased entry of the aminoglycoside into the bacteria (158). Enterococcal endocarditis is such an example, as penicillin monotherapy results in bacteriostatic activity and very high relapse rates after treatment (149), while the combination of penicillin plus an aminoglycoside is bactericidal (157).

Other organisms for which synergy seems to be important with regard to the penicillins includes Pseudomonas aeruginosa. Again, a combination of an antipseudomonal penicillin plus an aminoglycoside may result in increased bactericidal activity. This has been demonstrated in vitro and animal studies (5, 77, 118), but there is limited data in humans to support these findings. In vitro synergy between the extended spectrum penicillins (azlocillin, mezlocillin) and ciprofloxacin has also been demonstrated (153, 178, 225). Immunocompromised patients are a population who may benefit the most from antipseudomonal synergy. There is data to suggest that synergistic combination therapy results in increased survival versus non-synergistic combinations of drugs (124, 130, 204).

Antagonism of Antibacterial Combinations

Antibacterial antagonism is defined as a resulting effect that is significantly less in combination than with either of the two drugs when used as monotherapy. This effect has been demonstrated with the penicillins in combination with

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chlortetracycline in patients with pneumococcal meningitis, when penicillin monotherapy was more effective that the combination of agents (133). Combinations of penicillin plus chloramphenicol have demonstrated in vitro antagonism against pneumococci (188), however, clinically this may be of little importance since the combination only diminished penicillins bactericidal activity (resulting in bacteriostatic activity) and chloramphenicol retains its antibacterial effect. Also, the use of chloramphenicol has decreased dramatically in the last decade due to the availability of newer agents that are equally efficacious and less toxic.

Antagonism can also occur due to a physical incompatibility with inactivation between two drugs when infused together. This can occur with carbenicillin or ticarcillin with an aminoglycoside. These drugs should therefore not be mixed in the same infusion.

Post-Antibiotic Effect

The PAE is defined as a persistent suppression of bacterial growth after effective exposure to an antimicrobial agent when serum concentrations of the drug have fallen to levels below the MIC. This effect differs between infecting organisms and between drugs. The mechanism of the PAE is not entirely clear, but may be due to persistent binding of the penicillin to penicillin-binding proteins (PBPs) and the time that is necessary for the organism to resynthesize new PBPs (218).

The PAE was first noted with penicillin G and Staphylococcus aureus (179), when it was noted that there was a short period of time where bacterial regrowth did not occur after exposure to the drug. Subsequently, this phenomenon has been described with the penicillins for other gram-positive organisms (42, 108), including Streptococcus pneumoniae andEnterococcus faecalis. The length of the PAE can range from 0-6 hours (Table 4), depending upon the penicillin.

As stated previously, the type of organism can affect the PAE. The penicillins do not exhibit an appreciable PAE against gram-negative organisms. Also, combinations of antimicrobial agents can result in a synergistic PAE. Combinations of penicillins plus various aminoglycosides have resulted in synergistic or additive PAEs for Enterococcus faecalis andEnterococcus faecium (86, 108), along with Staphylococcus aureus (100).

Models of Antibacterial Outcome Determination

Bactericidal activity of penicillins and other beta-lactams appears to be related to the Time > MIC, as demonstrated in several in vitro models. A number of studies of beta-lactam agents demonstrated that increased half-life and not peak concentration influenced bactericidal activity (97, 125, 254, 272). This implies that increased duration of drug exposure above the MIC would be more predictive of positive outcome versus increased drug doses and subsequent increased peak concentrations.

Data from animal models supports Time > MIC as the primary determinant of efficacy for beta-lactam agents (75, 247). In a neutropenic mouse model infected with Pseudomonas aeruginosa, the impact of different dosing intervals of ticarcillin was studied. Equivalent daily doses were administered every hour or every 3 hours. The mice that received drug every hour (a lower dose administered more frequently) had a greater antibacterial effect (88).

These findings were also supported by studies of Klebsiella pneumoniae pneumonia in rats (197), in Klebsiella pneumoniae lung and thigh infections in neutropenic mice (132),Pseudomonas aeruginosa infection in neutropenic rats (159), Staphylococcus aureus in rats recovering from hemorrhagic shock (142), and in Enterococcal endocarditis (231). Additional data (247) demonstrated that for gram-negative infections, a Time > MIC of 100% of the dosing interval was most closely associated with outcome, whereas for gram-positive organisms, a Time > MIC of approximately 50% was all that was needed to be effective. For gram-negative infections, continuous infusion of the penicillin may be most appropriate to maintain serum concentrations above the MIC for the entire dosing interval.

Clinical trials examining the impact of Time > MIC for beta-lactams in relation to outcome is limited. One study examined combinations of carbenicillin plus continuous infusion cefamandole, carbenicillin plus intermittent cefamandole, and carbenicillin plus continuous infusion tobramycin in febrile, neutropenic cancer patients (32). The most effective regimen was the carbenicillin plus continuous infusion cefamandole. Despite the fact that actual Time > MICs were not calculated, the most effective regimen most likely had the greatest Time > MIC, as the carbenicillin was administered every four hours, effectively providing serum concentrations that would remain above the MIC throughout the dosing interval.

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A study of cefmenoxime in 14 critically ill patients examined bacterial eradication rates as a function of Time > MIC (203). A relationship between increased Time > MIC and increased eradication rates of gram-negative pathogens was found.

Some recent clinical data has supported time > MIC as an important predictor of outcome. Some data suggests that a time > MIC of > 50% of the dosage interval is most appropriate for cephalosporins (53). The use of cefuroxime as a single drug in the setting of in vitro resistance was associated with an increase in mortality, but this was not seen with discordant therapy when penicillins, ceftriaxone, or cefotaxime were used. This finding may have been attributed to the dosage of 750 mg three times daily which does not provide coverage of time > MIC > g/mL (µ50% of the time for organisms with MICs of 4 269) A higher dosage in the order of 1500 mg q8h may be more appropriate versus resistant pneumococci where time > MIC is > 50%.

The Role of Continuous Infusion of Penicillins

In vitro data support more frequent administration of piperacillin in suppression of microbial growth (170). As previously stated, data in humans comparing continuous infusion with intermittent dosing is limited. The study by Bodey et al appears to support such dosing, however some small studies did not demonstrate any differences in response rates (129, 270). The study by Zeisler et al. (270) was not randomized and the study by Lagast et al. (129) only included 45 patients, most likely lacking sufficient power to detect a statistical difference.

The advantage of continuous infusion would be the potential maximization of efficacy and potentially decreased costs (270). Disadvantages, however, include patient inconvenience with a continually infusing solution, lack of knowledge about proper dosing, and compatibility issues with other necessary intravenous drugs (248). Many of these concerns may be addressed by educational efforts. Other concerns include adequate tissue penetration with continuous infusion. Some studies have demonstrated good penetration of continuous infusion beta-lactams into extravascular space (181, 244). Other data appear to support intermittent injections resulting in increased tissue penetration, as seen in models of rabbit fibrin clots (14, 131), however the concentrations achieved with continuous infusion may be adequately above the organism MIC to treat the infection. A limitation of this model, however, is that the clots are implanted in the rabbit's back and may not be an appropriate representation of physiology.

Continuous infusion may be most beneficial in patients with impaired host defenses or in life-threatening infections. In these cases, patient convenience is less of an issue and the potential benefit from maximizing efficacy is greatest. Dosing by continuous infusion can be accomplished by use of nomograms (246) or by monitoring a steady-state serum concentration (after 4-5 half-lives or approximately 4-5 hours into the infusion for most penicillins) and adjusting the dose in relation to the serum concentration and the organism MIC. Use of a bolus dose may be used so that the patient's serum concentrations will reach a therapeutic level quickly.

MECHANISMS OF ACTION

Penicillins are bactericidal agents that exert their mechanism of action by inhibition of bacterial cell wall synthesis and by inducing a bacterial autolytic effect.

Inhibition of Bacterial Cell Wall Synthesis

Penicillins exert their bactericidal activity primarily by inhibiting bacterial cell wall synthesis. Though the exact mechanism of action is not fully elucidated, it appears that penicillins bind to penicillin-binding proteins (PBPs), which are enzymes (transpeptidases, carboxypeptidases, and endopeptidases) that play an important role in the formation and maintenance of the cell wall structure. The cell wall is made up of peptidoglycan, or murein sacculus, which is a polymeric component consisting of long polysaccharide chains of N-acetylglucosamine and N-acetylmuramic acid cross-linked by shorter peptide chains. The formation of peptidoglycan can be divided into three stages, including precursor formation in the cytoplasm, linkage of precursor products into a long polymer, and finally cross-linking by transpeptidation. It is the final transpeptidation process that is inhibited by penicillins by acting as a structural analog of acyl-D-alanyl-D-alanine (the substrate of the enzyme) and acylating the transpeptidase enzyme. The peptidoglycan structure, and therefore the cell wall structure, is weakened, leading to cell death (234, 236, 266). Other mechanisms of cell death are also possible. Binding to PBPs 1A, 1B, 2, and 3 results in a bactericidal effect (219), however binding to PBPs 4, 5, and 6 is not lethal. Also, there are differences in PBPs between gram-positive and gram-negative bacteria and there are differences in affinity between penicillin compounds to various PBPs. These differences can affect spectrum of activity.[7,8,9]

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Penicillin-Induced Bacterial Autolytic Effect

There are several PBPs that the penicillins simultaneously inactivate. Inhibition of certain PBPs may be related to the activation of a bacterial autolytic process by inactivation of endogenous inhibitors of these autolysins or murein hydrolases (235). These enzymes cleave parts of the cell wall to make room for peptidoglycan synthesis for cell wall expansion (109). With inhibition of cell wall synthesis, bacterial lysis can occur due to increased osmotic pressure. This autolysis may be cell cycle dependent, that is, most likely to occur while the cell is dividing (147). Certain "tolerant" species of staphylococci and streptococci have been isolated which are autolysin-deficient. These organisms are inhibited, but not killed by penicillins (233).

MECHANISMS OF RESISTANCE

A limitation to the clinical use of penicillins is the emergence of resistant organisms. Antimicrobial resistance can arise during therapy by selective pressure or can be present due to acquisition of a naturally resistant strain. A classic example of penicillin resistance is the case of Staphylococcus aureus, which was susceptible to penicillin G when the compound was first discovered (around 1941). Since that time, resistance occurs in >95% of strains, leading to the necessity of use of alternative compounds such as the antistaphylococcal penicillins or vancomycin. Resistance of other gram-positive and gram-negative organisms also occurs, which can lead to challenges in treatment of active infection. Resistance rates for different organisms vary according to geographic location and are summarized in Table 5 (93, 117, 160, 168, 200, 206). Of particular concern in the United States is the emergence of penicillin-resistant (and multi-drug resistant) pneumococci and methicillin-resistant staphylococci, as treatment options in these scenarios are limited (8, 237).

There are three main mechanisms of resistance to penicillins, including:

• enzymatic degradation of the penicillin,

• inability of the penicillin to penetrate the cell membrane to reach its target site,

• an alteration in the PBP target site.

Enzymatic Degradation

Inactivation by beta-lactamase enzymes is the most common mechanism of resistance to the beta-lactam agents. The beta-lactamase reacts with the beta-lactam bond by hydrolysis forming acidic derivatives and subsequent loss of antibacterial activity. There are several classification schemes for the numerous beta-lactamases, including those of Jack and Richmond (116), Richmond and Sykes (191), and Bush (44, 45). The Bush scheme classifies according to substrate preference and susceptibility to clavulanate inhibition. A limitation of these schemes, however, is that they can be confusing due to numerous codes and abbreviations (140).

Both gram-positive and gram-negative organisms produce beta-lactamases, mediated either by plasmids or chromosomes. An important difference is that gram-positive organisms generally produce more enzyme because it must be excreted into the extracellular space for the antibiotic to be inactivated, while the gram-negative bacteria's enzymes are located in their periplasmic space.

Gram-positive bacteria that produce beta-lactamases (particularly Staphylococcus) can transfer resistance through plasmids or transposons. Plasmids are extrachromosomal genetic material that are autonomous, self-reproducing and can be conjugating. By conjugation, the genetic information is transferred to other Staphylococcus species, including aureus andepidermidis. Transposons are DNA elements that can move from one part of the bacterial chromosome to another. Genetic information can be transferred to other bacteria through movement of the transposon to a plasmid or from direct transfer to another bacteria's chromosome, known as conjugative transposons (216). Beta-lactamases of Staphylococcus can be inducible by use of beta-lactam antibiotics, meaning that after exposure to a beta-lactam agent, the organism can greatly increase beta-lactamase production. The inducible production generally ceases after the beta-lactam is removed (172).

As stated previously, gram-negative bacteria secrete beta-lactamases into the periplasmic space and are effective in protecting the PBPs located on the bacterial inner membrane from the antibiotic. These enzymes can be either chromosomally-encoded or plasmid-encoded (227). They are produced either constitutively (production of a constant amount of beta-lactamase regardless of exposure to beta-lactam agents) or are inducible and can affect beta-lactam compounds in different ways. Some agents are quickly destroyed, while others are destroyed at a much slower rate and therefore have increased antibacterial activity.

Production of stably derepressed mutants is a concern during therapy with beta-lactam agents that are weak inducers of beta-lactamase production, such as extended-spectrum and third generation cephalosporins. These mutants produce

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increased quantities of beta-lactamases (hyperproduction) despite removal of the inducible antibiotic. This is most likely to occur with the chromosomally- mediated Bush Group I enzymes for which the preferred substrate is cephalosporins. Rapid emergence of resistance can occur in this circumstance, particularly in infections caused by Pseudomonas aeruginosa or Enterobacter cloacae (50, 141), due to selection of the mutants after the more susceptible organisms are killed during treatment. In this instance, the mutants can proliferate and can become the predominant infecting organism. The only effective beta-lactam would be a carbapenem, as Class I beta-lactamases can hydrolyze all other types of beta-lactams agents.
Extended-spectrum beta-lactamases (ESBLs) are plasmid mediated with a wide substrate profile. These enzymes are a relatively recent problem, affecting some strains of Klebsiellasp. as well as some strains of Enterobacter and E. coli. The emergence of ESBL-producing organisms has been linked with the widespread use of extended-spectrum cephalosporins (154,190). A carbapenem is a drug of choice against these organisms, while beta-lactamase inhibitor combinations may also be effective (93).

Video: Mechanism of Resistance -- Destruction
Reduced Penetration of the Penicillin
It is easier for penicillins to acetylate the PBPs in gram-positive bacteria because these bacteria have only a thick cell wall layer protecting the PBPs on the inner membrane. Gram-negative bacteria, however, have an outer membrane composed of a lipopolysaccharide and phospholipid bilayer and between the layers is a periplasmic space. An inner membrane is composed of peptidoglycan. Another space separates the inner membrane with the cytoplasmic membrane. PBPs are located in the cytoplasmic membrane and are protected by beta-lactamases. In the outer membrane there are proteins, known as porins, which act as channels for nutrients and waste products into and out of the bacteria. Penicillins may enter the gram-negative bacteria by this route. Porin permeability to penicillins depends upon size of the molecule, hydrophilicity, and electrical charge (267). Decreases in the number of porin channels have been reported to be a mechanism of resistance to beta-lactam agents (105). Most research has been conducted with the outer-membrane proteins (Omp) of E. Coli. Omp F and Omp C are the two main porins, with Omp F being most permeable to beta-lactam agents. Some mutants which lack Omp F porins can be resistant to beta-lactams due to decreased and slower penetration through the remaining porins (Omp C) and subsequent increased beta-lactamase degradation (66).

Alteration of the PBP Target Site
Binding to the PBP is necessary for the penicillin to exert its antibacterial effect. There are natural differences in the affinity for penicillin to a PBP. For instance, the affinity of the Enterococcal PBP to the antistaphylococcal penicillins is very low versus a high affinity to penicillin G or ampicillin. This accounts for the resistance seen in the case of oxacillin and Enterococcus.

Mutations can occur which can result in changes in susceptibility of an organism, which is “normally” susceptible to a particular penicillin, usually by producing PBPs with a decreased affinity to the penicillin. An alteration in PBP2 by Staphylococcus to PBP2a results in methicillin resistance, as PBP2a exhibits a decreased affinity for methicillin and most other beta-lactam agents (102). With Staphylococcus aureus (241) this type of production of PBPs with decreased affinity for the penicillin is inducible by exposure to the agent, resulting in decreased susceptibility to low concentrations of the drug.

An important example of bacteria that can develop such mutations that confer resistance is Streptococcus pneumoniae that is penicillin-resistant. The resistance mutation is genetically coded with "mosaics" that are made up of native pneumococcal DNA and DNA that is presumably from another streptococcal species, such as viridans streptococci, more resistant to penicillin (93,127). The genes that appear to be most affected are PBP 2b and 2x.

The current interpretive MIC breakpoints for penicillin as determined by the National Committee for Clinical Laboratory Standards (NCCLS) are <g/mL (resistant) (µg/mL (intermediate), and ≥2.0 µ0.06 ≤g/mL (susceptible), 0.12-1.0 165). In the United States, the prevalence of penicillin-non-susceptibility has risen from 4% in the 1980s to approximately 35% in 1997-1998 (8). Because of resistance, penicillin may not achieve adequate concentrations in the cerebrospinal fluid to treat meningitis if the infecting organism is intermediate or highly resistant to the drug. The clinical impact of penicillin resistant Streptococcus pneumoniae outside the setting of the central nervous system has been uncertain, however one large prospective study of 844 hospitalized patients with positive blood cultures for Streptococcus pneumoniae examined the impact of resistance, antibiotics administered, and clinical outcome. Of the isolates, 15% were intermediate and 9.6% were resistant to penicillin, but penicillin resistance was not a risk factor for

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mortality and NCCLS breakpoints were not predictive of clinical outcome for penicillin or ceftriaxone (but were for cefuroxime), suggesting that penicillin-resistant pneumococcus is not clinically relevant for parenteral therapy of pneumococcal pneumonia (269)

Video: Mechanism of Resistance -- Mutation

Methods to Overcome and Prevent Resistance

Because of concerns over infectious organisms that are emerging resistant to our standard therapies, there is a need for prevention. Infection control practices should be followed, which include hand washing and changing gloves between examination of patients. These methods can limit the dissemination of a resistant organism in a hospital environment (95). Unfortunately, such practices are not routinely followed by health-care providers despite educational efforts (94, 68).

Optimization of antimicrobial use in hospitals is desirable as it is has been demonstrated that use (and overuse) of broad-spectrum antimicrobials is associated with emergence of resistant organisms (50, 249), particularly with ESBL-producing organisms (154, 190) and it is suspected with penicillin and vancomycin resistant enterococcus. Antibiotic control programs have been implemented in many institutions with some success (79, 264). Successful policies, however, can be time and labor intensive and require a full institutional commitment in the form of adequate personnel for implementation and medical staff support for the program.

Pharmacologically, there are strategies to overcome and prevent resistance. The use of combination antimicrobial therapy is a method to provide adequate coverage against suspected organisms (14). There is animal model data to suggest that combination chemotherapy that is synergistic may have a benefit in prevention of emergence of resistance (89, 118), however clinical data is limited.[10,11,12]

PHARMACOKINETICS

The pharmacokinetics of the penicillins varies between compounds. Absorption between oral agents varies greatly, with amoxicillin and dicloxacillin producing adequate serum concentrations and penicillin G and carbenicillin producing very poor serum concentrations. The penicillins are widely distributed in the body, with adequate levels achieved in serum, tissues, bile, and synovial fluid. Penetration into the cerebrospinal fluid (CSF) in patients with uninflamed meninges is relatively poor with only 0.5-2% of serum concentrations attained (173). When the meninges are inflamed, however, penetration increases to approximately 5-20% of serum concentrations, as demonstrated in rabbit models (202, 229). The primary route of elimination for most penicillins is renal, with some hepatic metabolism. Some compounds, however, are primarily eliminated by the hepatic route.

The absorption, distribution, metabolism, and excretion will be described for each class of penicillins. Pharmacokinetic properties for the penicillins are summarized in Table 6.

Natural Penicillins

Aqueous crystalline penicillin G, or benzylpenicillin, administered intravenously is the most commonly utilized formulation for this class of penicillins. This route of administration is preferred in ill patients due to increased serum concentrations achieved versus oral or intramuscular (IM) routes of administration with penicillin G or other natural penicillins. The drug is widely distributed with an apparent volume of distribution (Vd) of 0.35 L/kg. Distribution into the CSF is minimal with uninflamed meninges, but increases with inflammation. CSF concentrations can be approximately 5% of serum concentrations (205). Elimination is primarily (90%) renal (10% by glomerular filtration, 90% by tubular secretion) (40,73). There is, however, some hepatic elimination. The pharmacokinetic advantage to this drug is that high serum concentrations are achieved rapidly, but the half-life is approximately 30 minutes, necessitating redoing every 4-6 hours.

Penicillin G is poorly absorbed orally, with a bioavailability of 15-30%. The environment of the stomach decreases its absorption due to gastric acid breakdown. In hypochlorhydric patients, such as the elderly, oral penicillin G has an increased absorption due to an increasing gastric pH. Penicillin V, administered orally, has an increased absorption compared to penicillin G due to its increased acid stability (nearly double the peak serum concentrations). Low concentrations are attained in tissues. Concurrent administration of food can decrease the absorption of the oral natural penicillins, most likely due to binding of the penicillin onto the food particles. Because of poor absorption and limited clinical utility, oral penicillin G is no longer available in the United States.

Procaine penicillin G (PPG) and benzathine penicillin G (BPG) are repository forms of penicillin administered intramuscularly (IM), with prolonged absorption and subsequent extended serum concentrations of penicillin G. PPG serum concentration can last for up to 24 hours, while low level BPG serum concentrations (0.10 - 0.15 units/mL) can

| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54| Monthly Peer Reviewed & Referred Journal |

| Volume 6, Issue 4, April 2023 |

| DOI:10.15680/IJMRSET.2023.0604033 |

last for up to 3-4 weeks. The advantage of these long acting agents is that dosing can be less frequent if the organism is susceptible to the lower levels achieved, such as in the case of BPG and Treponema pallidum, the causative agent of syphilis, where MICs are usually 0.03 units/mL. PPB contains 120 mg procaine with every 300,000 units penicillin G. Patients who are hypersensitive to procaine may experience adverse reactions, particularly when high doses (e.g. 4.8 million units PPG) are used.

Penicillinase-Resistant Penicillins

Methicillin is not orally absorbed and is therefore only given by the intravenous route. Nafcillin has poor oral absorption and its use is generally limited to intravenous or intramuscular routes. Oxacillin, cloxacillin, and dicloxacillin can be administered orally, however oral oxacillin produces a peak serum concentration nearly ¼ that of dicloxacillin.

Penetration into the CSF with inflamed meninges is variable, due to increased protein binding (50-92%). Penetration into the bile is highest with nafcillin of approximately 4000% of serum concentrations (164). Methicillin is eliminated primarily through the kidney by glomerular filtration or tubular secretion. Oxacillin is both renally eliminated and hepatically metabolized. Nafcillin, however, is primarily hepatically metabolized; therefore a dosage adjustment in renally impaired patients is not necessary.

Aminopenicillins

Unlike the natural penicillins, these agents exhibit increased stability to gastric acid hydrolysis. Amoxicillin's bioavailability is greater than that seen with ampicillin (75-90% with amoxicillin versus 30-50% with ampicillin). Because of this difference, oral ampicillin has been favored for treatment of a localized Shigella infection when lack of absorption is desirable. The incidence of diarrhea is increased, however, with this agent due it's effect on normal flora of the gastrointestinal tract. Food delays the absorption of ampicillin and amoxicillin, however the extent of absorption is decreased only for ampicillin.

Penetration of ampicillin into the CSF in patients with inflamed meninges occurs with CSF concentrations of approximately 1.5 µg/mL being attained after a single 1-g dose. Elimination of the drug is primarily renal, but about 10% of the drug is metabolized hepatically. Both drugs are removed by hemodialysis (30-40%).

Bacampicillin is a prodrug of ampicillin and is hydrolyzed to ampicillin by esterases during absorption and distribution. Increased serum concentrations of ampicillin are seen due to increased absorption (bioavailability of 80-95%).

Extended-Spectrum Penicillins

The absorption of carbenicillin (the only orally available extended-spectrum penicillin) is poor with a bioavailability of 30-40%. Serum concentrations achieved are inadequate to appropriately treat systemic infection; therefore, it's clinical use is limited to urinary tract infection and in some instances, prostatitis. The use of this drug, however, has decreased since the availability of orally administered quinolones for these indications.

Ticarcillin, mezlocillin, and piperacillin penetrate fairly well into the CSF in patients with inflamed meninges. Continuous infusion piperacillin in 4 meningitis patients receiving 325-425 mg/kg/day attained a mean CSF level of 23 µg/mL (68). They also distribute well into bile, with concentrations of piperacillin nearly 50 times higher than that seen in the serum (92,199). Penetration into diseased biliary tracts (e.g. cholecystitis) is limited, and adequate concentrations may not be achieved in this setting. Elimination of these compounds is by both renal and nonrenal routes.

Effects of Renal Impairment and Dialysis on the Clearance of Penicillins

Because many of the penicillins are renally excreted, impairment in renal function can result in prolonged half-lives and subsequent increased serum concentrations of drug (18) and can increase the propensity for adverse effects. It is therefore important to adjust doses or dosing intervals for many of the penicillins in these patients (Table 7). Penicillin G is a renally excreted drug and it's clearance can be related to creatinine clearance (CrCL) using the equation, penicillin clearance in mL/min = 35.5 + 3.35 * CrCL in mL/min. The daily dose of penicillin G can be calculated using the equation dose (in million units per day) = 3.2 + CrCL/7 (40). Other penicillins, including mezlocillin and piperacillin (24, 64) should also have their dosing regimen adjusted in renal impairment. With these drugs, however, biliary excretion also occurs, resulting in serum concentrations that are not in proportion to the degree of renal impairment. Oxacillin, cloxacillin, and dicloxacillin, while partially renally excreted, have only moderate increases in half-life (1.5-2-fold) in anuric patients (22, 41, 258), therefore dosage adjustment is most likely only necessary in severe renal impairment. Carbenicillin should be avoided in patients with renal impairment and renal failure as urinary concentrations are inadequate for treatment of urinary tract infection (the drug's only clinical indication).

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Many of the penicillins are cleared during hemodialysis (50-90% of serum concentrations) (22, 77), therefore a supplemental dose after dialysis is recommended for penicillin G, ampicillin, piperacillin, ticarcillin, and mezlocillin. Nafcillin and oxacillin are not appreciably cleared by hemodialysis, so supplemental dosing is not necessary.
Peritoneal dialysis does not significantly remove any of the penicillins; therefore supplemental dosing is not necessary.

Effects of Hepatic Insufficiency on the Pharmacokinetics of the Penicillins
Most penicillins are primarily renally eliminated and do not require a dosage adjustment on hepatic impairment. Because of the nonspecific nature of liver function tests (ALT, AST, GGT, etc.) and the fact that increases in these markers may not correlate with intrinsic hepatocellular activity, it is difficult to recommend precise dosage adjustments for hepatically eliminated drugs. Some penicillins that may warrant a dosage adjustment in hepatic impairment include nafcillin and mezlocillin. An up to 50% dose reduction of nafcillin may be appropriate in patients with a combination of renal and hepatic insufficiency. Mezlocillin's dose may be reduced by 50% or the dosing interval doubled in patients with severe hepatic impairment (43, 155).

Effects of Pregnancy on the Pharmacokinetics of the Penicillins
Pregnant patients have increased volumes of distribution and may result in decreased serum concentrations of drugs. This has been demonstrated with piperacillin (106) and ampicillin (126), but may occur with other penicillins as well. In a comparative study with piperacillin and mezlocillin, a shorter half-life and increased clearance was seen in post-partum patients receiving piperacillin versus non-pregnant patients, but was not seen in post-partum women receiving mezlocillin (152). This data implies that dosage increases may be more important in post-partum patients when using piperacillin, as this drug may be more affected by the physiologic changes induced by pregnancy.

DOSAGE

A summary of common adult and pediatric dosage regimens for the penicillins are shown in Table 7 (156). Many pediatric dosages are specified on a per kilogram basis. It is important to keep in mind that the pediatric dosage should not exceed the usual adult dose when using this method of dosing, particularly in a large child. Formulations available are listed in Table 1 and costs for typical courses of therapy are shown in Table 8.

Natural Penicillins
Penicillin G dosages are usually described in units. One unit is defined as a concentration of drug that produces a certain size zone of growth inhibition around an Oxford strain of Staphylococcus aureus. One unit is equivalent to 0.6 µg of crystalline sodium salt of penicillin G, therefore 250 mg equals 400,000 units. Aqueous crystalline penicillin G is administered intravenously at dosages of 6-20 million units daily, either in 4-6 divided doses or by continuous infusion. Benzylpenicillin is available as a sodium or potassium salt, either providing 20 meq of sodium or 1.7 meq potassium per 1 million unit. The potassium salt is most often used clinically, except in patients with severe renal failure, where the sodium salt may be more appropriate.

BPG and PPG should not be administered subcutaneously due to severe pain and induration at injection site. In adults, the injection should be made into the gluteus maximus or midlateral thigh. Intravenous injection may result in severe neurotoxicity and should be avoided.

Penicillinase-Resistant Penicillins and Aminopenicillins
The penicillinase-resistant penicillins are available as sodium salts of the drugs. Dosages for methicillin are expressed as methicillin sodium, while the other agents in this class have their dosages expressed as the base compound (e.g. 1g methicillin sodium = 900mg methicillin). Of the aminopenicillins, bacampicillin 400 mg is equivalent to 280 mg of ampicillin.

Extended-Spectrum Penicillins
These compounds are available as disodium salts and contain a significant amount of sodium with each dose. Ticarcillin sodium has the most sodium load with 5.2 mEq/gram (120 mg/gram). Carbenicillin (intravenous form), carbenicillin indanyl (oral form), mezlocillin, and piperacillin contain 4.7, 2.6, 1.85, and 1.85 mEq/gram, respectively. This increased sodium load can be problematic in patients with congestive heart failure and renal impairment.

For patients on continuous renal replacement, dosages should be modified (Table 9).

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PENICILLIN HYPERSENSITIVITY

Incidence

Allergy to penicillin is estimated to occur in 1-10% of patients receiving the drug (66). Manifestations can range from a maculopapular rash to an anaphylactic reaction. While anaphylaxis is relatively rare (0.004- 0.015% of patients (113), the reaction can be potentially fatal with rates of approximately 3-9% in such patients (113, 201).

Mechanism and Types of Allergic Reactions

Penicillin is degraded into several products, including benzylpenicilloyl, or major determinant, which makes up 95% of the breakdown products. The remaining 5% is termed the minor determinants and include a mixture of benzylpenicillin, benzylpenicilloate, and benzylpenilloate. Benzylpenicilloylamine may also be included as a minor determinant, though its clinical relevance is questionable (20). Antibodies to the major and minor determinants can exist and an immune response can be elicited upon binding of these determinants to tissue proteins, forming a hapten-protein complex and hence, a complete antigen (135). Antibodies to the major determinant can include IgE, IgG, and IgA. Only IgE antibodies have been demonstrated to the minor determinants. A sensitivity to the beta-lactam ring or to the side chain of semisynthetic penicillins may also be mechanisms of eliciting an immune response.

A Type I, or immediate anaphylactic reaction can occur , usually within 2-20 minutes of drug administration. When contact is made with the antigen, IgE antibodies present on mast cells and basophils degranulate releasing various mediators, including histamine, prostaglandins, leukotrienes and others. Histamine release increases capillary permeability, and stimulates bronchial smooth muscle and nerve endings. Bronchoconstriction, laryngeal edema, and urticaria occur, along with hypotension (31, 177). While sensitivity to the major determinant can cause an anaphylactic reaction, sensitivity to the minor determinants are more closely associated with that allergic manifestation (135). This may be explained by the high binding affinity of the minor determinant to IgE. With exposure to the major determinant, IgG is also produced, along with IgE, and may compete with IgG for binding to the antigen. Minor determinants do not elicit IgG and therefore there is no competition for antigen binding (135, 136).

Type II reactions are cytotoxic reactions that can result from exposure to major determinant and are mediated by IgG, reacting with penicillin adsorbed on red cells. Manifestations include a Coombs-positive non-acute hemolytic anemia and usually occur in a small percentage of patients receiving increased doses in intravenous penicillin for a prolonged period of time (192). The anemia is reversible upon drug discontinuation.

A Type III hypersensitivity to penicillin can result due to circulating antigen-antibody complexes that can deposit in the skin, kidneys, and blood vessels and cause tissue damage through activation of complement. This type of reaction is usually due to IgG or IgM antibodies, though IgE may play a role in enhancing complex deposition (180). A serum sickness-like syndrome can occur 1-3 weeks after the start of penicillin therapy or even after drug discontinuation and can manifest as rash, fever, arthralgia, and lymphadenopathy (210). The syndrome will diminish when the drug is completely cleared from the body.

Delayed hypersensitivity, or Type IV, reactions can also occur with exposure to penicillin. Lymphocytes and macrophages are believed to mediate these reactions, which can manifest a number of ways. Contact dermatitis can occur secondary to skin exposure. Acute interstitial nephritis can occur with any penicillin but is most commonly associated with methicillin and it is believed to be caused by a Type IV reaction. Renal insufficiency can occur, along with hematuria, eosinophilia, eosinophiluria, and proteinuria. This effect is usually reversible upon drug discontinuation (139).

Risk Factors

Though allergy can occur at any age, patients between 20-49 years are at increased risk for anaphylaxis (113). Reactions may be more frequent and severe with parenteral formulations of drug. In addition, it is believed that as many as 85% of patients who reacted to penicillin may not react upon a second exposure if the time interval from the last exposure is prolonged (110, 210). It may, however, be difficult to discern the 15% of patient who will indeed have an allergic reaction upon rechallenge without skin testing. Traditionally, atopic individuals were believed to be predisposed to development of a penicillin allergy. The data suggests, however, that there is no relationship (98). Family history of allergy is also not a risk factor.

Diagnosis

There are many indications where a penicillin is a drug of choice or the drug of choice. Patients with a label of “penicillin allergy” will have an alternative therapy prescribed or will need to be desensitized to the agent. Alternative

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| Volume 6, Issue 4, April 2023 |

| DOI:10.15680/IJMRSET.2023.0604033 |

therapies can be less effective (e.g. enterococcal endocarditis) and desensitization can be a time-consuming process. Therefore, accurate diagnosis is important. Two methods of diagnosis include patient history and skin testing.

A detailed history about the allergic reaction is important is discerning between a true allergy and a simple gastrointestinal (GI) intolerance. Nearly 20% of patients with a penicillin allergy label described symptoms of a GI intolerance when a detailed history was obtained (185). Those patients could potentially receive a penicillin if necessary, despite the allergy label. Patient histories can be unreliable, however, and some may have been too young to fully remember the reaction. Reliance on history alone can result in overdiagnosis of allergy.

Skin testing for allergy may also be performed and can be used to detect propensity for a Type I reaction. Positive skin tests have been observed in 7-19% of patients with a positive history for allergy (48, 87, 2113-5mm greater than a saline control at 10-20 minutes. The major determinant, benzylpenicilloyl poly-L-lysine is commercially available as Pre-Pen® at a concentration of 10-6 M. Alone, this will detect 90% of allergic patients. To increase this percentage, the minor determinant mixture (MDM) must also be used, as up to 10% of patients react only to these determinants (87,≥). Approximately 0.02-0.03 mL is injected intradermally and wheal size is measured 10-20 minutes after injection. A positive test is considered a wheal size of242), and patients sensitive to the MDM are at highest risk of a Type I reaction (136). Even the combination of the major determinant mixture and benzylpenicillin (a minor determinant) can result in false-negatives in 3% of patients (98). In fact, it may be that side-chain specific reagents are necessary to truly exclude the possibility of allergy in patients with a clinical history (211).

There are several disadvantages and limitations to routine skin testing of all patients with a history of penicillin allergy. First, the MDM must be compounded freshly, as a commercial preparation is not available (189), which can be time-consuming and costly. Second, skin testing can be associated with precipitation of an anaphylactic reaction in sensitized individuals, however this is rare and may be avoided by performing a scratch test and observing for a wheal and flare reaction. Recent data has suggested that the likelihood of sensitization by skin testing is small (175). Third, skin testing does not identify patients at risk for Type II-IV reactions, though these are generally not immediately life-threatening effects in the way anaphylaxis is. Lastly, a negative skin test is only valid for 48 hours prior to administration of the penicillin. [13,14,15]In patients where an acceptable therapeutic alternative is available, such a substitution may be more appropriate that skin testing. Skin testing would be an alternative in patients with a positive history of an allergy and with an infection that a penicillin would be a drug of choice. If a patient has a positive skin test there is a 67% chance of an allergic reaction occurring upon penicillin exposure (37), therefore a therapeutic alternative should be used or desensitization to the penicillin compound should be instituted before treatment with the drug. In patients with a positive history of penicillin allergy with a negative skin test, penicillin use appears to be safe (145), but caution is recommended.

Desensitization

In instances such as Enterococcal endocarditis, neurosyphilis, and in infections with organisms resistant to other antibiotics, desensitization should be considered in a patient with a likelihood of a Type I allergic reaction occurring (desensitization is not effective in preventing Type II-IV reactions). A protocol of administration of gradually increasing doses of the agent every 15 minutes can increase the threshold of IgE induced mast cell degranulation (162). The procedure should be continuously supervised (intensive care setting preferred) and epinephrine should be available. Intravenous, subcutaneous, or oral routes may be used for the procedure. An advantage to the oral route is that it is shorter and can possibly be safer, though in one study 5 of 25 patients receiving oral penicillin desensitization acutely developed urticaria, pruritus, and angioedema (220). Once the desensitization protocol has been completed, treatment doses may be initiated. Interruption of penicillin treatment by > 48 hours is an indication for repeat desensitization (210).

Cross-Reactivity with Other Beta-Lactams and Related Compounds

There is a concern over the potential for allergy to other beta-lactam compounds, such as cephalosporins, aztreonam, and the carbapenems, in patients allergic to penicillin. Estimates of cross-reactivity with cephalosporins range from 2-10% (182, 195), though there is data to suggest that the incidence is much lower (6). No major or minor determinants exist with cephalosporins, which could account for the low cross-reaction potential. Cross reaction with the carbapenems may also occur, however the monobactams (aztreonam) appear the have a low propensity for eliciting an immune response and have not shown a cross-reaction with penicillin antibodies when tested in vitro (1). The bulky side chain, rather than the beta-lactam ring may be the site of immunologic reactivity. The in vitro studies (1, 201) also demonstrated that cross-reaction between aztreonam and ceftazidime occurred, which is expected since the two

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| Volume 6, Issue 4, April 2023 |

| DOI:10.15680/IJMRSET.2023.0604033 |

compounds have identical side chains. Though the risk of cross-reactivity appears to be low, in patients with a history of severe allergy it may be prudent to avoid the use of cephalosporins as good therapeutic alternatives are available.
The potential for a cross-reaction with penicillamine has also been explored, as penicillamine is a metabolite of penicillin degradation. A study examined 40 patients with a positive history of penicillin allergy. Sixteen patients skin tested positive for sensitivity to penicillin only and 1 patient had a positive penicillamine skin test (21). This data suggests that the incidence of cross-reaction is low, but that penicillamine should be administered with caution to these patients.

II. DISCUSSION

ADVERSE EFFECTS

The penicillins are associated with several adverse effects. These adverse effects will be discussed according to body system affected.

Gastrointestinal Effects

Perhaps the most common adverse reaction to orally administered penicillins is gastrointestinal effects. Diarrhea can occur in up to 20% and 5% of patients receiving oral ampicillin and amoxicillin, respectively. The incidence may be increased to up to 40% in children. Other effects, such as nausea, vomiting, and epigastric distress may also occur. Diarrhea has also been reported in patients receiving intravenous penicillins (approximately 3%).

Antibiotic-associated pseudomembranous colitis caused by Clostridium difficile, may occur during or immediately after therapy with a penicillin due to changes in normal bowel flora from the broad spectrum coverage and overgrowth of this organism. While Clostridium difficile is “sensitive” to ampicillin and amoxicillin, it produces spore form, which survives. In the scenario of diarrhea associated with presence of Clostridium difficile and depending upon the severity of illness, appropriate treatment with metronidazole or oral vancomycin should be considered.

Skin Effects

Rash may occur with administration of any penicillin. Patients are over twice as likely to develop a rash while receiving ampicillin or amoxicillin (5-10%) versus the other penicillins (2%) (138). The ampicillin rash is maculopapular and is often self-limited. Patients who have infectious mononucleosis, cytomegalovirus infection, chronic lymphocytic leukemia, or are on concurrent allopurinol are at increased risk of development of such a rash.

Hematologic Effects

Neutropenia can occur with administration of any penicillin at an estimated incidence of 3-8%. Risk factors include high doses for a prolonged (> 10 day) period of time (166, 176) and hepatic impairment (212). The mechanism may be due to immune complex deposition on the neutrophil cell membranes (198). Patients should be monitored for this adverse effect if prolonged treatment courses are used.
Inhibition of platelet aggregation can occur due to alterations in adenosine diphosphate responses, particularly with ticarcillin and carbenicillin. Prolonged bleeding times can result, along with actual bleeding (2, 4, 82, 226). Patients with thrombocytopenia and/or azotemia appear to be at increased risk. Increased bleeding times were seen in a study of 156 patients receiving ticarcillin (73%), piperacillin (43%), mezlocillin (25%), or cefotaxime (17%). Though some patients were receiving chemotherapy, which could confound results, the trend remained after those patients were removed from the analysis. Bleeding occurred in 34%, 17%, and 2% of patients receiving ticarcillin, piperacillin, and mezlocillin, respectively (82). This effect generally reverses upon drug discontinuation.

CNS Effects

Increased doses and resultant serum concentrations of penicillin G have been associated with encephalopathy, particularly in patients with severe renal impairment (30). Seizures can also be induced with elevated CSF concentrations of any penicillin (208). Predisposing factors include renal impairment, a history of a seizure disorder, meningitis, or intraventricular antibiotic administration (15). If neurologic symptoms develop, the dose of penicillin should be reduced or discontinued. If seizures develop, benzodiazepines may be effective as treatment.

Metabolic Effects

Hypokalemia has been reported with the penicillins (39), possibly due to effects on renal tubules and subsequent potassium loss. This effect is more common with the carboxypenicillins. Hyperkalemia can result from use of penicillin G potassium, and reports of death have occurred (240). Hypernatremia may also occur with the carboxypenicillins due to the increased sodium content in their formulations. Patients with renal impairment should be monitored for potential electrolyte disturbances.

Hepatic Effects

| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54| Monthly Peer Reviewed & Referred Journal |

| Volume 6, Issue 4, April 2023 |

| DOI:10.15680/IJMRSET.2023.0604033 |

Transient increases in transaminases can occur. Hepatitis or cholestasis can occur with high dose oxacillin and is generally reversible upon drug discontinuation (38).

Thrombophlebitis

Intravenous administration of penicillin G, nafcillin, oxacillin, and methicillin can cause thrombophlebitis. Tissue necrosis can occur with extravasation of nafcillin. If extravasation occurs, hyaluronidase can be used as a local antidote at the site of injury.

Jarisch-Herxheimer Reaction

This reaction occurs in patients being treated with a penicillin (usually penicillin G) for a spirochetal infection (usually syphilis, but can include leptospirosis, Lyme disease, and others) and is a result of release of pyrogens from infecting organisms (268). In patients with syphilis, the incidence is 50% in primary syphilis and rises to 75% in patients with secondary syphilis. The reaction usually begins within 2 hours of initiating syphilis treatment and it consists of fever, chills, sweating, tachycardia, hyperventilation, flushing, and myalgia. The duration is about 1 day and it can be treated with aspirin or prednisone (238).

Miscellaneous

When procaine penicillin G is used intramuscularly, <1% of patients will experience a procaine reaction consisting of dizziness, auditory, visual, and/or taste disturbances, neuromuscular twitching, and a fear of imminent death. This reaction has been associated with doses of 4.8 million units and typically lasts up to 10 minutes (99).

DRUG INTERACTIONS

The penicillins are associated with relatively few drug interactions as compared to other drugs, such as some quinolones and protease inhibitors. Notable interactions are listed below.

Aminoglycosides

Inactivation of the aminoglycosides by the penicillins has been documented in vitro (184, 193) and can particularly be a problem if the penicillin and aminoglycoside are mixed in the same infusion solution and are allowed to sit for 30 minutes or greater. Clinically, this interaction can occur in patients with severe renal impairment where drug elimination and serum concentrations are prolonged, increasing the time that the drugs are in contact with one another (28, 79, 103). It appears that amikacin is the most stable aminoglycoside to penicillin-induced inactivation (120), therefore this aminoglycoside may be preferred in patients with end-stage renal disease who require a combination of a penicillin and aminoglycoside for treatment.

Probenecid

Probenecid competitively inhibits renal tubular secretion of penicillins and therefore increases serum concentrations of the penicillins (91, 252). Studies with piperacillin demonstrated that probenecid increases the peak concentration by 30% and decreases the volume of distribution by 20% (232). This interaction has been used clinically in patients receiving procaine penicillin G for treatment of gonorrhea to increase the serum concentrations of the penicillin.

Mezlocillin and Oxacillin

Oxacillin clearance was decreased by 38% when administered concomitantly with mezlocillin (121), therefore it is recommended to decrease the dose of oxacillin by 50% in severely renally impaired patients receiving this combination.

Penicillin VK and Neomycin

The absorption of penicillin VK is decreased by nearly 50% when administered with neomycin (49). Concomitant use of these drugs should be avoided.

CLINICAL INDICATIONS

The penicillins are utilized for treatment of many different indications.

Bone and Joint Infections

The most common pathogen causing infectious arthritis is Staphylococcus aureus. Other causative organisms include Neisseria gonorrhoeae, Streptococci, and gram-negative bacilli. It is recommended that empiric therapy be based upon synovial fluid Gram stain results, patient age, and sexual activity (213, 214). A penicillinase-resistant penicillin (e.g. nafcillin 2g IV q6h) can be used to treat a Staphylococcal arthritis, however if Neisseria gonorrhoeae is suspected, ceftriaxone or other third generation cephalosporin would be recommended. Streptococcal arthritis does not respond well to the penicillinase-resistant penicillins, therefore penicillin G (2mu IV q4h) or clindamycin should be used (213, 214). Length of therapy ranges from 1-4 weeks, with the longer duration for Staphylococcal disease.

| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54| Monthly Peer Reviewed & Referred Journal |

| Volume 6, Issue 4, April 2023 |

| DOI:10.15680/IJMRSET.2023.0604033 |

Osteomyelitis may be caused by a number of different organisms, including Staphylococcus aureus (most common), gram-negative rods, group A streptococci, Pseudomonas aeruginosa, and anaerobes (particularly with direct extension osteomyelitis). Penicillins are recommended as treatments of choice for several types of osteomyelitis, including penicillin G (4 mu q6h) for penicillin-sensitive Staphylococcus aureus, nafcillin or oxacillin (2g q6h) for penicillin-resistant Staphylococcus aureus, and penicillin G (4 mu q6h) for streptococcal infection (137). Duration of therapy should be 4-6 weeks. Children with Staphylococcal osteomyelitis have been treated successfully with oral antibiotics and may be switched to oral therapy (with dicloxacillin or cephalexin) after two weeks of a positive response to intravenous therapy (230). For Staphylococcal osteomyelitis, rifampin may be used in combination with the penicillin to enhance the antimicrobial response (171).

Central Nervous System Infections

Acute bacterial meningitis is caused by a number of different organisms, usually depending upon the age of the patient. In young adults and children, Neisseria meningitidis is a common pathogen for which intravenous penicillin G is the drug of choice. Reduced susceptibility (MICs of 0.1-1.0 µg/mL), however, has been reported in certain areas (119, 243, 263), but penicillin G may still be effective against these organisms (119).

Another common pathogen causing meningitis is Streptococcus pneumoniae. Traditionally, intravenous penicillin G or ampicillin have been drugs of choice for penicillin-susceptible strains. Strains with intermediate resistance1.0 µg/mL) are becoming more common and CSF fluid levels achieved with penicillin G may not exceed the MIC or MBC of these organisms (≥ (MIC 0.1-1.0 µg/mL) and high-level resistance (MIC 187). In other body sites of infection, penicillin-resistance to the pneumococcus can be overcome by increasing the penicillin dose, however in meningitis, potential neurotoxicity may result. Empirically, vancomycin plus a cephalosporin is recommended as treatment for a gram-positive cocci meningitis or a pneumococcal meningitis until susceptibility to penicillin G is determined (187).

Haemophilus influenzae produces beta-lactamase in approximately 32% of cases of acute meningitis where it is the causative pathogen (253). The utility of the penicillins is therefore limited in these infections and other alternatives, such as the third generation cephalosporins should be chosen for treatment empirically. If beta-lactamase negative, therapy can be changed to ampicillin.

Other pathogens that can cause meningitis for which penicillin G or ampicillin are drugs of choice include Listeria monocytogenes and Streptococcus agalactiae. When treating Listeria meningitis, gentamicin is often used in combination with ampicillin because of in vitro synergy, though adequate evidence of this in humans has not been demonstrated (194).

Brain abscesses may be caused by streptococci, microaerophilic streptococci (Streptococcus milleri), or anaerobes, such as Bacteroides sp, as well as other organisms. High dose penicillin G (4mu IV q4h) in combination with metronidazole if often used empirically for treatment (61, 262) for at least 4-6 weeks. Penicillin G's penetration into brain abscess fluid is acceptable, however degradation of penicillin G may occur due to enzymes present in the abscess (60, 265).

Endocarditis

Endocarditis is a serious infection of the endocardial surface of the heart. The most common organisms causing endocarditis include viridans Streptococci, Enterococcus, and Staphylococcus sp. Intravenous penicillin G is the drug of choice for treatment of viridans Streptococci and Streptococcus bovis0.1 µg/mL, including a 4 week course of penicillin G 10-20 mu/day continuously or in 6 divided doses (≤ endocarditis. Several regimens can be used for treatment of organisms with an MIC of 122, 148) or a 4 week course of penicillin G plus a 2 week course of an aminoglycoside (streptomycin or gentamicin). A two-week course of the combination of penicillin G at the above doses plus an aminoglycoside may also be used and there is data using PPG 1.2mu IM q6h with streptomycin successfully for treatment for two weeks in uncomplicated cases (259, 260). In patients with organisms with MICs between 0.1 µg/mL and 0.5 µg/mL, or having nutritionally-deficient streptococci, the combination of 4 weeks of penicillin G at the higher dose with a 2 week course of an aminoglycoside is recommended (26), as animal models suggest that the combination is superior to penicillin alone in reducing nutritionally-deficient streptococci colony counts (107).

Enterococcal infections should always be treated with a combination of a penicillin plus an aminoglycoside, as neither agent alone is bactericidal against this organism and the combination is synergistic (158, 250). A 4-6 week course of intravenous penicillin G (20-30 mu/day continuously or in 6 divided doses) or ampicillin (12g/day continuously or in 6 divided doses) plus gentamicin or streptomycin is the recommended treatment regimen (26).

| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54| Monthly Peer Reviewed & Referred Journal |

| Volume 6, Issue 4, April 2023 |

| DOI:10.15680/IJMRSET.2023.0604033 |

To appropriately treat Staphylococcal endocarditis, it must be determined whether prosthetic material is involved and if the organism is methicillin-susceptible. If methicillin resistant, vancomycin with rifampin and gentamicin should be used. For those patients with methicillin susceptible Staphylococci without the presence of prosthetic material, an antistaphylococcal penicillin (intravenous nafcillin or oxacillin) can be used. The dosage is 1.5-2g every 4 hours for 4-6 weeks. Gentamicin may be added for the first 3-5 days of therapy.

If prosthetic material is involved, the causative organism is more likely to be a coagulase-negative staphylococcus6 weeks), gentamicin is utilized for the first 2 weeks of the regimen, and rifampin 300mg every 8h orally is used for the entire treatment course. If methicillin susceptible, nafcillin or oxacillin can be used; if methicillin resistant, vancomycin must be used (≥ (usually methicillin-resistant). Treatment is more prolonged (26).

Penicillins are often used for prophylaxis of infective endocarditis in certain at-risk patients (e.g. prosthetic valve in place or congenital heart anomaly) undergoing dental procedures/surgery, or minor gastrointestinal or genitourinary procedures. The prophylaxis is believed to treat the bacteremia that occurs during these procedures which could cause endocarditis. While no prospective study has proved the effectiveness of such prophylaxis, oral amoxicillin 3.0 g given 1 hour prior to the procedure and 1.5g 6 hours later had traditionally been a standard regimen recommended (72). A 2.0 g dose demonstrated adequate serum concentrations in a normal volunteer study and may result in decreased gastrointestinal adverse effects (55) and recent recommendations therefore include an initial 2.0 g dose with no follow-up antibiotic dose (54). In penicillin-allergic patients, clindamycin, cefadroxil, or azithromycin may be substituted.

Intra-Abdominal Infection

Infections in the abdomen are often caused by mixed flora, including anaerobes and facultative aerobes. Bacteroides fragilis must be adequately covered empirically and is typically resistant to the penicillins except for beta-lactam/beta-lactamase inhibitor combinations. It is recommended that mild to moderate community-acquired infections a combination of beta-lactam/beta-lactamase inhibitor or a cephalosporin with activity against Bacteroides fragilis be utilized. Imipenem monotherapy or combinations of aztreonam,metronidazole, and aminoglycoside may be used for severe infections (33).

Obstetrics and Gynecological Infections

Penicillin has been studied in women as prophylaxis for infectious complications of premature rupture of the membranes. Patients received either intravenous penicillin G 1mu every 4 hours with oral penicillin VK as followup or placebo. Significantly fewer infections occurred in the patients receiving penicillin (78).

Penicillin and ampicillin have also been studied as prophylaxis of group B streptococcal infection in infants of mothers with birth canal colonization when administered intrapartum. Bactericidal concentrations of ampicillin are achieved in the amniotic fluid within 5 minutes of a 2g infusion (29). A meta-analysis demonstrated that there appears to be a benefit of such prophylaxis, but appropriate timing of therapy and methods to determine vaginal colonization are not yet known (3). Oral ampicillin has also been studied (1000mg every 8 hours for 7 days) with positive results (163). In women who are colonized with group B streptococci at weeks 35 to 36 of the pregnancy, the CDC recommends intrapartum antibiotic use, with penicillin G as the drug of choice at a dose of 5 million units IV, then 2.5 million units every 4 hours until delivery (9).

Postpartum endomyometritis, often caused by anaerobes, can be effectively treated with ampicillin or mezlocillin, unless the causative organism is Bacteroides fragilis. Response rates of 80-90% were seen in one prospective study of these agents (217).

II. RESULTS

Respiratory Tract Infections

Pharyngitis is commonly caused by Streptococcus pyogenes and should be treated in order to prevent rheumatic fever and complications such as sinusitis and otitis media (101). Penicillin is treatment of choice since it is cost-effective, has a narrow spectrum of activity, and resistance is not currently a widespread problem (56). Adults can be treated with oral penicillin VK 250-500mg four times daily for 10 days or 500 mg twice daily. Once a day penicillin is not effective (90). Alternatively, benzathine penicillin can be utilized in patients if compliance is considered to be a problem (63). Acute otitis media, an infection of the middle ear, commonly occurs in children and can be caused by a number of organisms, including S. pneumoniae (40%), H. influenzae (30%), and M. catarrhalis (10%). Treatment is complicated by the fact that H. influenzae and M. catarrhalis produce beta-lactamase 30-90% of the time and culture of ear fluid by

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needle aspiration is not often done, therefore a culture and sensitivity report is rare. Amoxicillin is considered a drug of choice for treatment of this infection, particularly in children with their first episode of otitis media, because there is an increased likelihood of response to this agent due to activity against the likely infecting organisms and the fact that the cost of the agent is relatively low. Since amoxicillin would not be effective against beta-lactamase producing organisms, patients should be monitored for improvement in signs and symptoms of infection within 48-72 hours. If treatment failure occurs, alternative therapy with activity against beta-lactamase producing organism, such as the combination of amoxicillin-clavulanic acid or a cephalosporin should be instituted.

Sinusitis caused by S. pneumoniae and beta-lactamase producing H. influenzae. If there is suspicion of penicillin-resistant pneumococcus, the dose of amoxicillin should be increased to a maximum of 3g/day to attempt to overcome this resistance. H. influenzae has a high prevalence of resistance to the penicillins due to beta-lactamase production. Use of penicillins should be limited to penicillin/beta-lactamase inhibitor combinations.[16,17,18]
Treatment of acute exacerbation of chronic bronchitis can be accomplished with amoxicillin/clavulanic acid or a cephalosporin, as beta-lactamase producing organisms are prevalent. While more expensive, these therapies may be more cost-effective than amoxicillin (65).

Pneumonia can be divided into community-acquired pneumonia (CAP) and nosocomial pneumonia. Community-acquired pneumonia is often treated empirically to cover the most likely organisms, including Streptococcus pneumoniae, Hemophilus influenzae, and atypical pneumonia (Mycoplasma pneumoniae and Legionella pneumophila) (17). The penicillins that was included in recent guidelines for empiric oral treatment of CAP include high-dose amoxicillin (1g po q8h) or amoxicillin/clavulanate 875 mg po twice daily (256, 169). Other choices include cefuroxime or cefpodoxime, or a macrolide or doxycycline) for uncomplicated pneumonia. Some data suggests that azithromycin is more effective clinically and radiologically than intravenous penicillin G for suspected pneumococcal community-acquired pneumonia (34) perhaps due to its activity against atypical pathogens, however optimal therapy in patients with pneumococcal bacteremia is not known. In hospitalized patients, second or third generation cephalosporins or beta lactam/beta-lactamase inhibitor combinations are among the recommended agents (16, 17, 36, 169).

In patients with documented pneumococcal pneumonia that requires hospitalization, intravenous penicillin G may be used for 7-14 days (35). Nosocomial pneumonia is often due to gram-negative rods and treatment with an extended spectrum penicillin plus an aminoglycoside may be used in certain circumstances. Resistance patterns may vary between institutions, therefore treatment strategies should be individualized.

Sexually Transmitted Diseases
Neisseria gonorrhoeae, the causative organism of gonorrhea, was at one time universally susceptible to penicillin. Now, penicillinase-producing gonococci are prevalent world-wide (207). Because of difficulties in determining susceptibility and the need to have a quick and effective method of treatment available, ceftriaxone,cefixime, or an oral quinolone are now the recommended treatments.

Penicillin G is considered the drug of choice for treatment of syphilis, caused by Treponema pallidum. In patients with primary or secondary syphilis, BPG 2.4 mu IM q week for 2-3 weeks is an effective form of therapy. Oral amoxicillin 3g bid in combination with probenecid 1g, for 14 days is another alternative (161). In patients with tertiary or neurosyphilis, or in patients with HIV infection, penicillin G 2-4 mu IV q4h for 10 days should be utilized. Penicillin is most effective against T. pallidum if there are serum concentrations > 0.03 µg/mL for at least 7 days (114). If serum concentrations fall to below the MIC for 18-24 hours, spirochetal regrowth will occur (74). There is concern that BPG does not achieve adequate concentrations in the CSF to eradicate T. pallidum, therefore the CNS would not be treated appropriately (144, 239). It may be, however, that the treponemal burden is low early in the disease process in immunocompetent patients and treatment with BPG may be sufficient (114, 271). Some clinicians may wish to use more aggressive therapy, however. Patients with HIV infection and early syphilis may fail treatment with BPG and develop neurosyphilis (96) therefore these patients should be treated as if they had neurosyphilis, particularly in the later stages of HIV infection. In patients with neurosyphilis, failure of high-dose penicillin may occur (96).

Infants with congenital syphilis may be treated with either intravenous penicillin G or PPG. The data suggests, however that CSF concentrations achieved with intravenous penicillin G are significantly higher than that achieved with PPG (12), therefore intravenous penicillin G may be preferred.

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Skin and Soft Tissue Infections

Penicillins are commonly used are treatment for skin and soft tissue infections. Impetigo is commonly caused by either group A streptococci orStaphylococcus aureus and can occasionally result in acute glomerulonephritis. BPG (1.2 mu in adults), penicillin VK, or amoxicillin have been used as treatment, but treatment failure may occur if the causative organism is Staphylococcus aureus (62). Use of a penicillinase-resistant oral penicillin (e.g. dicloxacillin) is an effective alternative (27). Bullous impetigo, usually caused by Staphylococcus aureus, may be treated with an oral penicillinase-resistant penicillin. Staphylococcal scalded skin syndrome should be treated with an intravenous penicillinase-resistant penicillin.

Erysipelas,commonly caused by group A streptococci, is a type of superficial cellulitis which may be treated successfully with oral penicillin VK (250-500mg q6h) (27). If the infection is more severe, intravenous penicillin G may be used. Cellulitis is a more extensive infection, which may be due to a number of different streptococci or Staphylococcus aureus. A penicillinase-resistant penicillin should be used empirically, either orally or intravenously, depending upon the severity of infection.

More severe skin infections, including necrotizing fasciitis, can be caused by group A streptococcus (streptococcal gangrene), along with other organisms, such as anaerobes and gram-negative rods. In skin infections caused by streptococcus, aggressive therapy with penicillin G has been utilized yet is still associated with morbidity and mortality (27). It is thought that the high organism inoculum seen in these infections is indicative of an increased number of organisms that are not actively replicating, against which penicillin is less effective (224). There is experimental data to suggest that penicillin in combination with clindamycin may be more effective, since clindamycin's mechanism of action is cell cycle independent (223, 224).

Gas gangrene is a complication of a surgical or traumatic wound that can result in severe pain, skin discoloration, and edema. Clostridium perfringens and other Clostridial species are the common causative organisms. While surgical debridement is a cornerstone of therapy, antibiotic treatment is essential. The drug of choice is penicillin G intravenously 10-24 mu daily in divided doses (57). Decreased susceptibility of Clostridium perfringens has been seen in vitro however (151), and some animal model studies have demonstrated poorer results in the penicillin treated animals versus animals that received other antibiotics such as metronidazole or clindamycin (222). The clinical significance of these findings is unclear, but some clinicians are using combinations of penicillin G and another agent for treatment of this serious infection.

Naturally occurring cutaneous anthrax, caused by Bacillus anthracis spores, can occur in patients exposed to wool (128). Intravenous penicillin G (1MU q 4-6 hours) has been demonstrated to effectively result in negative cultures of previously positive blister fluid (196) and is considered the treatment of choice.

Oral penicillin VK is often used in patients after receiving an animal bite, particularly a cat bite. Antimicrobial prophylaxis is often indicated after such bites as the infection rate is high and is often caused by Pasteurella multocida (143). Penicillin VK's coverage against this organism is good and a dosage of 250-500 mg every 6 hours for 10 days is often utilized. The oral flora of a cat or dog can also include Staphylococcus aureus and anaerobes; therefore some clinicians may choose amoxicillin/clavulanic acid to cover other possible organisms adequately. Human oral flora includes Staphylococcus aureus, Eikenella corrodens, and anaerobes, therefore these bites should be treated with amoxicillin/clavulanic acid.

Other traumatic wounds may require antimicrobial prophylaxis, as well. In a study of 599 patients with traumatic wounds of the hands or feet with underlying bone, tendon, or joint lesions, a penicillin G injection was compared with 6 days of oral penicillin VK or no treatment. Patients receiving intravenous penicillin G were significantly less likely to develop infection versus no treatment and patients receiving oral therapy had more gastrointestinal complaints. A single dose of penicillin G may be a useful alternative as prophylaxis in these patients (146).

Urinary Tract Infections

Treatment of acute pyelonephritis depends upon urine gram-stain and culture results. Amoxicillin may be used for treatment of enterococcal infection, but cephalosporins are probably a better choice for coverage of Staphylococcus (e.g. Staphylococcus saprophyticus). In the past, ampicillin and amoxicillin were drugs of choice for treatment ofE. coli infection, however it is reported that 25-35% of isolates are now resistant (112). If use of a penicillin compound is desired, a combination beta-lactam/beta-lactamase inhibitor can be used (either orally or intravenously).

Lower urinary tract infection can be treated with single dose therapy and amoxicillin 3g is a regimen that has been used (173), but because of increasing resistance, other agents may be more desirable. Some experts suggest that with single

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dose or a 3-day course of therapy, the beta-lactams are inferior to other agents such as trimethoprim-sulfamethoxazole at early and late follow-up [19,20]

IV. CONCLUSION

Anthrax Resulting from Bioterrorism

Penicillin G can be used as an adjunct to therapy for the treatment of inhalational, gastrointestinal, or oropharyngeal anthrax resulting from bioterrorism, however it should not be used as a sole agent (115). Data from an outbreak in late 2001 resulting from intentional anthrax infection noted that the isolates of Bacillus anthraciswere producers of constitutive and inducible beta-lactamases and non betalactamase stable penicillins, and are not likely to be clinically effective (46). Penicillin G continues to be indicated for naturally occurring infections (10). Amoxicillin may also be used as an option for completion of therapy for cutaneous anthrax after treatment with ciprofloxacin or doxycycline and after clinical improvement is documented (115).

Amoxicillin may be used for completion of a 60-day course of anthrax post exposure prophylaxis at a dosage of 500 mg three times daily in patients who have received a fluoroquinolone or doxycycline for 14-21 days and if there are contraindications to use of those drugs, e.g. children and pregnant women [21]

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| ISSN: 2582-7219 | www.ijmrset.com | Impact Factor: 7.54| Monthly Peer Reviewed & Referred Journal |

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