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A Basic Overview of Penicillins and Their Use in Small Animal Medicine

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by Janel Ames*

There are many factors to consider when deciding upon antimicrobial therapy. Some of them are suspected etiology, host status, organ system affected, and the properties of the drug being considered. Microbicidal drugs, such as penicillin, are superior to bacteriostatic drugs in immunosuppressed patients, severe and/or overwhelming infections where rapid action is required, and for long-standing infections to eliminate the pathogen, preventing carrier states or relapses.[1]

Due to the thick cell wall of bacteria and their capability of concentrating solutes, bacteria have a high intracellular osmolality. Penicillin causes cell wall defects by inactivating bacterial transpeptidase, which prevents the maintenance of an osmolar gradient, causing formation of spheroblasts, cell lysis, and death.[1]

Many penicillins have been developed. They can be divided into; natural penicillins, semi-synthetic penicillins such as penicillinase-resistant penicillins, broad spectrum (amino-) penicillins, and antipseudomonas and extended spectrum penicillins (See table one).

Natural penicillins

Natural penicillins (e.g. penicillin G, penicillin V, and phenethicillin) were some of the original penicillins produced. They have a limited range of activity and are highly susceptible to beta-lactamases which are produced by many staphylococci and Gram-negative bacteria. They are also inactivated by gastric acid. These are efficacious only against Gram-positive bacteria.[2,3]

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Penicillinase-resistant penicillins

Penicillinase-resistant penicillins (e.g. methicillin, naficillin, cloxicillin, dicloxicillin, and oxacillin) were developed by adding substituents onto the aromatic ring of penicillin to sterically inhibit beta-lactamases.[2] Methicillin was the first semisynthetic penicillin developed but is poorly absorbed orally due to gastric acid instability, and is not very potent. All of the later developed drugs in this group are well absorbed orally except for naficllin. All of these are effective against Gram-positive beta-lactamase producing bacteria.[4]

Temocillin is a recently developed penicillinase-resistant penicillin which is active against almost all Gram-negative bacteria except *Pseudomonas*. Because of this, it is effective in treating coliform infections, especially enteritis and mastitis. It is poorly absorbed orally, but when administered parenterally it has an unusually long half-life in humans.[5]

Broad-spectrum penicillins

The broad spectrum penicillins (e.g. ampicillin, amoxicillin, and hetacillin) are a very important group of drugs due to their activity against both Gram-positive and some Gram-negative organisms. They are, however, susceptible to penicillinase. This group is stable in gastric acid, and therefore effective orally. Amoxicillin and ampicillin have equal activity, but amoxicillin is absorbed better orally and has more rapid action.[2] Hetacillin is inactive as it exists in a preparation, but is more stable in gastric acid then amoxicillin and ampicillin, and therefore it is absorbed best. After it enters the circulation, it is metabolized to ampicillin and becomes active. Amoxicillin and ampicillin are two of the most widely used penicillins because of their wide range of ac-

TABLE ONE: Properties of penicillin derivatives (taken from Greene[4]).

Generic Name	Trade Name	Route of Administration	Gastric Acid Stability	Beta-Lactamase Resistance	Antimicrobial Spectrum
NATURAL PENICILLINS					
Penicillin G	Many	PO, IM, IV	Poor to fair (20%), food decreases	No	Narrow (gram-positive organisms)
Penicillin V	Many	PO	Good (60%)	No	Narrow (gram-positive organisms)
Phenethicillin	Many	PO	Good	No	Narrow (gram-positive organisms)
BETA-LACTAMASE-RESISTANT PENICILLINS					
Methicillin	Staphcillin, Celbenin	IM, IV	Poor	Yes	Narrow (gram-positive beta-lactamase-producing organisms)
ISOXAZOLYL PENICILLINS†					
Nafcillin	Unipen, Nafcil	IM, IV	Variable (not recommended for oral use)	Yes	Narrow (gram-positive, beta-lactamase-producing organisms)
Cloxacillin	Tegopen	PO	Good	Yes	Narrow (gram-positive, beta-lactamase–producing organisms)
Dicloxacillin	Veracillin, Pathocil, Dynapen	PO	Good (50%), food decreases (30%)	Yes	Narrow (gram-positive beta-lactamase-producing organisms)
Oxacillin	Prostaphlin, Bactocil	PO, IM, IV	Good	Yes	Narrow (gram-positive, beta-lactamase-producing organisms)
AMINOPENICILLINS††					
Ampicillin	Many	PO, IM, IV	Good (40%), food decreases	No	Extended (gram-positive cocci, some gram-negative organisms)
Amoxicillin	Omnipen	PO, IM	Excellent (75%)	No	Extended (gram-positive cocci, some gram-negative organisms)
Hetacillin	Hetacin	PO	Good (40%)	No	Extended (gram-positive cocci, some gram-negative organisms)
ANTIPSEUDOMONAS PENICILLINS§					
Carbenicillin	Pyopen, Geopen	IM, IV	Poor	No	Greater against gram-negative organisms, Pseudomonas, anaerobes
Ticarcillin	Ticar	IM, IV	Poor	No	Less active than penicillin G on gram-positive organisms
EXTENDED-SPECTRUM PENICILLINS					
Mezlocillin	Mezlin	IM, IV	Poor	No	Greater against gram-negative organisms
Piperacillin	Pipracil	IM, IV	Poor	No	Greater against gram-negative organisms

PO = oral; IM = intravenous; IV = intravenous
†Also includes flucloxacillin and floxacillin.
††Also includes bacampicillin, cyclacillin, epicillin, pivampicillin, and talampicillin.
§Also includes azlocillin, indamylcarbenicillin, carindacillin, and carfecillin.

tivity and their ability to produce good plasma concentrations, although at similar dosages they are less effective than crystalline penicillin G.[15] Other derivatives in this group are bacampicillin, cyclacillin, epicillin, pivampicillin, and talampicillin.[4]

Antipseudomonas and Extended-spectrum penicillins

Antipseudomonas penicillins (e.g. carbenicillin and ticarcillin) are more active against *Pseudomonas* and some anaerobes. They are inactivated by beta-lactamases and gastric acid. Their activity is increased when aminoglycoside antibiotics are also given.[4,7]

Penicillanic acid sulfone (sulbactam), 6-halopenicillanic acids, 6-acetyl methylene penicillanic acid, and naturally occurring clavulanic acid, olivanic acids, and thienamycin are beta-lactamase inhibitors that can potentiate the penicillin antibiotics. Clavulanic acid is an ideal example of this group. It is a potent, irrreversible inhibitor of beta-lactamase of staphylococci and many Gram-negative bacteria. It closely matches its antibiotic partners, especially amoxicillin, (see figure 1) and has little antibacterial activity of its own that might interfere with the action of the intended primary antibiotic. The minimum inhibitory concentration required for amoxicillin is markedly reduced when used with cloxacillin against beta-lactamase producing isolates. Clavulanic acid's wide range of effectiveness makes it a useful potentiator of many penicillins. This combination is effective in the treatment of dog and cat staphylococcal

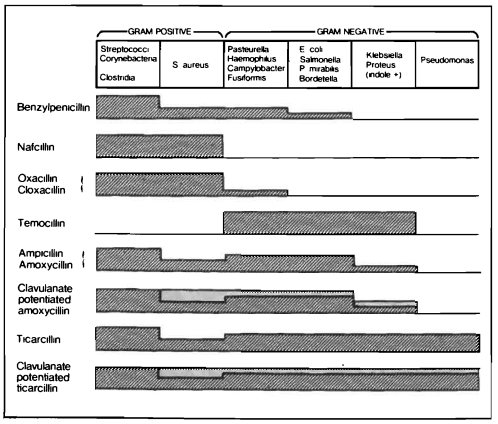

Figure 1. Effect of clavulanate potentiation on the antibacterial spectrum of amoxicillin and ticarcillin. Taken from: Wishart, David F.: Recent Advances in Antimicrobial Drugs: The Penicillins. *JAVMA* 185:1107, 1984.

skin lesions and pyodermas. The use for soft tissue, urinary, and respiratory infections in humans indicates that the use in small animals may spread in time.[5]

Sulbactam is also an excellent example of this class of drugs because it is an irreversible beta-lactamase inhibitor, yet provides no useful antibiotic activity. Its main difference when compared to clavulanic acid is the two to five-fold decrease in potency.[5]

Methicillin and cloxacillin can also provide protection for beta-lactam rings. They compete for the penicillinase allowing a second "protected" antibiotic (e.g. penicillin G or ampicillin) to exert its antibacterial effect virtually unhindered.[6] There are four main criteria that are met by these two drugs. They are as follows: 1) Their action is primarily due to beta-lactamase inhibition, 2) The "protector" drug has a much greater affinity for the penicillinase than the "protected" drug, 3) There is little or no hydrolysis of the "protector" drug by the penicillinase, 4) The "protector" drug shows no antibacterial activity at the effective protection concentration.

Staphylococcal penicillinase has a low affinity for methicillin. Therefore, it is not effective in protection of other penicillins from this penicillinase.[6]

Since most penicillins are excreted in the urine, the blocking analog probenecid can be given simultaneously to increase penicillin serum levels. This offers yet another alternative method to increase the efficacy of the penicillins.

Although many types of combination therapy may sound promising, and often are very effective, great care must be taken to ensure that the substances used together will be advantageous. For example, penicillins should never be mixed with blood, serum, or other proteinaceous fluids or with other antibiotics before they are administered. Penicillins are antagonistic *in vivo* with tetracyclines and chloramphenicol. Penicillins are somewhat unpredictable when combined in therapy with erythromycin, novobiocin, and lincomycin. No antagonism is seen with sulfonamides. There is possible synergism when penicillins are used with aminoglycosides, cephalosporins, and polymyxins.[4] Deleterious drug interactions may have their effect by altering the body's metabolism, excretion, distribution, or protein binding of one or both drugs.[4]

Clinical usage of penicillins

In the interest of providing a practical outlook on the clinical use of penicillins, several organ systems and some common problems and solutions will be discussed next. Although it is far from a complete guide, it provides a basic introduction to the use of the penicillins.

The foremost problem in treating upper respiratory diseases is the large number of commensal bacteria present. Because of this it may be very difficult to decide if there is a bacterial infection that needs to be treated. Next, one must decide which is the causative agent, or agents. Pathogenic upper respiratory infectors include staphylococci, bordetellae, and mycoplasmas. Penicillin is often a good choice for therapy here because of its penetration of the nasal mucous membranes. Ampicillin can be effectively used to prevent secondary infections in cases where the problem may be neoplasia, fungal infections, or trauma to the mucosa.[8]

In the treatment of lower respiratory tract infections, in addition to the usual factors one must use in choosing an antibiotic, such as susceptibility of the organisms, one must also consider the permeability of the alveolar membranes, and the normal tracheobronchial flora such as streptococci, staphylococci, *Pasturella multocida,* and *Klebsiella pneumonia.* Disease states are commonly caused by *Klebsiella, Achromobacter, Pseudomonas,* and *E. coli.* Larger, highly lipid-soluble antibiotics that contain a benzene ring generally penetrate bronchial secretions more easily. When also considering cost and toxicity, ampicillin and amoxicillin can be considered as a first choice therapy for most lower respiratory tract infections.[9]

Complete urinalysis from urine collected by cystocentesis is a quick and reliable way to diagnose urinary tract infection. Tentative identification of the etiologic agent can come quickly after inoculating blood agar and MacConkey agar. Primary pathogenic bacteria seen are *Proteus mirabilis, Staphylococcus* spp., alpha-hemolytic streptococci, *Pseudomonas* spp., *E coli, Klebsiella* spp., and *Enterobacter* spp. Susceptibility tests for all species of bacteria present must be done initially, and frequently after therapy has begun, due to the rapid transfer of resistance within bacterial populations. Penicillins such as ampicillin are very effective in cases where susceptibility is found (especially versus *Proteus mirabilis,* staphylococci, and streptococci). This is because of high urine concentrations of the drug due to renal excretion. Because of the short half-life of the drug and the renal excretion it is important to only allow the patient to urinate immediately prior to the next treatment. Recurrent infections can be avoided by instituting a long-term low-dose therapy.[10,16]

When dealing with canine skin infections *Staphyloccus intermedius* is the pathogen most commonly found. Because of the penicillinase production by the majority of isolates, beta-lactamase-resistant penicillins are usually the first choice for treatment if a penicillin is to be used. Drugs from other classes of antibiotics such as erythromycin and lincomycin, are often more effective. Oxacillin has been described as an excellent drug for the treatment of canine pyodermas. If penicillins are used, drainage of abcesses, removal of foreign bodies, and debridement of damaged tissues must be done to promote bacterial growth, without which these drugs are quite ineffective.[11] Anaerobic infections can be treated with ampicillin or carbenicillin.[16]

Feline abcesses normally respond well to injected procaine penicillin G and benzathine penicillin. If oral therapy is desired, ampicillin and amoxicillin are good choices.[11]

A special problem is encountered in cases of gastroenteritis, because of the high concentration of the natural microbial flora present. Overabundance of one of several species of bacteria is not necessarily indicative of its etiolgical importance. Some bacteria that are often seen as specific infectors where antibiotic therapy is indicated are *Yersinia enterocolitica, Campylobacter jejuni,* and *Salmonella* spp.[12] Since these are better treated by non-penicillin antibiotics, the issue will not be persued further here, but it should be emphasized that any systemic antimicrobial can alter the GI flora and removal of beneficial bacteria can give pathogens an easy route to infection. Any antimicrobial used, especailly for gastrointestinal disease, must be selective.

Carbenicillin and ticarcillin are used, although infrequently, in ophthalmic disease. These act with gentamycin against *Pseudomonas.* Ampicillin, amoxicillin, and hetacillin are sometimes used for intraocular infections because of their effectiveness against many different bacteria and their ability to cross the blood-ocular barrier. Generally the aminoglycosides have been found to be much more effective for treatment.[4,16]

Penicillin and ampicillin are the preferred antibiotics in neonatal patients. A primary reason is the abiltiy to sustain low doses for long periods of time with low probability of excretion and toxicity problems.[16]

Penicillin and naficillin are possible choices in complex orthopedic cases. Pyoarthritis is commonly caused by species of *Staphylococcus, Streptococcus,* and *Mycoplasma.* Due to the inflammation all antibiotics readily pass into the capsular fluid.[16] Sensitivity testing will indicate the best choice of therapy.

Antimicrobials have become drugs not only of use, but also of abuse. Many clients, and some clinicians, have taken the "give 'em a dose of penicillin and call me in the morning" attitude. Although the disease may appear to indicate penicillin therapy, other factors often make the therapy ineffective. One must be aware of many variables concerning the host, the etiologic agent, and the drug. (See figure 2).

The primary concern when considering the host is the immunological status. Most therapy is designed to enhance, not replace, the host's defense mechanisms. When the patient is severely debilitated not only will the body's reaction against the microorganism be lessened, but the reaction to the drug may also be altered. Reduced absorption, distribution, delivery, metabolism, and excretion may lead to failure of therapy to improve the patient's condition, or worse, debilitating the patient even more. Therefore this must be seriously considered. This also means that supportive therapy must be considered, such as fluid replacement and correction of electrolyte and acid-base balances. In addition this includes cleaning of the wound to relieve obstruction, removal of as much as possible of the invading disease-causing agent, and removal of debris.[4,14] This will help to restore normal function and aid in the healing process.

A factor that is neglected in a surprising number of cases is the etiologic agent. First one must establish that there definitely is a microbiological cause to the disease. Clinical signs are not enough. For example, inflammation and a febrile state alone are not justification for antimicrobial therapy. One must also consider the possibility of multiple agents

Figure 2: Factors involved in failure of antimicrobial therapy. Adapted from; Greene, *Clinical Microbiology and Infectious Diseases of the Dog and Cat,* and Roberts, Therapeutic Failures with Antimicrobial Drug Treatment.

Host — immunosupression	Microorganism — resistance
— underlying disease	— susceptibility
— poor physical condition	— virulence
— foreign bodies	
Clinician — presumptive diagnosis	
— experience, 'best guess'	
Antimicrobial therapy — poor bio-availability	
— incorrect dosage	
— drug interactions	
— short-term therapy	
Compliance — non-compliance to therapy by client	
— management variables	
Response — foreign bodies	
— abscess with poor drainage	
— accelerated elimination	
— lack of supportive care	

or underlying disease.[4,14] Although positive identification and susceptibility testing is not always required, or sometimes even possible, it cannot be emphasized enough that this is the best way to decide upon treatment. One must not substitute convenience for accuracy. It has the potential, in the long run, for saving time and money on unneeded and unhelpful therapy, and possibly saving the patient's life. Unfortunately a complete work-up is not always possible. In these cases knowledge and experience must be trusted, and close observation is necessary.

Although superficially it may seem simple to decide upon a drug for therapy, it is not. Unfortunately just finding a drug that can supress growth of the organism is not enough. Many questions must be asked. For example: What is the bio-availability of the drug? Is it compatible with other drugs being used? Should short-term or long-term therapy be administered? What dosage is appropriate? Only when these questions are answered can an appropriate drug therapy be decided upon.

As time goes by and more is learned about the drugs we use, the possibilities for therapy become seemingly endless. Unfortunately time also becomes a limiting factor, as it is impossible for any one clinician to learn about them all. Hopefully, though, one can take a few drugs, such as the more popularly used penicillins, and learn them thoroughly. One must remember, though, that it is equally, if not more important to learn when *not* to use a drug than when to use it. A basis for that knowledge can be built with time and experience.

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