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What is the right drug?

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"Make things as simple as possible, but not one bit simpler." - Albert Einstein

Einstein offers excellent advice and is applicable to just about any aspect of swine practice. Choosing the correct antimicrobial drug for therapy of bacterial infections in pigs is one of those decisions that require the veterinarian to make it as "simple as possible" for those who will be administering the therapy. The decision process of determining the "right drug" is not simple but involves multiple steps requiring critical pieces of information:

- the diagnosis
- the stage of the disease (acute, chronic)
- target pathogen(s)
- the sensitivity pattern of the target organism
- the dose and delivery method of the antimicrobial
- the pharmacokinetics of the antimicrobial
- withdrawal period (and the age/weight of the target animal)
- the size and dynamics of the population to be treated
- the expectations of outcomes and probability of success
- cost

Before any antibiotic is used in any form in pigs of any age, certain steps must be taken to assure "proper" usage. The basic tenet of any treatment or procedure in medicine (veterinary or human) is to "do no harm". In pork production, doing no harm must also include any act, which would cause the pork to be adulterated in any way. The presence in food of a residue of an animal drug above permitted levels causes the food (not only pork) to be adulterated. The ability for veterinarians and pork producers who produce and market pork to have systems to control and monitor the use of antibiotics is essential to providing appropriate and proper therapy while avoiding residues in the end product. A discussion on antibiotic use should always begin with whether antibiotic use is indeed justified in the first place. The FDA-CVM is very concerned with the food safety as well they should be and have addressed "proper" antibiotic use in more than one Compliance Quality Guides (CPG's). These CPG's have been the basis for many of the Good Production Practices (GPP's) used in the Pork Quality Assurance Plus™ (PQA+) program as it exists today. While the U.S. swine industry has been the beneficiary of several new and very effective antimicrobial tools in the past couple of decades, it has also seen the loss of some valuable tools. It is likely further restrictions will continue to be placed on antimicrobial use.

Certainly, technology has placed some great tools in the hands of practitioners as an aid in antimicrobial selection but there are still issues with applicability in the field. It is not always practical and certainly the practitioner, because of time constraints, routinely must begin treatment prior to receiving culture and sensitivity results. There have been several tools developed to aid in the decision process but still, pharmacodynamincs and pharmacokinetics remains a "black box" to many practitioners.

There are data gaps in the pharmacokinetics and pharmacodynamics in swine, with few clinical studies, requiring the practitioner to interpolate and in some cases, make educated guesses to predict outcome. For a great explanation of pharmacokinetics in swine medicine, refer to the 2005 Leman Conference proceedings in a paper by Mike Apley: "An antimicrobial targeting toolbox for the swine practitioner".[1]

Dr. Apley is clear that "susceptibility testing result does not guarantee the treatment outcome of the specific animal from which the isolate was collected. The result indicates that the animal is in a population of an animal-drug regimen pathogen relationship with a characteristic relationship between the probability of the different possible clinical outcomes. There may be failures with "S" isolates and there may be successes with "R" isolates. When these susceptibility testing criteria are applied to situations in which clinical and/or pharmacokinetic data have not been correlated to clinical outcome, then this relationship of "S," "I," and "R" to clinical outcome may or may not exist."[2]

Utilizing a decision tree approach along with constant education and training aids in the application of these

valuable (and in some cases expensive) tools and in the end, reduce pain and suffering of pigs while treating infectious disease and improving economically important production parameters.

Steps for choosing the "right drug"

Step one: Diagnosis

The first step in approaching a disease problem is to attempt to diagnose and identify an agent or agents or other factors which are responsible for the clinical signs that are present. This step should involve the herd veterinarian and under his or her direction, the proper diagnostic laboratory or other health or environmental advisors. All serious pork producers should be aligned with a veterinarian who shares his or her concerns with good production practices. The relationship between the farm and the veterinarian should be such that a *valid* veterinary/client/patient relationship (VCPR) is established. The American Veterinary Medical Association has established a definition of a valid VCPR which to this point has been accepted by the FDA-CVM. The AVMA states that a VCPR is *valid* if the following conditions are met:

> 1) The veterinarian assumes the responsibility for making medical judgements regarding the health of the animal(s) and the need for medical treatment, and the client (owner or caretaker) agrees to follow the instructions of the veterinarian,
>
> 2) the veterinarian has sufficient knowledge of the circumstances to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s), i.e., the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s) and/or by medically appropriate and timely visits to the premises where the animal(s) are kept; and,
>
> 3) the practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy.

As you can see, the VCPR places heavy emphasis on diagnosis, while allowing therapy to begin based on a presumptive diagnosis. It also clearly states that the veterinarian must be accessible in case of treatment failure or adverse reactions. A presumptive diagnosis usually implies that it is a preliminary diagnosis often made before or at the time of submission of specimens for laboratory confirmation. The veterinarian has to rely on past experience and medical judgement for the presumptive diagnosis so that an "educated guess" can be made as to the proper initial therapy. Depending on the malady being addressed, this initial therapy may or may not include antibiotics. Should the veterinarian choose antibiotics as part of the therapeutic regimen, besides choosing the particular antibiotic to use, he must also decide on dosage, route of administration and duration of the initial therapy. The veterinarian must then be available for follow up in the event of treatment failure or in the event that diagnostic tests confirm a different diagnosis than the presumptive or preliminary diagnosis. It is sometimes necessary to begin therapy based on clinical signs and then use the response to therapy (or the lack of response) as part of the diagnostic toolbox being considered. The veterinarian and producer must work together to diagnose the situation so that the intervention strategy is correct for this case and future cases. Antibiotics are not the answer for poor management or substandard ventilation so the discovery of production problems other than disease may be just as important in the step toward proper treatment.

Producers and managers may encounter disease processes such as porcine respiratory disease complex (PRDC) and the most urgent need is stop the suffering and losses as well as the reduction on production performance. This is when having a full toolbox of efficacious and convenient antibiotics are important. Often, the first reaction is to immediately seek treatment recommendations to rescue the situation. This is could be called a "shoot first and ask questions later" approach when at times the most important issue to address is the actual diagnosis.

It is impractical to think that a veterinarian will make every diagnosis and treatment decision so training technicians and lay personnel to identify and categorize disease into primary categories is essential. Since the "silver bullet" for every disease and sydrome has yet to be discovered, the caretaker must learn to recognize primary clinical signs and then categorize the diagnosis into primary groups such as respiratory and enteric. It is important to stress that there will almost always be more than one problem or disease within a population and a "one size fits all" approach is rarely on the menu.

Caretakers are forced to make thousands of decisions each day as they walk the barns and jump the pens. They are looking for those abnormal pigs and when they find the abnormality, they must then categorize it before making the ultimate decision of what to use for treatment. The most important skill for identifying sick pigs is to know what normal pigs look and act like.

Step two: Detail age and size of target animals and stage of disease process

Once the presumptive diagnosis of an "infectious agent" is made, the decision tree leads us to its next branch, which is selecting the appropriate therapeutic agent. This may be an antibiotic if the preliminary diagnostics leads us to believe that an infectious agent is present. Only the veterinarian

and the owner or caretaker should establish the need for antibiotic intervention. Choosing the incorrect treatment medicine will lead to a poor response and therefore an unnecessary expense and exposure to risks. Decide on the treatment in the context of a valid VCPR and base the decision on the veterinarians' knowledge and experience of similar situations and problems in this herd as well as other similar herds in the same region or practice area. Be ready to alter the treatment recommendation based on any diagnostic work including but not limited to culture and in vitro sensitivity testing.

Antimicrobial sensitivity information on isolates from state diagnostic labs are readily available and can be used in lieu of or ahead of lab results on a premise or flow specific isolate. When a presumptive diagnosis is reached, historic sensitivity results from either a specific system or state diagnostic labs provide data that will help choose an therapeutic agent most likely to work.

The decision to use antibiotics leads the veterinarian to yet another choice. Whether to use an FDA approved over-the-counter (OTC) or a prescription (Rx) medication that can be obtained and used only on the order of the licensed veterinarian. OTC drugs are those that the FDA has determined that adequate directions for use have been written so that the producers can easily interpret and use these products safely and effectively. OTC products can be purchased by the producer without a prescription. Veterinary prescription (Rx) products require a prescription since the FDA has determined that directions for safe and effective use cannot be easily written within the context of the label. In determining the status of a drug, the FDA considers:

- The margin of safety to the animal;
- The effects of accidental overdose;
- The difficulty in diagnosing the condition for which the drug is to be used and,
- The safety of the drug for the people who administer it.

Rx drugs carry the following label, which distinguishes them from OTC medicines:

"Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian."

Some OTC drugs have the statement: *"For veterinary use only"* on their label. This statement simply means that the drug in question is for use only in animals.

Beyond the choice of which type of drug to use (OTC or Rx), the veterinarian can also prescribe an extra-label usage of either an OTC or an Rx medicine if *and only if* a valid VCPR exists. Extra-label uses of a drug include any use of a drug in any way not written specifically on the label. A few examples of extra-label uses are:

- Changing the route, dose, frequency or duration of use of the drug
- Altering the species from that for which it is labeled
- Using the drug to treat diseases other that those specifically mentioned on the label

The choice to use medicines via the extra-label route only becomes an option when products are not specifically labeled for the condition you are treating or available products are not effective for the condition being considered. Extra-label use is ***ONLY*** allowed in conjunction with a *valid* VCPR.

The veterinarian and the producer assume added responsibility when drugs are used in an extra label manner. Make sure to observe the following when using the extra-label option:

- The veterinarian has made a presumptive diagnosis;
- The veterinarian has issued written directions;
- Identify all animals (individuals or groups) which are treated;
- Follow closely the recommended withdrawal times associated with the drug.

Not only is it important to choose the proper antibiotic or drug, but the producer and veterinarian must also decide on the delivery form and route of administration that will be appropriate in a particular situation. The three most common delivery forms in swine are 1) injectable; 2) oral via drinking water and; 3) oral via feed additive. Most antibiotics are not available in all three forms so the choice of antibiotics is sometimes altered by the delivery methods available. Available time and resources, number and size of the animals, acuteness of disease and skill of the producers are all factors that may weigh into the decision of what is the proper antibiotic.

Certain new antibiotics are labeled to be used prophylactically and thus their usage must begin before the onset of the expected disease outbreak.

Step three: Properly administer the antibiotic

Once the proper antibiotic has been chosen, the next task is to determine the proper dosage, route, frequency, and duration of therapy. Some of the delivery forms of antibiotics (i.e. feed grade antibiotics) are self-evident as far as the route of administration (oral). However, if the antibiotic is in injectable form, the label must be consulted to determine the recommended route which may be subcutaneous (SQ), intramuscular (IM), or one or more of other less common routes of administration such as intravenous (IV), intraperitoneal (IP), or intranasal (IN).

Injectables

Nearly all the injectable antibiotics for swine are to be given SQ or IM. In pigs, the neck serves as a site for both of these routes of administration. In smaller pigs which can be picked up easily, the fold of skin in the flank and "underarm" area serves as a good injection site for the SQ route. The hind leg ham area should never be used as a site for injections. If there is no recommendation for route of injection on the bottle, consult your veterinarian. Remember that any deviation from directions on the label makes the use "extra-label" and requires a valid VCPR.

The injection site determination also affects the choice of needle for injection. The Pork Quality Assurance Plus program describes in detail how to select the proper needle size based on route of injection and size of the animal being injected. A good rule of thumb is to use the smallest needle size possible to cause the least amount of stress, tissue and skin damage, and minimize the amount of leakage at the injection site. The size of the animal also affects the method of restraint and the choice of needle size.

Always clean and store syringes and other equipment appropriately between uses. Proper maintenance of syringes is also a good production practice.

Injectable antibiotics should not be mixed with other antibiotics or compounds before administering to the animals. All antibiotics are unique chemical compounds that may undergo chemical reactions when mixed with another antibiotic or compound which may inactive both drugs or even make them harmful to the health of the animal. Mixing of two distinct compounds may constitute an "off-label" use. Extra-label use even under a valid VCPR does not allow for compounding or mixing of two antibiotics that are not labeled for that purpose.

Water medications

Antibiotics administered orally via drinking water usually involve a porportioner. The porportioner or water medicator should be clean, well maintained and calibrated so that the desired dosage of medication is delivered to the animals. The dosage is determined by the amount of water that is consumed and the concentration of the antibiotic that is porportioned into the drinking water. The label directions should be followed closely and if there are questions concerning mixing, storing, or duration of treatment, the veterinarian should be consulted. The rules governing extra-label use of antibiotics also apply to water medications and thus a valid VCPR must exist.

Stock solutions should be mixed fresh daily and consumption should be monitored daily to ascertain that the animals are receiving the recommended dose of the antibiotics.

After a water medication is administered, the medicator and the water lines leading to the pigs should be flushed thoroughly with fresh water. Make sure that fresh water is re-supplied after removing the medicated water.

Feed medications

Antibiotics intended to be delivered in the feed for swine must be used strictly according to label instructions. There is no allowance for extra-label use of feed grade antibiotics for growth promotion or therapeutic uses. Veterinarians even within the confines of a valid VCPR do not have the authority to recommend or condone extra-label uses of a feed grade antibiotic. The veterinarian must be involved in the Veterinary Feed Directive (VFD) which at the time of this writing involves only one antibiotic for swine: Pulmotil® a brand of tilmicosin. The VFD is a relatively new creation specifically intended to closely monitor the use of new feed grade antibiotics that are approved as Rx drugs in any other form. A VFD must be obtained prior to obtaining this class of antibiotic and a valid VCPR must exist before a veterinarian may issue a VFD.

In another move toward a more flexible labeling system, feed grade chlortetracycline (CTC) feeding rates have been changed from a present grams of material per ton to 10milligrams per pound of body weight daily. The gram level per ton of complete feed is based on the weight of the pigs to be treated and their daily feed consumption. This revised system could conceivably provide for rations with inclusion rates for CTC that range from 100 grams per ton to has high as 2600 grams per ton.

When using feed as the delivery method for antibiotics, the producer must follow label directions. When processing the feed on the farm, the operation must follow Good Manufacturing Practices (GMP) and follow appropriate on-farm feed processing procedures. It is up to the producer to follow the proper sequencing and flushing of mixing and delivery equipment when appropriate. The producer is ultimately responsible for any violative residues and must follow label directions and observe withdrawal times when using feed grade antibiotics.

Step four: Properly identify treated animals

Animals treated with antibiotics must be identified either individually or by group. The FDA requires records on treated animals be kept for at least twelve months following marketing of the animals that were treated. The records should include the i.d. of the animal(s), the name of the product they were treated with, route of administration, dosage, withdrawal time, and the purpose for the treatment and the estimated marketing date. Keeping these records will reduce the chances or unnecessary and ineffective drug usage as well as the chances for marketing swine with violative residues.

Good records will also be invaluable in the event of violative residues be found in market hogs. If violative residues of antibiotics should occur, the producer name will be entered into the FDA's permanent database of tissue residue violators. An FDA inspector may visit the farm. Good records may assist in the investigation.

Step five: Monitor response to therapy and alter treatment plan accordingly

After the initiation of any antimicrobial therapeutic plan, it is very important to follow results in an attempt to assess success or failure. Response to any therapy is unlikely to ever be 100% successful. It is imperative to always have realistic expectations and set out with the goal of therapy which is commensurate with the situation. Gauging success is often the most difficult aspect of antimicrobial therapy. Rarely, if ever, is it possible to create "controls" within a barn or set of barns to compare the response to therapy to untreated pigs within a population. In most cases, success is assessed as the subjective opinion of the barn personnel. Success may be characterized by lower mortality, few pigs requiring retreatment or simply a cessation of clinical signs and symptoms.

Beyond choosing the "right drug"

Successful outcome to any therapeutic event demands much, much more than the choice of the drug. Even if there was a "one drug fits all" article out there, the correct application of that tool is essential for success. It is the not only the "right drug" but treating the "right" pigs with the "right" dose at the "right" time, in the "right" route and the "right" frequency. It is never as simple as it first may appear but it cannot be so complicated that it impedes its application. In the end, the key is to train, educate and place the right tools and as much information as possible in the hands of those who are treating the pigs.

References

1. Apley, M. An antimicrobial targeting toolbox for the swine practitioner. *Proceedings of the Allen D. Leman Swine Conference* 32, 76–83. 2005

2. Apley, M. Value, Strengths/Limitations of MIC Results in Clinical Practice. *Proceedings of the 2008 Iowa State Swine Disease Conference for Swine Practitioners. 111–119.*