Applied antibiotic stewardship What does that really mean?

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Abstract

Antibiotic use in livestock is under increasing scrutiny by various regulatory, industry, and consumer groups. In the future, production systems will likely be required to document antibiotic use to allow access to some supply chains. The veterinary practitioner is in a unique position to help guide antibiotic use, as well as guide the standards by which use is documented and evaluated. This discussion focuses on identifying times and places where antibiotic stewardship might be applied, the tools necessary for application, and likely challenges encountered.

Key words: antibiotic stewardship, antibiotic use

Résumé

L'utilisation des antibiotiques est de plus en plus sous la loupe des organismes de règlementation et des groupes de l'industrie et de consommateurs. À l'avenir, on exigera probablement que les systèmes de production documentent l'utilisation des antibiotiques pour avoir accès à certaines chaînes d'approvisionnement. De par son positionnement unique, le praticien vétérinaire peut aider à guider l'utilisation des antibiotiques de même qu'à établir les normes pour la documentation et l'évaluation de l'utilisation. Cette discussion vise à établir quand et où appliquer la gouvernance des antibiotiques, les outils nécessaires à l'application et les défis susceptibles d'être rencontrés.

Overview

Much of the material driving this discussion stems from participation in a project funded by an FDA cooperative grant which focused on exploring potential methods of measuring antibiotic use in feedlots and dairies in the United States. As measurement methods were discussed, the larger issue of infectious disease management surfaced. It is from countless hours of debate about which uses or measures might matter that this material about antibiotic stewardship has been gathered. This information is far from complete, and undoubtedly will be revised continuously as we learn more about how to properly care for our drug tools to maintain their utility for treating infectious disease. Practitioners have a huge role to play in identifying the questions that need to be answered to move forward with applicable and ethical antibiotic stewardship. While there have been many broad, overarching statements about stewardship, this discussion focuses on what possibilities might exist at the practitioner level, and what questions might need to be answered for antibiotic stewardship to be applied at the farm level.

Antibiotic Stewardship – What is the Definition?

The American Association of Bovine Practitioners (AABP) has a guideline document entitled Key Elements for Implementing Antibiotic Stewardship Plans in Bovine Veterinary Practices Working with Beef and Dairy Operations.[1] This document defines antibiotic stewardship as "the commitment to reducing the need for antibiotic drugs by preventing infectious disease in cattle, and when antibiotic drugs are needed, a commitment that antibiotics are used appropriately to optimize health and minimize selection for antibiotic resistance." This has been a consistent theme for the AABP, having also stated in a 2013 guideline entitled Prudent Antibiotic Use Guidelines for Cattle, "The veterinarian's primary responsibility is to help design management, immunization, housing and nutritional programs that will aid in reducing the incidence of disease and, thereby, the need for antibiotics."[2]

The American Veterinary Medical Association (AVMA) also recently defined antibiotic stewardship and core principles.[3] "Antibiotic stewardship refers to the actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antibiotic drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health." Core principles as defined by the AVMA are… "Antibiotic stewardship involves maintaining animal health and welfare by implementing a variety of preventive and management strategies to prevent common diseases; using an evidence-based approach in making decisions to use antibiotic drugs; and then using antibiotics judiciously, sparingly, and with continual evaluation of the outcomes of therapy, respecting the client's available resources." More details on the principles are provided on the AVMA website.

While all of these definitions of antibiotic stewardship are useful for defining the overall construct of efforts, they lack in guiding how a veterinarian actually defines where the key areas of focus should be for an individual client. As a profession and a society, we are new to recognizing antibiotics as a fragile resource. Our tools for making decisions about

antibiotic use are rudimentary at best. However, due to the recent consumer interest in antibiotic use, some "tools" to guide stewardship are being presented to us for immediate application.

Multiple beef marketing entities have their own definitions of antibiotic stewardship. For example, McDonald's recently published their new beef antibiotic policy.[8] This policy establishes a time line of less than 4 years for creating "reduction targets" and reporting progress in reaching these targets. Additionally, they outline guidelines for treatment indicating that use should be "informed by susceptibility testing", and advocate use of a "tiered approach" for drug choice. Targeted reductions, tiered approaches to drug selection, and a focus on the inclusion of susceptibility are common recommendations in many policies aimed at promoting antibiotic stewardship. Unlike the broad statements made by veterinary associations, these policy guidelines propose more specific actions, regardless of whether or not these actions are truly applicable to all situations.

Monitoring Antibiotic Use - Does it Indicate Stewardship?

One potential approach to sustaining animal welfare, animal production, and preservation of antibiotic efficacy is to enable investigation of the factors that distinguish the lowest antibiotic use producers from the highest use producers. Through a grant sponsored by the FDA, our research group has explored what antibiotic use monitoring might look like for feedlots and dairies within the United States. Reasons for variation in antibiotic use measured by almost any metric may be very complex because of multiple factors which contribute to differences between farms. In addition to these external measurement differences, the method of measurement also resulted in relative differences in use.

Once it is recognized that the first components of antibiotic stewardship are to accurately characterize disease challenges and to then aggressively pursue non-antibiotic alternatives, the goal of an effective antibiotic use monitoring program becomes clear. The main purpose of the system should NOT be to generate data for punitive actions, or for the enactment of arbitrary antibiotic use reduction targets. Antibiotic monitoring systems are useful only for driving further questions about why use might differ. In some cases, confounders such as animal movement, or industry economic changes caused a difference in use. Other times it is possible to identify an opportunity or tool that allows a farm to use less – this is the ultimate goal of monitoring. The explorations of the reasons behind changes in use, or differences in baseline use are the first step in moving closer to an optimum system balance. Use monitoring should help to define normal in a non-isolated context.

The Challenge of Measuring Use

The continuous association of antibiotic use measures with disease has remained a top priority in this project. The main objective being to facilitate the development of measures that can be used to drive true antibiotic stewardship, which requires disease management at both the prevention and treatment levels. Therefore, decisions about which data to record and analyze are driven by an attempt to accurately and transparently describe use in a way that acknowledges the disease, drug, dose, number of administrations, and the interval between administrations. Each method of measurement has unique characteristics and varied relationships to disease pressure.

Numerous metrics or measures of antibiotic use have been extensively reviewed, but still lack standardization.[4,5,6,7,9] Due to this lack of standardization, various methods of measurement were explored. These measures were then compared to evaluate each measure's utility to farm management, consistency with other measures, and relationship to factors that may affect antibiotic selection pressure. It should be noted that all measures are constructed from the addition of various different diseases or drugs. These measures are comparable to adding up the weight of apples and oranges: it is an amount summation of different items. The end result is the total "amount of fruit". Any implications of quality or type require more granular data and further "boots on the ground" exploration. Thus, it is re-emphasized that benchmarking using these measures is only appropriate as a tool directing further questions about use.

Numerator Measures considered for benchmarking include:

Disease Incidence – Recorded disease events associated with any treatment, single or multiple. A disease event is defined as a "new event" when treatment occurs more than 7 days after any treatment for the same disease in the same animal. This measure is included as a potential tool to help differentiate or evaluate disease prevention or disease pressure differences between farms. As a benchmark, the Disease Incidence is presented as the total count of detected disease events occurring during the year divided by the average number of animals present on the farm in that year. This provides a benchmarking incidence estimate based on an animal-year denominator. It is recognized that case definition as well as other confounders may have drastic influence on this measure. It should also be noted that non-antibiotic treatments were included in this category, as it is not a useful measure without them.

Regimens – A regimen description includes the drug, dose, number of administrations, and time interval between administrations. It is counted as 1 when it is aimed at a single disease event. For the same drug there might be significant

variability in the details of each regimen, both within farm as well as between farms. For other drugs, the regimens are nearly identical within and between farms. Due to this variability, definitions of regimens for each drug are simultaneously reported by their central tendency and associated variation. When there is no combination therapy (treating an animal with multiple drugs for the same disease event), the number of regimens very closely approximates the disease incidence if non-antibiotic regimens are included.

Days of Therapy (DOT) – Days of therapy has been recommended for use by the Infectious Disease Society of America (IDSA).[4] It is a pragmatically defined number of days for which treatment was delivered for a disease event. For short-acting, single-administration drugs it can be defined as the number of calendar days treatment is administered regardless of frequency of administration, or total number of doses.

However, there are significant challenges associated with using DOT for single-injection, long-acting formulations. Note that even when pharmacokinetics and pharmacodynamics (PK/PD) is used to try to define this measure for long-acting drugs, it is still not a measure of the duration of exposure to the drug, as there is currently a lack of evidence for the majority of single-injection drugs which precisely determines the end point for when the drug stops exerting any effect on any microbial species. If more than 1 day is assigned, determining the end point of activity is dependent on, and complicated by, the specific bacterial MIC's, i.e., a single drug could have numerous DOT specific to each type of bacteria. Both therapeutic and resistance-selection characteristics of an antibiotic are dependent on the PK/PD of the antibiotic and the characteristics of the pathogen and microbiota populations to which they are exposed. Simply setting the DOT to 1 day would misrepresent the therapeutically effective duration that is achieved with many formulations. This problem is technically true for all drugs, but with short-acting drugs the re-dosing interval creates a standard that can be more readily agreed upon, and lingering drug effects last for hours rather than days. In systems (such as feedlots) where there is frequent use of long-acting formulations, the DOT would have little value as the data is lacking to determine a generalized time endpoint for multiple organisms. Further research is necessary to compare in vivo resistance selection pressure exerted by differences in the number of DOTs when compared across multiple different drugs.

Animals Exposed – This measure is still under development and multiple definitions have been discussed. It refers to the number of animal bacterial populations (microbiomes) exposed to a drug and is calculated as the number of animals receiving an antibiotic at any point during the reference period (1 yr). One option is to calculate it as the percent of animals exposed to any antibiotic 1 or more times during the reference period. This same measure can also be stratified by drug, i.e., if an animal receives different drugs they would each count as a new exposure if the drug differs from previous treatments. For benchmarking purposes it is expressed as a percentage of animals "exposed". This number is likely not useful from a disease management perspective, but may have potential use in the research setting where the goal is to measure the relationship between use and resistance selection pressure.

Defined Daily Doses (DDD) - Although commonly used throughout the world for quantifying antibiotic use, calculation of DDD requires assumptions about regimens (dose, duration, frequency, and animal weight at the time of treatment). Data may or may not be available to accurately estimate these values. The number of DDDs is calculated by taking the total grams of drug divided by an agreed upon standard dose multiplied by the estimated animal weight at the time of treatment:

$$\frac{\text{Total grams of drug}}{\text{Standard dose x animal weight}}$$

In some systems, such as adult dairy cows, it is a relatively reasonable estimate because the necessary assumptions are often correct and relatively easy to estimate. For example, much of the use in dairy is driven by intramammary formulations that are not dosed mg/kg and/or animal weight at the time of treatment can be reasonably estimated. When this same measurement is applied to growing dairy replacement heifers or beef cattle, these assumptions can vary wildly from reality. The IDSA recommends DOT rather than DDD for human monitoring applications, as similar assumptions complicate this measure in human medicine.[4] Regardless of the complications associated with its calculation and implications for exposure, DDD is a very common measure of antibiotic use in all species. Reported denominators vary, but a very common measure is DDDs/animal year.

Measures used for livestock use in other countries

The European Medicines Agency (EMA) releases annual reports on sales data of antibiotics labeled for use in food animals. This document details the EMA's antibiotic sales data reported as a DDD per population correction unit (PCU). The EMA provides a list of the standard doses used for this calculation. A population correction unit is used as a denominator to account for the weight of all animals produced in that year. This creates a final metric reported as DDDs/kg. This metric is designed to compare use across species and countries, creating a numeric value which is of questionable utility.

The breadth and depth of antibiotic use monitoring in animals varies widely throughout the world. The World Organization for Animal Health (OIE) has guidelines, standards, and a phased attempt at collection of antibiotic use in animals. For some counties, their OIE involvement may be only the general guidelines from OIE.[10] Other nations have more intense monitoring and have instituted restrictions on antimicrobial use in food animal production. A few examples include Denmark's DANMAP, Netherlands' MARAN, and Sweden's SVARM.[4] These monitoring programs have very

well defined targets for use reduction, as well as intensive surveillance programs for resistance monitoring.

The Challenge of Susceptibility Testing

The recent McDonald's policy states multiple times that antimicrobial use should be "guided by susceptibility". Antibiotic Susceptibility Testing (AST) standards have been created by the Clinical and Laboratory Standards Institute (CLSI).[10] This has allowed standards for testing that are reproducible and provide a basis on which comparisons can be made. This is useful information, but its application in the clinical setting can be quite complex.

Mean inhibitory concentrations (MIC) are set at standard "inoculum" amounts. In other words, they are determined with a known and standard number of bacteria present. Classifications of resistant vs susceptible are also made with these standard inoculums. In the clinical setting the inoculum is unknown, and likely contains multiple bacterial species.

In addition to the complex interactions and differences among bacterial populations, measurements of drug concentrations are challenging to interpret as well. Plasma concentration is the primary means of drug measurement because it is constantly accessible and repeatable. However, it does not necessarily equate with the concentration of drug presented to the bacterial population at the site of infection. Therefore, classifications of R or S are useful in comparing the pathogen to the rest of its population, but the relationship between the pathogen MIC concentration tested and the in vivo drug concentration at the site of infection might vary. A resistant bug is not as easily killed by the drug as isolates that fall in the category of susceptible, but beyond this it is difficult to predict a regimen's likelihood of treatment success.

Regimen Selection – Choices that affect Stewardship

Even in the face of renewed efforts to prevent disease, bacteria adapt or overcome our prevention efforts and some level of disease exists. At this point stewardship involves the selection of a treatment regimen. This regimen consists of a drug, route, dose, frequency, and duration. Ideally this regimen is selected in a manner that achieves that best balance between maximal treatment success and minimal resistance selection pressure.

Our tools for drug choice involve using pharmacokinetic knowledge and susceptibility results in combination with clinical outcomes to optimize therapy. Pharmacokinetic knowledge indicates which tissue the drug might end up in, and susceptibility data indicates whether or not the organism has some capacity to resist drug action above and beyond the innate capacity of that particular bacterial species. As mentioned previously, the process of applying susceptibility data to regimen design is rarely straightforward, and suitable techniques for truly predicting treatment outcomes are rarely encountered.

Route generally varies with drug choice, and must remain consistent with drug labeling in order for withdrawal times to be known. In general, there is rarely a reason to vary the route of administration, except perhaps in cases of acute septicemia, a relatively rare scenario in beef cattle practice. However, what might deserve some consideration is the magnitude of resistance selection pressure exerted by various routes of drug administration. Although this varies by drug, to some extent route determines the bacterial population that receives the bulk of drug exposure. For example, the gastrointestinal flora would receive a higher exposure with an orally administered drug than with a parenterally administered drug excreted predominantly by the kidneys. If the clinical outcome of treatment with these 2 drugs is identical, does good stewardship mean that we choose the drug likely to exert less selection pressure? To be clear, we do not yet have comparative evidence of selection pressures by route of administration, but perhaps it is something that should be explored as we look for regimens that demonstrate antibiotic stewardship.

For the majority of drugs used for respiratory disease, single dose subcutaneous regimens are the most common. However, for diseases such as liver abscesses, control of anaplasmosis, or other disease categories, regimens vary in duration. What evidence do we have for our current choices about duration of therapy? There is great room for improvement in this area of clinical decision making. Where to draw the line between long enough and too long is a challenging complex task that often differs if viewed from a population level rather than an individual level.

Action items to move towards stewardship (Year 1)

1. Define "normal use" in a context larger than just 1 farm, or better yet larger than 1 veterinary practice group. This means to quantify use by a measure that is useful to you as a practitioner. A good starting point might be to collect usage data from 3 producers over the next year, and try to use existing record systems whenever possible. Identify challenges encountered, time necessary, and potential impact on revenue (yours and theirs).
2. Seek to identify a specific disease that is driving use on each of the farms, and make 1 change in the next 12 months to try to decrease use associated with that disease. This might be a change in prevention strategy or case definition. Can any regimen parameters be changed to improve or maintain treatment outcomes while decreasing resistance selection pressure? Could fewer drug classes be used on a farm? What other potential opportunities for change can you identify? Please make your local research groups aware of your questions and potential opportunities.
3. Have at least 3 conversations discussing antibiotic stewardship: 1 with a producer new to the concept,

1 with a person unfamiliar with animal agriculture, and 1 with a trusted colleague who is also struggling with how best to apply stewardship principles.

Conclusion

A solid working definition of stewardship requires using available scientific knowledge, health data, resistance data, and practice experience to find the best balance of population welfare, individual welfare, resistance selection pressure, and system economic survivability. This is no small task! However, by many standards it is not a deviation from the act of "practicing medicine".

The new twist is that entities both from outside our profession and outside our industry have strong opinions about where to draw the line between acceptable and unacceptable disease rates, treatment rates, prevention plans. While it can seem puzzling, irritating, and/or daunting for our actions to be so heavily scrutinized, with this scrutiny comes a tremendous opportunity to improve our quality of practice, animal welfare, treatment success rates, and become more accountable and transparent than we have ever been in the past. It seems hopeful that our profession will become leaders in the practice of antibiotic stewardship across many species.

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