Rational Use of Antibiotics in Veterinary Practice

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Veterinary antimicrobials are the same as, or closely related to, antimicrobials used in human medicine. In the past this had led to the suggestion that emerging resistance to antimicrobials in human pathogens was associated with the overuse and misuse of antimicrobials in veterinary medicine. The decision whether the antimicrobial therapy is required should be based on the specific basis. This decision can be based on certain questions that the clinician can ask himself.

1. Is the antimicrobial therapy indicated on the basis of the clinical findings or it is prudent to wait?
2. Have the appropriate samples for the microbiological procedures been collected?
3. What is likely pathogen?
4. Is the prior evidence (clinical trails) that the antimicrobial therapy will confer clinical benefit?

Based on these, empirical therapy is initiated then it reassessed on the basis of the microbiological findings. If the specific pathogen is identified, can a narrow spectrum agent be substituted for the drug initially used? Similarly, it is assessed if a combination is better option. The adjunct measures as drainage of abscess, removal of foreign body, reducing the dose of the immune suppressant drug etc. are important for the success of antimicrobial therapy.

Empirical Therapy : The antimicrobial agents are used before the pathogen is identified or susceptibility tested are performed. This use of antimicrobial agents is empirical (presumptive) therapy. This is usually based on the experience of the clinician and is given with the presumption that the early intervention will improve the clinical outcome. The initiation of the empirical therapy should follow a specific and scientific approach. Clinical diagnosis of the microbial infection may be based on anatomical

evidence of the infection like pneumonia, cellulitis, sinusitis etc. Simple procedure like gram staining and cytology can provide important information. Based on this, necessity for the initiation of empirical therapy is assessed. It is indicated where there is significant risk of serious morbidity if the therapy is withheld. The selection of the drug for empirical therapy is based upon clinical diagnosis and spot microbiological procedures. If no information is available, then a broad spectrum agent is given which has spectrum against the likely pathogen. Among other factors which determine the selection of the drug include the disease state, pharmacokinetics of the agents, interaction with other agents, toxicity etc.

Culture and Susceptibility Test (CST) : Culture and susceptibility test not only identifies the infecting pathogen but also provides specific data regarding the drug efficacy. The distinction between a gram positive and negative or anaerobic and aerobic microorganism can determine the choice of the agent. Although, the empirical therapy starts after the collection of the sample for the culture and susceptibility test still the information obtained is useful in conditions like drug resistance, for selection of less toxic or cheaper agent. On an average the initial antimicrobial therapy is substituted in one third of the cases.

The susceptibility tests are performed by two methods (1) disk diffusion method (2) tube dilution method. Each method has its limitations but still provides useful information. In disk diffusion, the size of zone of inhibition is directly related to the MIC of the antimicrobial agent against particular microbe, thus this method so semi quantitative. The drawback is that not microbes grow rapidly and this is suitable only for rapidly growing aerobic organisms. The tube dilution method, has serial dilutions of the antimicrobial agent, determines the MIC and MBC against a particular organism. Determination of MBC is of great importance inimmunocompromized patients. The interpretation of culture and susceptibility test is very crucial. The pathogen is considered as susceptible or resistant to a particular antimicrobial agent by comparing the MIC value with the break point MIC. Break point MIC is the plasma concentrations that can be achieved by administering clinical acceptable doses and route of administration. More is the difference between these two determinants more efficient will be antimicrobial agents. Apart from the susceptibility data, the characteristics of the antimicrobial agent and host factors can also determine the choice of the antimicrobial agent.

Bactericidal versus Bacteristatic: Antimicrobial agent can classified bactericidal or bacteristatic. The agents which are static have a much large difference between the concentrations which is inhibitory (MIC) and which are cidal (MBC). This is in contrast to the cidal which have less difference in these values. In general, the antimicrobial agents acting on the cell wall are cidal, whereas those acting on the protein synthesis are static. However there are antimicrobial agents classified as static can have cidal effect against some microbes e.g. Chloramphenicol is cidal to *H. Influenzae,* similarly vancomycin has static effect on *Enterrococci* sp.

Bactericidal and bacteristatic antimicrobial agents are of equal importance for the treatment of infections in the immunocompetent patients. However, in the immunocompromize and neutropenic patients, bactericidal antimicrobial agents selected over static agents. Apart from this, certain conditions like endocarditis, meningitis, neutropenic cancer patients are treated only with cidal agents.

Bactericidal Agents	Bacteristatic Agents
Aminoglycosides	Chloramphenicol
Bacitracin	Clinamycin
Beta-lactams	marcolides
Metronidazole	Sufonamides
Isoniazid	Tetracycline
Polymixin	Trimethoprim
Quinolones	
Rifamicin	
Vancomycin	

Bactericidal agents can be divided into two categories

(1) exhibit concentration dependent effect e.g. aminoglycosides, quinolones

(2) exhibit contact time dependent effect e.g. penicillins, vancomycin In concentration dependent effect, the cidal affect i.e. both extent and rate increases with the increasing concentrations. Thus maximizing the concentrations will improve the efficacy of the antimicrobial agent and decreases the selection of the resistance bacteria. Clinically this is used in the aminoglycoside therapy. Aminoglycosides are now used as a single high dose rather than repeated divided doses. Drugs producing contact time dependent

cidal effect, their efficacy does not increases by increasing concentrations and cidal effect is present till MBC is maintained. Thus these antimicrobial agents are given frequently in divided doses. These drugs also lack post antibiotic effect.

Post Antibiotic Effect The persistent suppression of microbial growth after limited exposure to the antimicrobial agent is known as post antibiotic effect (PAE).

PAE = T- C where

T- Time for tenfold increase in number of treated microbes

C- Time for tenfold increase in number of control microbes

Antibacterial agents with Post Antibiotic Effect	
For Gram-positive cocci	For Gram-negative bacilli
Aminoglycosides Carbapenems Cephalosporins Chloramphenical Clindamycin Macrolides Penicillins Quinolones Sulfonamides Tetracyclines Trimethoprim Vancomycin	Aminoglycosides Carbapenems Chloramphenical Quinolones Tetracyclines Rifamycin

The exact mechanism of the post antibiotic effect is not clear but the proposed mechanism include

(1) recovery after non lethal damage to cell membrane

(2) persistence of the antimicrobial agent in the periplasmic spaces

(3) the need for enzyme synthesis for growth

Many antimicrobial agents show post antibiotic effect against gram-positive cocci but only a few show post antibiotic effect against gram-negative bacilli. It is perceived that the *in vivo* post antibiotic effect is for much larger duration because of post antibiotic

leucocyte enhancement (PALE). PALE reflects the increased susceptibility of the microbes to phagocytosis by neutrophils. The increased phagocytosis could be due to sub inhibitory concentrations induced morphological changes, decreased growth and adhesion and toxin production. Clinical relevance of the post antibiotic effect is beginning to be appreciated. Aminoglycosides and quinolones have concentration dependent, thus high dose of aminoglycosides once daily administration results in enhanced efficacy and extended post antibiotic effect. Secondly, the adaptive resistance phenomenon is taken care off. Adaptive resistance is decreased cidal effect seen on second administration. Adaptive resistance in aminoglycosides is due decreased energy dependent uptake by microbes. This also reduces the chances of toxicity and cost of treatment.

Antimicrobial Agent Combinations : Most infections should be treated with single antimicrobial agent but there are conditions where the combination therapy is required.

1. To provide broad spectrum empirical therapy. This is usually with antistaphylococcal agent and agent that have activity against gram negative bacteria.
2. To treat poly microbial infections as in abdominal abscess. This involves both anaerobic and aerobic bacteria. Aminoglycosides or third generation cephalosporin along with metronidazole can be used.
3. To reduce the emergence of resistance as in treatment of tuberculosis.
4. To decrease the dose and related toxicity
5. To obtained enhanced microbe killing

When two antimicrobial agents are administered together, it could lead to additive, synergistic, or antagonistic effect. The interaction between two is best explained by FIC index. FIC index value of $\leq$0.5, 1 or $\geq$2 indicate synergistic, additive and antagonistic effect.

Synergism : The best established is combination is that of aminoglycosides and βlactams against Enterococcal induced endocarditis. Similarly, monotherapy of this disease with vancomycin and penicllins results in the static effect however when used in

combination they produce cidal effect. Combination of sulfonamide with cotrimazole have synergistic effect, Similarly, βlactamase inhibitors (clavulanic acid) and βlactamase susceptible βlactams show synergistic effect Three mechanisms of antimicrobial synergism are

1. blockade of sequential steps in microbial metabolism
2. inhibition of enzymatic hydrolysis
3. enhancement of antimicrobial agent uptake

Antagonism

Inhibtion of Bactericidal activity by Bacteristatic agents Bactericidal agents such as tetracycline and chloramphenicol can antagonize the cidal effect of β-βlactams. The bactericidal effect requires the microbes to grow at log phase. Thus the antagonism is thought to be due to inhibition of bacterial growth by static agents. Chloramphenicol and tetracycline antagonize the effect of the aminoglycosides by inhibiting the energy dependent uptake.

Induction of Enzymatic Inactivation Enterobacter sp. possesses inducible β-lactamase. β-lactams like ampicillin , cefoxitin and imipenem are potent inducers. If these agents are combined with intrinsically active but β-lactamase sensitive agent like Pipericillin, will result in antagonism.

Pharmacokinetic Considerations

Route of Administration Oral and im routes of administration are unreliable in critical patients so iv route is preferred. Impaired absorption of antimicrobial agents can occur in pathology of the GIT. Some agents are not absorbed from GIT so are given by parenteral routes eg vancomycin, penicillinG, antipsuedomonal penicillins. Other compounds viz chloramphenicol, cotrimazole, quinolones, metronidazole, clinamycin have similar pharmacokinetic properties after oral or parenteral administration.

Altered Pharmacokinetics Impiared renal and hepatic function warrants dosage adjustments of these compounds elminated by these organs

Dosage adjusted in Renal impairment	Contraindicated in Renal impairment	Dosage adjusted in hepatic impairment
Aminoglycosides Azetreozam Cephalosporins Clarithromycin Penicillins Quinolones Vancomycin Cotrimazole	Methenamine Nalidixic acid Sulfonamides tetracyclines	Methenamine Nalidixic acid Sulfonamides tetracyclines

Tissue and Body Fluid Distribution Antimicrobial agents have different extent of distribution in different tissues and body fluids

Tissue Distribution Pattern of Antibacterials			
Drugs Distributed to Extracellular Fluid	Drugs Distributed to Total Body Water	Drugs concentrated in urine	Drugs concentrated in bile
Beta lactams Aminoglycosides	Chloramphenical Clindamycin Doxycycline/ minocycline Erythromycin Fluorinated quinolones Potentiated sulfonamides	β-lactams Aminoglycosides Fluorinated quinolones Potentiated sulfonamides Vancomycin	Clindamycin Doxycycline/ minocycline Macrolides (erythromycin) Rifamycin Cefaperazone

Drugs that accumulate in WBCs
• Clindamycin • Erythromycin (Macrolides) • Fluorinated quinolones • Rifamycin

Drug Penetration of Blood-Brain Barrier		
Readily Enter CSF	Enter CSF (in presence of inflammation)	Do not Enter the CSF
Chloramphenical Doxycycline/ minocycline(free) Fluorinated quinolones (?) Metronidazole Rifamycin Potentiated sulfonamides	Penicillins Fluorinated quinolones Cephalosporins- cefatoxime ceftriazone ceftazidime vancomycin	Aminoglycosides Carbenicillin Cephalothin Cefazolin Cefatetan Clindamycin Erythromucin Tetracycline

Host Factors : Effect of the local microenvironment can detrimental to the antimicrobial agents activity. The host factors which reduce the concentration of drug at site of the infection can effect the effectiveness of the antimicrobial agent. Changes in the health of the host can alter the drug disposition. The volume of the fluid compartments which vary with age can also be reduced in dehydration. The altered microenvironment may profoundly alter the drug effect. Purulent exudates are hyperosmolar, acidic and hypoxic thus can impair the antimicrobial agent efficacy. Drugs such as aminoglycosides tend to bind with debris or degradation products. Acidic pH is detrimental to antimicrobial action of these agents also the host defenses are also adversely affected.

Monitoring the Therapeutic response : It can be monitered clinically and micribiologically. Sterile culture sample indicate eradication of infection. Clinically patient's systemic manifestations of infections- malaise, fever, leucocytosis should abate. The speed of responsse is generally directly related to the duration symptoms prior to the start of therapy. The duration of therapy is usually depends upon pathogen, site of infection and host factors. The clinical failures of the antimicrobial therapy could be related to error in CST, inadequate dose, erratic absorption of drug. Other factors like inadequate immune response, malnutrition and malignancy can also affect drug response. The presence of abscess or foreign should also be considered. Superinfection and development of resistance could be other factors.

Effect of the Microenvironment on the Antibacterial Efficacy	
Environmental Factor	**Effect**
Acidic pH	Penicillins iinactivated at pH < 6.0 Aminolycosides and fluoroquinolones more effect in alkaline pH
Hypertonicity/ hypersommolarity	Impaired efficacy of β-lactams
Pus	Acidic pH Hypertonic Hyperosmolar Protien binding of selected drugs Binding to the sediments (aminoglycosides
Low Oxygen tension	Aminoglycosides inactive Growth of organism slowed– decreased efficacy of drug Impaired phagocytic activity
Large inoculums	Greater concentration of inactivating enzymes Greater concentration of drug required

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APPENDIX: DOSE RATES/WITHDRAWAL TIMES OF ANTIMICROBIALS

Penicillin	Dosage, Route, and Frequency
Sodium penicillin G	10,000-20,000 IU/kg, IV or IM, QID
Potassium penicillin G	25,000 IU/kg, PO, QID
Procaine penicillin G	10,000-30,000 IU/kg, IM or SC, SID-BID
Benzathine penicillin G	10,000-40,000 IU/kg, IM (horses) or SC (cattle), every 48-72 hr
Penicillin V	15,000 IU/kg or 8-10 mg/kg, PO, TID
Cloxacillin	10 mg/kg, IM or PO, QID
Ampicillin	5-10 mg/kg, IV, IM, or SC, BID-TID 10-25 mg/kg, PO, BID-QID
Amoxicillin	4-7 mg/kg, IM, SID-BID 11 mg/kg, PO, BID (dogs) or SID-BID (cats)
Sodium carbenicillin	10-20 mg/kg, IV or IM, BID- TID
Potassium clavulanate:amoxicillin (1:4)	10-20 mg/kg (amoxicillin) and 2.5-5 mg/kg (clavulanate), PO, BID
Probenecid (prolongs blood levels of penicillins that have short plasma half-lives or that are costly)	1-2 mg/1,000 IU penicillin G (dogs), PO, QID
Amoxicillin-clavulanic acid	10-20 mg/kg, PO, BID- TID
Imepenem	1-7 mg/kg, IV or IM, TID- QID
Ticarcillin	15-110 mg/kg, IM or IV, every 4-8 hr

Penicillin	Species	Withdrawal Time (days)	Milk Discard Time (days)
Procaine penicillin G	Cattle	10 (at label dosage)	3
	Sheep	9	
	Pigs	7	
Benzathine penicillin G	Cattle	30	
Ampicillin	Cattle	6	
Amoxicillin	Cattle	30	2

Cephalosporin	Dosage, Route, and Frequency
Cephalothin	20-35 mg/kg, IM or IV, TID- QID
Cephapirin	30 mg/kg, IM or IV, every 4-6 hr
Cefazolin	20-25 mg/kg, IM or IV, TID- QID
Cephalexin	10-30 mg/kg, PO, TID- QID
Cefadroxil	22 mg/kg, PO, BID
Ceftiofur	1.1 mg/kg, IM, SID

Cephalosporin	Withdrawal Time	Milk Discard Time
Ceftiofur	0 days	
Sodium cephapirin (intramammary)	4 days before slaughter	4 days
Benzathine cephapirin (dry-cow treatment)	42 days after latest infusion	3 days after calving—milk not used for food

Aminoglycoside	Dosage, Route, and Frequency
Gentamicin	3-6 mg/kg, IM or SC, SID- BID
Kanamycin	12-15 mg/kg, IM or SC, SID-BID
Streptomycin/dihydrostreptomycin	7.5-12.5 mg/kg, IM or SC, BID
Amikacin	5-7.5 mg/kg, IM or SC, BID
Netilmicin	3-6 mg/kg, IM or SC, SID- BID
Neomycin	15 mg/kg, PO, SID- BID
	0.5-1 g/quarter, intramammary, SID

Route	Approximate Withdrawal Time (days)
Oral	20-30 (3 for neonatal pigs)
Parenteral	100-200 (40 for neonatal pigs [often not approved for food animals])
Udder infusion	2-3* (often not approved for food animals)

Quinolone	Species	Dosage, Route, and Frequency
Nalidixic acid	Cats, dogs	3 mg/kg, PO, QID
Norfloxacin	Dogs	10-20 mg/kg, PO, BID
Enrofloxacin	Cats	5 mg/kg, PO, SID or divided BID
	Dogs	5-20 mg/kg, PO, SID or divided BID
		2.5 mg/kg, SC, once then PO
	Beef cattle (not veal or dairy)	7.5-12.5 mg/kg, SC, once
		2.5-5 mg/kg, SC, SID
	Pigs	2.5-5 mg/kg, PO or IM, SID
	Preruminant calves	2.5-5 mg/kg, PO or SC, SID
Marbofloxacin	Cats, Dogs	2.75-5.5 mg/kg, PO, SID
Difloxacin	Dogs	5-10 mg/kg, PO, SID
Orbifloxacin	Cats, dogs	2.5-7.5 mg/kg, PO, SID

Sulfonamide	Species	Dosage, Route, and Frequency
Sulfathiazole	Horses	66 mg/kg, PO, TID
	Cattle, sheep, pigs	66 mg/kg, PO, every 4 hr
Sulfamethazine	Cattle	220 mg/kg, PO or IV, SID (initial dose; half for subsequent doses)
Sulfadiazine	All	50 mg/kg, PO, BID
Sulfadimethoxine	All	55 mg/kg, PO, SID (initial dose; half for subsequent doses)
Sulfaethoxypyridazine	Cattle	55 mg/kg, PO, SID
	Pigs	110 mg/kg, PO, SID (initial dose, half for subsequent doses)
Sulfapyridine	Cattle	132 mg/kg, PO, BID (initial dose, half for subsequent doses)
Succinylsulfathiazole	All	160 mg/kg, PO, BID (initial dose, half for subsequent doses)

Sulfonamide	Species	Withdrawal Time (days)	Milk Discard Time (hr)
Sulfamethazine	Cattle	10*	96
	Pigs	14	
Sulfabromethazine	Cattle	10	96
Triple sulfonamide solution‡	Cattle	10	96
Sulfadimethoxidine	Cattle	7	60

Tetracycline	Species	Dosage, Route, and Frequency
Tetracycline	Cats, dogs	7 mg/kg, IM or IV, BID
		20 mg/kg, PO, TID
Oxytetracycline	Cats, dogs	7 mg/kg, IM or IV, BID
		20 mg/kg, PO, TID
	Cattle, sheep, pigs	5-10 mg/kg, IM or IV, SID
	Calves, foals, lambs, piglets	10-20 mg/kg, PO, BID-TID
	Horses	5 mg/kg, IV, SID-BID
Doxycycline	Dogs	5-10 mg/kg, PO, SID
		5 mg/kg, IV, SID

Tetracycline	Species	Withdrawal Time (days)
Oxytetracycline*	Cattle	15-22
	Pigs	22
	Poultry	5
Oxytetracycline (long-acting)*	Cattle	28
Chlortetracycline	Cattle	10
	Pigs	1-7

Drug	Species	Dosage, Route, and Frequency
Chloramphenicol	Cats	45-60 mg/kg, PO, IV, or IM, BID
	Dogs	45-60 mg/kg, PO, IV, or IM, TID- QID
	Horses	50 mg/kg, PO, TID- QID, or IV, every 2-4 hr
Florfenicol	Cattle	20 mg/kg, IM, repeated in 48 hr

Macrolide	Species	Dosage, Route, and Frequency
Erythromycin	Cattle	8-15 mg/kg, IM, SID-BID
	Cats	15 mg/kg, PO, TID
	Foals	25 mg/kg, IM, TID
Tylosin	Cattle	10-20 mg/kg, IM, SID-BID
	Pigs	10 mg/kg, IM, SID-BID 7-10 mg/kg, PO, TID
	Cats	10 mg/kg, IM, BID
Tilmicosin	Cattle	10 mg/kg, SC, once

Macrolide	Species	Withdrawal Time (days)	Milk Discard Time (hr)
Erythromycin	Cattle	14	36-72
	Pigs	7	
Tylosin	Cattle	21	96
	Pigs	14	
Tilmicosin	Cattle	28	0

Lincosamide	Species	Dosage, Route, and Frequency
Lincomycin	Cattle	10 mg/kg, IM, BID
	Pigs	10 mg/kg, IM, BID
		7 mg/kg, in-feed
	Dogs	20 mg/kg, PO, SID
	Cats	10 mg/kg, IM, BID
		25 mg/kg, PO, BID
Clindamycin	Dogs, cats	5-10 mg/kg, PO, BID