

Rational use of antibiotics in the critical care patient

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Introduction

It is our job as veterinarians to make decisions regarding the treatment of our patients. We aim to improve the condition of those patients with the treatments we choose, or at least to not make things any worse. When it comes to choosing antibiotics, not only do we have to consider any potential adverse effects on the current patient but to also think about antibiotic resistance in our hospital and the wider community.

Indications for antibiotic treatment

1. A documented bacterial infection causing illness. The presence of bacteria can be established by direct microscopic examination of an aspirate or smear or by growth in culture. The antibiotic is then selected on the basis of sensitivity testing.
Critical care patients can present problems with this approach: they are critically ill. If you suspect a bacterial infection is causing or contributing to the illness you will want to treat immediately and not wait 24 (often up to 72) hours before getting laboratory results and starting treatment.
2. A high index of suspicion that there is a bacterial infection present but you cannot prove it. An example is fever, a new cardiac murmur and vegetative valvular lesions in a dog with prostatitis but negative blood cultures.
3. Prophylactically or empirically...

Prophylactic antibiotic use: right or wrong?

Prophylactic use of antibiotics will not prevent an infection becoming established in animals that are predisposed to infection. Their use may actually select for infection with a resistant bacterial strain. They will interfere with the normal microbial population in the patient, allowing colonisation by resistant bacteria at sites other than the site of infection. Having said this, it has been suggested that broad spectrum antibiotic use is indicated in patients with certain pre-existing risk factors prior to obtaining proof of infection. This is where most of us really start to have difficulties making the “right” decision.

Empirical antibiotic therapy is the treatment of a suspected infection based on practical experience rather than scientific proof that there is an infection present. For example, we treat dog bite wounds empirically with antibiotics with gram positive and anaerobic cover as we know from experience that they are likely to be infected with Staphylococci, Streptococci, Pasteurella etc. We do not perform a culture and sensitivity (C&S) on every bite wound we see.

Basic principles of antibiotic use in critically ill patients

1. Establish a definitive diagnosis: a thorough clinical examination with the appropriate samples for C&S. Consider non-infectious causes of fever (see table 1).
2. If there is a high incidence of suspicion for bacterial infection, start appropriate empirical antibiotic treatment. Take into account the site of infection and the probable pathogens involved. Initial therapy should be with one broad-spectrum, primary antibiotic, given parenterally and at appropriately aggressive doses.
3. Change to appropriate definitive drug therapy when test results are obtained. The antibiotic chosen should as narrow spectrum as possible.
4. Change to oral therapy when appropriate.
5. Monitor the patient for:
 - a. signs of adverse reactions to the antibiotic chosen
 - b. changes in organ function that may necessitate changes in dose rates or intervals
 - c. clinical response to therapy
6. Re-evaluate thoroughly any patient in which antibiotic therapy seems to be failing. Is there another infection? Repeat C&S testing; evaluate the dose rate and interval taking into consideration potential drug interactions and the pharmacokinetics of the drugs used; consider the emergence of resistance.
7. Limit the duration of therapy whenever possible.

Diagnosis of infection

Direct microscopic examination of exudates or fluids is the quickest and most cost-effective test available. It can be performed in house with a minimum of specialised equipment. You can assess whether you have rod, cocci or filamentous shaped organisms and whether they are Gram positive or negative. Bacteria are readily seen in a smear of fluid when they are present in concentrations of 10^4 or 10^5 per ml. Initial antibiotic therapy can be based on this examination and then fine-tuned when culture results are obtained. (See tables 2 and 3)

When submitting samples to the lab, it is better to send too much than not enough. If there is a large volume of exudate, send plain and EDTA samples as well as a well-soaked transport swab. If you are debriding solid tissue, send fresh samples of the tissue as well as tissue for histopathology. Direct inoculation of the fresh tissue into a culture medium can yield good growth.

Culture and sensitivity testing

C&S testing of specimens that have been properly collected and transported to the lab will give important information about the organisms involved and the appropriate antibiotics to use. However, just because a bacterium is identified at the laboratory does mean it is responsible for the disease process.

False positive culture results can be due to contamination at the time of sample collection, transport or during the culture process. Light growth of organisms which are part of the normal flora is not a significant result in most cases.

False negatives can occur as a result of insufficient volume of material sampled, transport or culture of the organism under inappropriate conditions, or overgrowth and obscuration of the pathogenic organism by normal flora or contaminants. Mycoplasmas are a common example of organisms present but not isolated unless special culture techniques are used.

Test methods: A serial dilution of an antimicrobial in bacteriologic growth medium in microdilution wells is the reference method of susceptibility testing. Smaller laboratories and veterinary practices that have in-house labs use the agar diffusion technique.

Interpreting results:

The terms susceptible and resistant are relative. Susceptibility tests measure the lowest concentration of the antimicrobial that prevents growth of the microorganism, the minimum inhibitory concentration (MIC). This is assumed to be similar to the in vivo MIC. Coupled with knowledge of the location of the infection and the pharmacokinetics of the antimicrobial, sensitivity results can be used to predict whether the infection will be controlled by that antimicrobial.

In general, the results of C&S testing are applicable to the treatment of common, rapidly growing bacteria such as staphylococci, enterococci and Enterobacteriaceae. The results are a prediction of the expected result, not a guarantee, and are based on the blood and tissue levels achieved with standard dose rates and intervals. Extra label use of an antibiotic may significantly alter its distribution and efficacy.

Penetration of the antibiotic to the site of infection is required for effective therapy. Some tissues such as CSF and walled off, chronic infections, may have very low tissue levels of the antibiotic and therefore treatment can fail regardless of bacterial susceptibility testing.

Submission of samples for C&S will over time build a data base of the pathogens seen most commonly in your area. You can then use this information to start empirical therapy while awaiting laboratory results.

Bacterial resistance

The dictionary definition of resistance is “the acquired ability of a bacterium to survive in the presence of concentrations of a chemical which are normally lethal”³. Resistance to an antibiotic can either be intrinsic or acquired⁴.

Intrinsic resistance is due to the inherent structure or physiology of the bacteria i.e. penicillin resistance due to lack of correct binding proteins; anaerobic bacterial resistance to aminoglycosides as uptake of the antimicrobial into the bacteria is oxygen dependant.

Acquired resistance is the development of mechanisms by bacteria that prevent previously effective antibiotics from working. They include drug inactivation, decreased cell wall permeability to the drug, target changes so that the drug will no longer bind to

the bacteria and failure of the bacteria to metabolise the drug to its active form. Acquired resistance can develop by genetic mutation or by acquisition of genetic elements.

The use of antibiotics does not induce genetic mutations in bacterial populations. Simply by chance, a mutation giving a survival advantage to the bacteria will occur and be passed on because of the selection pressures applied to the population by the use of antibiotics.

The genes conferring resistance can transfer between bacteria of the same or different species or even different genera. Bacteria can have genes (linked or independent) coding for resistance to more than one antibiotic. Transfer of these genes can cause bacteria to become resistant to antibiotics they have never been exposed to. With the transfer of bacteria between animals, it is then possible to have bacterial resistance in an animal that has never had antibiotics.

An important point to remember is that when an animal has antibiotics, it is not only the target bacteria that are affected. In one study, dogs hospitalised in an ICU were 1.5 times more likely to have resistant E coli isolated from their faeces for every additional day they spent in the ICU⁵. In most cases, the dogs were not treated for enteral infections.

What can we do to minimise the occurrence of resistance?

Unfortunately, no strategy has been proven to completely prevent the emergence of resistance to antibiotics or to eliminate resistance once it has occurred. In theory, if the selection pressure provided by the presence of antibiotics is removed, the bacteria that carry resistance may decrease in numbers.

- Emphasise infection prevention and control over treatment with antibiotics.
- Do not under dose.
- Limit the duration of therapy.
- C&S testing and use of appropriate, narrow spectrum antibiotics
- Have policies for the use of primary, secondary and tertiary antibiotics.
- Monitor for the emergence of resistant in patients and in the hospital environment.

References

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Table 1: Examples of noninfectious sources of fever in critically ill patients

<p>Haemorrhage CNS (or ischemia) Retroperitoneal Gastrointestinal Pulmonary</p>	<p>Inflammatory conditions Trauma Cholecystitis Pancreatitis Post-op inflammation Immune mediated disease</p>
<p>Neoplasia Lymphoma Leukaemia Carcinoma</p>	<p>Others Pulmonary embolism Seizures Heat stroke Brachycephalic airway Laryngeal dysfunction Pain Anxiety External heat sources Hyperthyroidism</p>
<p>Medications Allergic reactions Transfusion reaction</p>	

Table 2: Common bacteria classified

Gram +ve aerobes	Gram -ve aerobes	Gram +ve anaerobes	Gram -ve anaerobes
Nocardia Staphylococci spp Streptococci spp	Pseudomonas E coli Salmonella	Bacteroides Clostridia spp	Enterobacteriaceae family: E coli, Proteus spp, Klebsiella spp.

Table 3: Antibiotic spectrum of activity (from notes by Dr Sarah Haldane)

Class	Examples	Spectrum				Action, other organisms
		Gm +ve		Gm -ve		
		Aerobe	Anaerobe	Aerobe	Anaerobe	
Amino-glycoside	Amikacin	+		++		Bacteriocidal (inhibit protein synthesis)
	Gentamicin			++		
Penicillin	Amoxicillin	++	++ Clostridia	+		Bacteriocidal (inhibit mucopeptide synthesis in cell wall)
	Ticarcillin	++	+	++ Pseudomonas	+	
Macrolide	Erythromycin	++	+	+	+	Bacteriostatic (bacteriocidal at high doses) Mycoplasma
Lincosamide	Clindamycin	+	+		+	Bacteriostatic (or bact'cidal depending on concentration)
Tetracycline	Doxycycline	+	+	+	+	Bacteriostatic Mycoplasma
Fluoro-quinolone	Enrofloxacin	(+)		++		Bacteriocidal (inhibits DNA gyrase)
Carbipenim	Imipenim	++	++	++	++	Bacteriocidal (inhibit cell wall synthesis)
Cephalo-sporin	Cefazolin 1 st generation	++	++	+	+	Bacteriocidal (inhibit mucopeptide synthesis in cell wall)
	Cefoxitin 2 nd generation	+	+ Bacteroides	+ E coli	+	
	Cefotaxime 3 rd generation	+	++ Bacteroides	++ E coli Pseudomonas Salmonella	++ Enterobacter	
Metronidazole			++		++	Bacteriocidal (disrupts DNA synthesis) Protozoa
Clavulanic acid		+	+	+	+	Inactivates beta lactamases
Potentiated sulphphonamide	Trimethoprim sulphadiazene	++		++		Bacteriocidal (inhibits folic acid synthesis) Coccidia