Infectious Disease:  
An Interactive Clinical Pharmacology Case Discussion  
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This session will focus on the interactive discussion of cases of infectious disease. The content of this manuscript may be useful to read in advance or following the session as it highlights principles to be used in the case discussions.

Introduction to principles of rational selection of antimicrobials
A veterinarian is often required to make the tentative diagnosis of a bacterial infection, and begin treatment without knowledge of culture results. For first-time infections, full courses of antimicrobial therapy may be prescribed without culture and sensitivity. Habitual use of a “broad spectrum” antimicrobial is to be discouraged. As a result, it is important to weigh all the evidence to make a rational decision for such empirical therapy. Empirical therapy is usually based upon:

1. History and P.E.
2. Clinical suspicion of microbes likely involved
3. Gram stain

Certainly, this is the time to consider whether the severity of the animal’s illness merits an immediate culture and sensitivity (C & S), as previous unsuccessful empirical antimicrobial therapy may lead to resistance, and can occasionally confound interpretation of subsequent C & S results.

Questions to ask before empirical therapy
So, more specific questions the veterinarian might ask before empirical therapy include:

1. What organ system is involved?
2. Is the problem acute or chronic?
3. What pathogen is most likely to be present in that organ system?
4. What antimicrobial is most likely to be effective against that pathogen?

General considerations
General factors to consider about the antimicrobial options include:

1. Antibacterial spectra: Gram- negative, gram- positive, anaerobic, rickettsial, and protozoal efficacy?
2. Bactericidal or bacteriostatic at achieved concentrations?
   a. Generally -static
      i. tetracyclines, chloramphenicol, macrolides, lincosamides (lincomycin), sulfonamides, and nitrofurans.
   b. Generally –cidal
      i. penicillins, cephalosporins, aminoglycosides, quinolones, polymyxins, and trimethoprim - sulfonamide combinations
3. Mechanism of action: Is there a post-antibiotic effect (PAE)? Are there synergisms or antagonisms with other drugs being used?
4. Limiting toxicities
5. Practicality of administration
6. Availability and cost

Anaerobic therapy
Successful antimicrobial culture and sensitivity is often not possible, so empirical choices are more frequently seen when anaerobes are suspected. Options for anti-anaerobe therapy include:

1. High doses of penicillin - resistance appears to be increasing
2. Chloramphenicol
3. Clindamycin
4. Metronidazole
5. Cefoxitin

Four-quadrant therapy
Serious systemic infections (bacteremia, septicemia, peritonitis) often call for immediate choice of “Four-Quadrant” therapy. The common choices are:

1.历史和P.E.
2. 临床怀疑可能涉及的微生物
3. GRAM染色

当然，这是考虑动物病情严重时是否需要立即进行培养和敏感性测试（C & S）的时间，因为先前不成功的经验性抗菌治疗可能导致耐药性，并且偶尔会影响后续C & S结果的解释。

在经验性治疗之前要问的问题
所以，更具体的问题是，兽医可以在经验性治疗之前问的包括：

1. 受影响的器官系统是什么？
2. 问题是急性还是慢性？
3. 最可能出现在该器官系统的病原体是什么？
4. 对这种病原体最有效的抗菌药是什么？

一般考虑
需要考虑关于抗菌药物选择的一般因素包括：

1. 抗菌药物光谱：革兰氏阴性，革兰氏阳性，厌氧菌，立克次体和原虫疗效？
2. 在实现浓度下是细菌杀灭还是细菌静止？
   a. 一般 -静态
      i. 四环素类，氯霉素，大环内酯类，林可酰胺类（林可霉素），磺胺类和硝基呋喃类。
   b. 一般 -杀菌
      i. 青霉素类，头孢菌素类，氨基糖苷类，喹诺酮类，多粘菌素和 trimethoprim -磺胺类组合
3. 作用机制：是否有后抗生素效应（PAE）？与其他药物是否协同或拮抗？
4. 限制性毒性
5. 实用性
6. 可得性和成本

厌氧菌治疗
成功的抗菌药物培养和敏感性测试通常不可能，因此经验性选择更频繁地出现在怀疑厌氧菌时。适合厌氧菌治疗的选择包括：

1. 高剂量的青霉素 - 耐药性似乎在增加
2. 氯霉素
3. 克林霉素
4. 甲硝唑
5. 头孢菌素
1. Quinolone + amoxicillin
2. Clindamycin + aminoglycoside
3. Beta-lactam + aminoglycoside
4. Penicillins + aminoglycosides
5. Cephalosporins + aminoglycosides + metronidazole
6. Ticarcillin + carbenicillin and amikacin for resistant Pseudomonas

**Prophylactic ("anticipatory") therapy**

With increasing amounts of antimicrobial resistance developing in higher volume practices, it is worth considering that prophylactic antimicrobial therapy, that is, use of antimicrobials to prevent an infection, is not a rational or evidence-based approach except in certain high-risk patients, like diabetics and other immunosuppressed patients. The empirical use of antimicrobials (e.g. ampicillin) during intravenous or urinary catheterization has been shown to be unnecessary and has likely led to the fact that ampicillin is now only 37% effective against Staphylococcus species and only 55% effective against E. coli. Indeed, as a response to the increased incidence of multi-drug resistant (MDR) nosocomial infections, some human hospitals and tertiary care veterinary hospitals have found it necessary to resort to committees composed of infectious disease, epizootiology, and clinical pharmacology experts to approve the use of an antimicrobial within the institutional practice.

**Guidelines for antimicrobial use according to organ system**

The following are guidelines for "first-guess" empirical therapy of infections in selected organ systems. When available, information from culture and sensitivity tests should almost always take precedence.

**Circulatory infections: Septicemia, bacteremia**

1. Try to identify the original site of infection
2. Positive blood cultures in suspected bacteremia are rare. Culture several times for aerobic and anaerobic organisms timed with rise in temperature if hyperthermic
3. If intestinal trauma, assume a mixed infection with gram-positive, gram-negative, and anaerobic organisms

**Common aerobic organisms causing bacteremia**

1. Staphylococcus
2. Streptococcus
3. Escherichia coli
4. Klebsiella
5. Enterobacter
6. Pseudomonas

**Oropharyngeal, pleuropulmonary, and intra-abdominal infections**

1. 25% involve anaerobes: Bacteroides fragilis most common
   a. Rational first-line empirical choice of antimicrobials: Clavulanic acid-amoxicillin or clindamycin
2. For procedures near the alimentary canal: gentamicin and cefazolin, or cefoxitin and cefotetan

**Bite wounds and traumatic wounds or abscesses**

- Streptococcus, Pasteurella, penicillinase-producing Staphylococcus are most common.
- Rational first-line empirical choice of antimicrobials: Clavulanic acid-amoxicillin
- Other drugs to consider include: oxacillin, dicloxacillin, cephalosporins, tetracyclines, quinolones, and trimethoprim-sulfadiazine/

**Lower respiratory tract: Pneumonia**

1. No predictable bacterial pathogen in dogs: E. coli, Klebsiella species, Pasteurella spp., Pseudomonas species, Bordetella bronchiseptica, or Streptococcus zooepidemicus
2. In cats, Bordetella and Pasteurella common
3. 2/3 are gram-negative and may be resistant to commonly used antimicrobials; C & S of transtracheal wash recommended

While waiting for the results, trimethoprim-sulfa, chloramphenicol, or quinolones are also rational choices. If a gram-positive organism is suspected or identified by Gram stain, alpha- and beta-hemolytic Streptococci, Staphylococcus spp. are common pathogens. Rational first-line empirical choice of antimicrobials include cephalaxin, trimethoprim-sulfa, clavulanic acid-amoxicillin, quinolones, amoxicillin, or ampicillin.

**Bronchial infections**

1. More lipid-soluble drugs, such as chloramphenicol, quinolones, and larger drugs, such as macrolides, may be preferred owing to better tissue penetration
2. When bronchial secretions are severe, gentamicin may be less effective because it penetrates secretions poorly
3. Anaerobes: clindamycin and metronidazole
4. Mycoplasma: clindamycin or a tetracycline

**Urinary tract**
1. Entire urinary tract is at risk when one region of the tract is infected.
2. Examination of the urine and of a Gram stain is always recommended prior to choosing antimicrobial therapy.
3. Particularly in cats, it is important to distinguish inflammation from infection.
4. ~75% gram-negative: E. coli, Proteus, Klebsiella, Pseudomonas, and Enterobacter
5. ~25% due to beta-hemolytic Streptococcus or Staphylococcus.
6. Two or more organisms may be found in about 20% of cases.
7. *In vitro* sensitivity of microorganisms translates to >90% treatment success

Therefore, for empirical therapy of UTI’s, broad-spectrum antimicrobials are recommended, but greatest consideration should be toward drugs which reach high concentrations in the urine: e.g. aminopenicillins, cephalosporins, and quinolones. For upper UTI infections (e.g. pyelonephritis), the agent should reach high concentrations in serum and, if possible, in urine.

The duration of treatment may require 4-6 weeks to achieve the goal of sterilization of the urine. Also, in some cases, after sterilization of the urine, preventive single evening doses of 50% to 70% of the daily dose of a urinary antiseptic or trimethoprim-sulfa may be required. In the case of pyelonephritis, greater than 6 weeks of therapy with an antimicrobial that has good tissue penetration (e.g., chloramphenicol, trimethoprim, or the fluoroquinolones) may be necessary.

**Prostatitis**
1. Penetration of most drugs during early inflammation
2. Penetration characteristics of an antimicrobial are critical – e.g. chloramphenicol
3. Chronic prostatitis – entry of basic drugs favored
   a. Gram positive: chloramphenicol, erythromycin, clindamycin, oleandomycin, quinolones, trimethoprim
   b. Gram negative: chloramphenicol, trimethoprim-sulfa, quinolones

**Pyometra and endometritis**
1. C & S should be performed on the uterine contents
2. E. coli infection is observed in most cases
3. Proteus and Streptococcus occasionally are found
4. Chloramphenicol, trimethoprim-sulfa, quinolones

If medically managed, intrauterine infusion of antiseptic or antibiotic solutions is of little value.

**Central nervous system**
1. High lipid solubility important: chloramphenicol, the sulfas, trimethoprim, metronidazole, and the quinolones
2. Penicillins and cephalosporins may enter an inflamed site during acute infection, but are excluded by blood-brain barrier in chronic conditions.

**Pyodermas**
The most useful way to consider most dermatological infections is as microabscesses.
1. Superficial: Coagulase-positive, penicillinase-producing Staph
   a. Consider methicillin-resistant Staph aureus (MRSA)
2. Deep: gram-negative organisms, fungi, and Mycoplasma
3. Most likely to be S. pseudointermedius in small animals rather than S. aureus
4. Relatively predictable susceptibility to β-lactamase resistant antimicrobials agents with a beta-lactamase inhibitor (e.g. Clavamox®)

Rational first-line empirical choice of antimicrobials: Dicloxacillin, oxacillin, high doses of amoxicillin and clavulanic acid, cephalosporins, erythromycin, lincomycin, trimethoprim-sulfa and the quinolones. Erythromycin and lincomycin should be used only as primary choices, because cross-resistance develops.

**Orthopedics**
1. Sterile orthopedic surgery, particularly long procedures, generally is considered to be high-risk surgery that merits antimicrobial prophylaxis.
2. With known infections, a culture of the wound or joint fluid is mandatory.
3. Treat for no less than 4-6 weeks.

**Osteomyelitis**
1. Most commonly involves Staphylococcus, Streptococcus, E. coli, Proteus, or Pseudomonas species.
2. Gram-negative: gentamicin, amikacin, or the quinolones usually are effective.
3. Gram-positive: cephalosporins, clavulanic acid-amoxicillin, and imipenem, a newer beta-lactam
4. For penicillinase-producing Staph: oxacillin and cloxacillin
Highly suggested general references
