E(eeek) coli: Dealing with Antibiotic Resistant Gram Negative Infections

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Objectives

(1) Review the pathogenesis, therapeutic approach and clinical epidemiology of MDR *E. coli* and *Pseudomonas aeruginosa.* from small animals.
(2) Describe the common mechanisms of antibiotic resistance amongst common companion animal pathogens.
(3) Be able to generate diagnostic and therapeutic approaches to managing resistant Gram negative infections.

Multidrug Resistant *E. coli*

E. coli is arguably the most important pathogen of small animals (except for maybe *Staphylococcus pseudintermedius*). It is a normal inhabitant of the gastrointestinal tract. It also causes a variety of infections including UTI, aspiration pneumonia, bacterial cholangitis, wound infections and pyometra. While many isolates of E. coli remain sensitive to many drugs used in companion animals the emergence of multidrug resistant (MDR) organisms continues to rise. Our laboratory defines MDR as resistant the fluoroquinolones and at least one aminoglycoside based on the Dutch Working Group Guidelines. It is very common to see, in MDR isolates, resistance to all families of beta lactams except the carbapenems. This is typical of organisms that produce extended spectrum beta-lactamases (ESBL). Treatment of *E. coli* infections can be difficult and consultation with microbiologists and infectious disease veterinarians is recommended.

Pseudomonas aeruginosa

P. aeruginosa is a common environmental organism that can cause severe opportunistic infections. P. aeruginosa thrives in moist environments and can often be isolated from medical equipment that is not properly stored or cleaned. It is common agent of wound infections, implant infections and otitis externa. This organism is also associated with "post-grooming furunculosis" a severe dermatologic infection associated with diluted shampoos. *P. aeruginosa* is inherently resistant to many classes of antimicrobials including penicillins, potentiated penicillins, 1st and 2nd generation cephalosporins, TMS, chloramphenicol, macrolides and nitrofurantoin.

Not Treating

It is important to note that "more resistant" does not mean "more pathogenic." It is important for you, as a clinician, to determine whether CLINICALLY this animal requires systemic antimicrobials to manage the disease. Consider the presence of other pathogens and the role the organism may play. Isolation of an organism is not always indication to treat. Remember BOTH of these organisms are normal flora of our patients and may be contaminants in the culture. Also, in human medicine, the "60-90" rule states that 60% of resistant infections will still "respond to antimicrobials." This reminds us that the goal should be clinical resolution of disease. In veterinary medicine we have no evidence to support or dismiss this concept.

Topical Therapy
Some Gram negative infections are accessible from the "outside". Topical therapy allows for HIGHER concentration of antimicrobials to affect the organisms for LONGER periods of time. It can be considered as monotherapy OR as adjunctive to systemic therapy. Examples of topical therapy include aminoglycosides, polymixin B and SSD ointment. Please note mupirocin ointment is not a good choice for suspected Gram negative bacilli infections.

First-Line Therapies
For uncomplicated suspected *E. coli* UTI the International Society for Companion Animal Infectious Disease recommends therapy with amoxicillin or TMS orally. If life threatening UTI is suspected (i.e. pyelonephritis, urosepsis) a fluoroquinolone should be considered. *E. coli* is now considered resistant to amoxicillin and amoxicillin/clavulanate if isolated from outside the urinary tract because of the PK/PD relationship of the "bug and drug." TMS is still a good option in appropriate patients. Fluoroquinolones and third-generation cephalosporins are ideally only used based on culture and sensitivity. The only available oral veterinary drugs with anti-pseudomonal activitiy are the fluoroquinolones. Resistance can develop during therapy and treatment failure does occur without documented resistance.

*Chloramphenicol (*NOT *Pseudomonas)*
Chloramphenicol is a broad-spectrum antimicrobial with Gram positive, Gram negative and anaerobic coverage. It should be dosed at 50 mg/kg TID to treat skin and urinary tract infections in dogs. In cats, 12 mg/kg BID is recommended; however, the clinical experience of the presenter is that this drug is rarely well-tolerated in cats. It is important to instruct owners of the risks (i.e. aplastic anemia in people) associated with this drug and how to handle it appropriately.

*Nitrofurantoin (*NOT *Pseudomonas)*
This first line human drug is considered second or third line in veterinary medicine. It is **urinary tract only drug** and should not be used in cases of pyelonephritis due to poor tissue penetration. Recommended dose is 4.4 m/kg TID. It should also be avoided in young animals. This drug has also been associated with a peripheral neuropathy in dogs and patients should be carefully monitored. **NOT TO BE USED IN CATS.**

Carbapenems
This class of antibiotics should be considered a last resort drug for treatment of resistant infections in veterinary patients. Their use should be supported by culture and sensitivity results and de-escalation should be performed when possible. This is the "drug-of-choice" for treating ESBL *E. coli* but other options should be ruled out first. This class of drugs also has anti-pseudomonal activity but resistance does occur in veterinary patients.