ANTIBIOTIC THERAPY IN AVIAN SPECIES

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Learning Objectives

- Review the challenges of antibiotic therapy in birds
- Describe criteria for antibiotic selection, in general and more specific to treatment of bacterial diseases in birds
- Review common antibiotics used, highlighting their advantages, disadvantages and limitations for use in avian species

Challenges of antibiotic therapy in birds

- Advanced stage of disease at presentation
- Few to no pharmacokinetic studies investigating antibiotic drugs in avian species
- Significant variability in absorption and metabolism of drugs between the different species of birds (example: canary vs. macaw vs. turkey)
- Faster metabolism when compared with dogs and cats → rapid drug elimination → may be difficult to establish therapeutic antibiotic concentrations
- Difficult administration, especially in the smaller bird species and/or with TID or more frequent drug administration
- Extra-label use of antibiotic drugs
- Potential for drug residues in the meat or eggs and restricted use in production animals (www.farad.org)

Criteria for antibiotic selection

- Ideal antibiotic therapy protocol
  - Reaches therapeutic concentrations quickly for an immediate effect
  - Easy to administer
  - Minimal to no toxicity
- To consider before starting an antibiotic
  - Collect all diagnostic samples before initiating treatment
  - Consider if treatment with antibiotic is necessary, i.e., is the cause of the presenting signs a bacterial disease? Take into consideration information from:
    - History
    - Physical exam
    - Clinical pathology
      - Elevated white blood cell count with heterophilia or monocytosis suggests the presence of an infectious disease
      - Chemistry panel results provide valuable information regarding liver and kidney function, which will aid in antibiotic selection (ex: not using aminoglycosides in cases of renal disease; not using sulfonamides in dehydrated animals)
    - Cytology
      - Psittacine normal flora
        - GI
          - Mostly gram-positive bacteria (*Lactobacillus* spp., *Bacillus*, *Corynebacterium* sp., non-hemolytic *Streptococcus*, *Micrococcus* sp., and *Staphylococcus epidermidis*.)
          - <10-14% of gram-negative bacteria
          - Few to no yeast; should not be budding
- Respiratory tract
  - Low numbers of Bacillus sp., Corynebacterium sp., and Lactobacillus sp. in the upper respiratory tract and trachea
  - Low numbers of Streptococcus sp. or Staphylococcus sp. in the upper respiratory tract
  - No gram-negative bacteria.
- Culture and sensitivity
- Imaging (to rule in or out non-infectious diseases such as trauma, toxicity, etc.)
  - When treating empirically, consider bacteria that commonly cause disease
    - Psittacine
      - Gram negative: Enterobacteriaceae, Salmonella, Klebsiella, Pseudomonas
      - Chlamydophila psittaci
      - Clostridium spp.
    - Passeriformes
      - Gram positives: Staphylococcus, Streptococcus, Enterococcus spp.
  - When reviewing the results of a culture and sensitivity, use the susceptibility characteristics and the MIC value
    - The term "susceptible" with a disk susceptibility test is mostly based on effective plasma drug concentrations in humans
    - As drugs are potentially metabolized and excreted at a higher rate in birds, a more frequent administration protocol may be required to achieve antibiotic concentrations comparable to humans
    - For these reasons, the MIC number should be used and preference should be given to antibiotics that are known to be effective at very low concentrations
- Mode of administration
  - Parenteral, per os, topical
    - Parenteral
      - IM
        - Because of their size, the IM route is rarely used for an extended period of time in birds
        - Care should be taken when giving IM injections in the pectoral muscles in free range birds
      - IV/IO: reserved primarily for the most severe cases of bacterial disease.
      - SC: most frequently utilized parenteral route of administration
    - PO
      - Used extensively, especially with at home administered antibiotics
      - Minimize frequency of administration → less handling of the bird → less stress
      - Given by syringe, in the water or in the food.
      - Some birds will initially accept a flavored oral suspension of an antibiotic but later refuse it
      - Difficult to administer antibiotics in pill form to most parrots but relatively easy in galliformes, waterfowl and raptors
      - Water based treatment
        - Should be avoided since
          - Therapeutic concentrations are rarely achieved
          - Many drugs are unstable in water for long periods
          - Change in flavor of the water → bird will not drink enough → under-dosing and/or death due to dehydration
        - Use should be limited to
          - Treatment of small birds that cannot be handled
          - Treatment of group of birds
      - Direct oral administration
        - Commercially available or compounded formulations preferred
        - Medication can be added to a favorite food item to facilitate administration
        - When in the hospital, gavage feeding can be used for accurate drug administration
The effect of this route of drug administration on the human-bird bond should be taken into consideration. Training, treats and reduction in frequency of drug administration should help reduce this problem.

- **Topical**
  - **Nebulization**
    - **Goals**
      - hydration of mucous membranes
      - mucolysis, expectorant, bronchodilation effects
      - Delivery of antibiotic or antifungal medications
    - 2 main types of nebulizer used
      - **Ultrasonic**
        - Relies on a vibrating mesh to produce an aerosol of drug
        - Inefficient to aerosolize suspensions
      - **Jet**
        - Uses a jet of air to draw up liquid through a capillary and atomizer
        - Advantages
          - Smaller particle side
          - Cheaper, more robust, and more readily available than ultrasonic models
        - Disadvantage: lower output rate.
    - Both types have been shown to damage certain drugs in nebulization; this, together with risk of toxicity, are the reasons supporting the recommendation to use only drugs or formulations made for nebulization in humans.

- **Particle size**
  - Determine effect required
    - Topical → particle size less important
    - Systemic → particle size important since small size is needed for absorption

- **Other factors that affect drug penetration besides particle size**
  - Flow rate: the faster the air flow the more likely the drug is to penetrate deeper
  - Deepness of breath: deeper breathing will enable deeper penetration compared to rapid shallow breathing
  - Airway anatomy: more tortuous results → more deposition
  - Disease: mucous and/or bronchoconstriction → more deposition

- **Toxicity**
  - **Direct**
    - Variable absorption of nebulized drugs from lungs and/or air sacs of birds
      - Few studies in birds
      - Gentamycin, ceftriaxone: not absorbed
      - Lincomycin, tylosin and oxytetracycline: absorbed well and achieve effective plasma concentrations after nebulization
  - **Indirect**
    - Ingestion of the medication in the feathers with grooming
    - Toxicity to humans
      - More clinical trials are needed to investigate protocol safety and efficacy in avian species

- **Skin**
  - Effective for local infections
Toxicity possible with ingestion
- Direct effect of creams and ointments in the feathers
  - Antibiotic impregnated polymethylmethacrylate beads
    - High concentration at the infection site
      - more efficient and with less side effects
      - Antibiotic concentrations at the site usually much higher than MIC for most pathogens may be effective against resistant organisms
- Elution of antibiotic from PMMA varies with:
  - Type of cement used to make beads
  - Size and surface area of the beads (more elution)
  - Antibiotic used
  - Concentration of the drug (more elution)
  - Amount of fluid contacting the beads.
- Antibiotic choices
  - Must be water-soluble, heat-stable (100°C), bactericidal, broad-spectrum, and available as a powder
  - Commonly used: aminoglycosides, cephalosporins, fluoroquinolones, penicillins, and clindamycin.

Frequency of administration
- Less frequent less stress with handling and higher compliance
- Important to understand the concept of time dependent vs. concentration dependent antibiotics
  - Concentration dependent drugs
    - Must reach a level of approximately 8-10 times the MIC to be most effective bactericidal most effective given once daily at high doses.
    - Efficacy is increased in these drugs by increasing the dose or by parenteral administration.
    - Ex: fluoroquinolones, aminoglycosides.
  - Time dependent drugs
    - Must remain above the MIC for most of the interval between doses
      - Usually has to be administered several times a day.
      - Increasing the efficacy usually involves increasing the frequency of administration.
    - Ex: cephalosporins, trimethoprim-sulfonamides, macrolides, tetracyclines

Volume to be administered
- Volume especially important for PO, SQ or IM administration
- For oral administration, small volumes are easier to administer, which requires the availability of a concentrated oral formulation (consider compounding pharmacies)
- Demonstrate drug administration while reviewing to go home instructions and make sure the owner can do the treatments recommended
- Verify compliance during follow up phone call and/or appointment.

Conditions at the infection site
- Abscesses, granulomas and presence of mucous make achieving adequate drug concentrations at the infection site difficult or impossible
- Water-soluble drugs (aminoglycosides, penicillins, cephalosporins) enter the extracellular fluid (where most bacterial infections occur) well but do not penetrate granulomas or areas with large amount of mucus
- Lipid soluble drugs (fluoroquinolones, tetracyclines) can potentially penetrate abscesses and cells, being effective against intra-cellular bacteria.
- Surgical debridement of granulomas and abscesses is recommended to increase tissue penetration and improve antibiotic efficacy
- After debridement, localized treatment (as described above) can be implemented, in addition to systemic antibiotic therapy
- Nebulization with a mucolytic agent can also aid antibiotic penetration in cases of respiratory infections.

Toxicity
Not species specific and based on clinical condition
- Renal disease and aminoglycosides
- Liver disease and doxycycline

Synergistic effect: nephrotoxicity enrofloxacin and ketoconazole

Class specific
- Direct
  - IM Enrofloxacin
  - Injectable penicillins?
  - TMS and GI disturbances (especially macaws)
- Indirect
  - Many antibiotics used orally in birds can cause dysbiosis resulting in secondary infections by resistant bacteria, yeast, and aspergillosis.
  - Prevention
    ✓ Monitor cloacal cultures and fecal gram stains for potential pathogens.
    ✓ Maximize husbandry and hygiene to reduce exposure to environmental pathogens.
    ✓ Minimize stress to reduce immune suppression
    ✓ Consider prophylaxis with antifungal drug
    ✓ Supplement with a probiotic

Antibiotic classes and its use in birds

Quinolones
- Enrofloxacin, ciprofloxacin, marbofloxacin
- Bactericidal and concentration dependent antibiotic

Spectrum
- Resistance has been seen in *E. coli*, *Klebsiella* spp., *Acinetobacter* spp., and *Pseudomonas aeruginosa*.
- Poor activity against many *Streptococcus* spp., *Enterococcus* spp., and anaerobes.
- *In vitro* activity against *Chlamydophila psittaci*, with inconsistent results in clinical trials → not recommended for treatment of chlamydiosis

Advantages
- Bactericidal at relatively low MIC
- SI:D administration
- Lipophilic → good tissue distribution
- Different modes of administration possible

Disadvantages
- Dysbiosis GI flora with prolonged treatment
- High pH → possible reaction at the injection site
- Not recommended to be given IV to birds
- Poor efficacy against *Pseudomonas*
- Marbofloxacin: may affect molt

Doses
- 15-30 mg/kg once daily
  - Lower dose used for bacteria with an MIC <0.25µg/ml
  - Higher dose used for more resistant bacteria (MIC 0.5-1µg/ml )

Uses
- Gram negative bacterial infections
- Bacterial infections of the gastrointestinal tract and respiratory tract
- Critical care/in hospital use
- Parenteral, oral, nebulization, topical
Aminoglycosides
- Amikacin, gentamicin, neomycin
- Bactericidal and concentration dependent antibiotic
- Spectrum
  - Excellent activity: gram-negative bacteria (including most *Pseudomonas aeruginosa*),
  - Good activity: *Staphylococcus*
  - Poor activity: *Streptococcus*, mycoplasma and *Chlamydophila*.
  - No activity active: anaerobes, facultative anaerobes at sites with low O\textsubscript{2} tension (abscesses)
- Advantages
  - SID-BID administration
  - Bactericidal, gram negative activity (including *Pseudomonas*)
- Disadvantages
  - Risk of nephrotoxicity: relatively common but reversible with short treatments at adequate doses
  - Poor absorption from the GI tract → limited use (injectable, topical in the GI or airway-nebulization)
- Doses
  - MIC required to control gram-negative aerobes with aminoglycosides is dependent on the drug used (> 3 x MIC)
  - Amikacin: 10-25 mg/kg/day
  - Gentamicin, tobramycin: 2.5-5 mg/kg/day
- Uses
  - Should be limited to 7 days and used with caution in dehydrated patients or those with compromised renal function
  - Gram negative bacterial infections including *Pseudomonas aeruginosa*
  - Bacterial infections of the gastrointestinal tract and respiratory tract
  - Critical care/in hospital use
  - Parenteral, oral, nebulization, topical
  - Amikacin: less toxic, wider spectrum →, most commonly used
  - Gentamicin: cheaper but more toxic than amikacin
  - Tobramycin: effective against *Pseudomonas* but more toxic than amikacin

Penicillins
- Penicillin, amoxicillin, ampicillin, ticarcillin, piperacillin
- Bactericidal and time dependent
- Spectrum
  - Early generation: good gram-positive spectrum, some gram-negative activity.
  - Later generation: improved gram-negative spectrum, only available as injectable formulations.
- Advantage
  - Bactericidal, gram negative bacteria (incl. *Pseudomonas*)
  - Good tissue distribution
  - Relatively low toxicity
- Disadvantage
  - Require dosing q4-8h
  - Reported toxicity of procaine to birds < 1kg (finches, canaries, budgerigars, cockatiels)
- Doses
  - Relatively high due to low bioavailability after oral administration
  - Ranging from 100-200 mg/kg BID and up to 4-6 times per day
  - Higher doses and/or more frequent administration needed when treating severe infections or infection caused by bacteria with high MIC
- Uses
  - Gram positive or anaerobic infections > gram negative infections
  - Bacterial dermatitis
  - Dog/cat bite wounds
  - Pododermatitis
- Post-operative for orthopedic surgery cases
- Bacterial infections of the gastrointestinal and respiratory tracts (alone or in combination with aminoglycosides)
- Parenteral, oral, nebulization, AIPMB

**Cephalosporins**
- Bactericidal and time dependent
- Spectrum
  - Early generation drugs
    - Cephalexin, cefazolin
    - Good: gram-positive bacteria, especially against *Staphylococcus* spp.
    - Limited: gram negative bacteria
  - Later generation drugs
    - Ceftazidime, cefotaxime
    - Improved gram-negative spectrum especially against *Pseudomonas*.
    - Available in injectable formulations only.
- Advantages
  - Bactericidal, gram negative bacteria spectrum (incl. *Pseudomonas*)
  - Good tissue distribution (including bone, CNS)
  - Relatively low toxicity
- Disadvantage
  - Require dosing q4-8h
  - Allergic reactions
  - Cost
- Doses
  - Time dependent and low bioavailability→higher doses and more frequent administration needed for severe infections in immunocompromised birds.
  - Most cephalosporins need to be dosed at 50-100 mg/kg every 4-6 hours to achieve therapeutic plasma levels
  - PK studies
    - Ceftiofur
      - 10mg/kg IM q4h cockatiels and q8h Orange-winged Amazons.
      - Long acting ceftiofur (Excede®) Guinea fowl: 10 mg/kg IM q72h
    - Cefovecin (Convenia®): 1 h dosing interval needed in hens→ not suitable
- Uses
  - Gram positive or anaerobic infections > gram negative infections
  - Bacterial infections of the CNS or bone
  - Severe bacterial infections of respiratory tract
  - Parenteral, oral, nebulization

**Sulfonamides +/- combinations (trimethoprim)**
- Spectrum
  - Effective against some protozoa, including toxoplasma and coccidia
  - Combination with folate reductase inhibitors such as baquiloprim, ormetoprim or trimethoprim→ bactericidal, broad spectrum (G+/- except *Pseudomonas*)
  - Resistance more common in *E. coli* and *Klebsiella*
- Concentration likely bacteriostatic at the doses used in birds
- Advantages
  - Broad spectrum (G+/-; except *Pseudomonas*)
  - Good tissue distribution (including CNS, eye)
  - Relative low toxicity
  - Oral suspension→ easy to administer
  - Low price
- Disadvantages
  - Bacteriostatic(?) in birds
Side effects

- GI (macaws, turkeys, chickens)
- Renal (with dehydration)
- HSR poultry
- Cannot be used in food producing birds
- Use for longer than 2 weeks may require vitamin supplementation

Doses

- Psittacine empirical dose: 16 mg/kg trimethoprim + 80 mg/kg sulfamethoxazole q12h clinically successful

Uses

- Gram positive and negative infections
- Bacterial dermatitis
- Mild to moderate bacterial infections of the GI or respiratory tract
- Parenteral, oral, nebulization

Tetracyclines

- Bacteriostatic and time dependent
- Spectrum: generally broad spectrum, although overuse in human and veterinary medicine has led to increased resistance
- Advantages
  - Broad spectrum
  - Lipophilic → good tissue distribution
- Disadvantages
  - Reported low plasma concentrations, below MIC for most bacteria → not effective
  - Injectable formulations can cause necrosis at injection site
  - Oral absorption is reduced in the presence of cations such as calcium or magnesium.
  - Prolonged treatment may have catabolic and immunosuppressive effects, reduce normal gut flora, and render the animal more susceptible to opportunistic infections.
  - Oral administration: decreased appetite, vomiting, dysbiosis
  - Hepatotoxic (12.5-25 mg/kg PO q12-24h in lorikeets)
- Doses: use low end of dose range for macaws and cockatoos
- Uses
  - Primarily for treatment of chlamydiosis and mycoplasmosis
  - Doxycycline: most commonly used tetracycline because it is more lipid soluble, readily absorbed after PO administration, and has a prolonged elimination half-life.
  - Parenteral, oral (individual vs. group treatment in the food or water), nebulization

Macrolides

- Clindamycin, azithromycin, tylosin
- Bacteriostatic, bactericidal at higher concentrations for certain antibiotics
- Time dependent
- Spectrum: generally broad spectrum, mostly gram positive and anaerobes
- Advantages
  - Good tissue distribution
  - Effective against Gram positive and anaerobic bacteria
  - Available as an oral suspension
  - SID-EOD administration
- Disadvantage
  - GI disturbance (decreased appetite, vomiting)
- Doses
  - PK macaws 10 mg/kg PO q48h (Carpenter et al, 2005)
- Uses
  - Chlamydiosis
    - Azithromycin 40 mg/kg PO q48h effective in eliminating C. psittaci infection in experimentally inoculated cockatiels (Guzman et al 2010)
Mycoplasmosis (tylosin)
- Anaerobic infections
- Bacterial osteomyelitis (clindamycin)
- Parenteral, oral, nebulization

Methronidazole
- **Advantage**
  - Effective against anaerobic bacteria and protozoa
  - Safe when given PO
  - Availability of oral suspension
- **Disadvantage**
  - Limited to no efficacy against other bacterial

Chloramphenicol
- **Advantage**
  - Broad-spectrum bacteriostatic to bactericidal drug, depending on concentration and bacterial susceptibility
  - Spectrum: aerobic and anaerobic gram-positive and gram-negative bacteria.
- **Disadvantage**
  - Side effects associated with handling chloramphenicol
  - Limited availability
  - Potential nephrotoxicity
  - Bacteriostatic activity
- **Doses**
  - Significant differences in PK between birds and mammals, and between avian species → dose extrapolation between species not recommended
- **Uses**
  - PO, parenteral, nebulization, topical

**References and Further Reading**

Mayer J, Donnelly T. Clinical Veterinary Advisor. Birds and Exotic Pets. Elsevier, St. Louis, Missouri, 2013 (several chapters)


