Sea Turtle Antimicrobial Selection
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Sources of Information

- Culture & Sensitivity testing
- Anecdote
- Expert consultation
- Extrapolation
- Metabolic Scaling
  - $\text{SMEC} = K(W^{0.25})$
  - $K = 10$ for reptiles
- Formularies
- Pharmacokinetic Studies
  - Gold standard
  - Pitfalls with the gold standard
<table>
<thead>
<tr>
<th>Antimicrobial Agents Used in Reptiles[^291]</th>
<th>Dose</th>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>15 mg/kg PO q48-72h[^146,208]</td>
<td>Tortoises/PD (desert tortoises); upper respiratory tract (mycoplasmosis)</td>
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<tr>
<td>Clindamycin</td>
<td>5 mg/kg PO q12h[^231]</td>
<td>Most species/gram-positive bacteria and anaerobes</td>
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<tr>
<td>Danofloxacin</td>
<td>6 mg/kg SC, IM[^97]</td>
<td>Loggerhead sea turtles</td>
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<td></td>
<td>6 mg/kg SC q48h × 30 days[^180]</td>
<td>Tortoises/mycoplasmosis</td>
<td></td>
</tr>
</tbody>
</table>

[^231]: Mader DR. 2011. Personal communication.
Enrofloxacin (Baytril, Bayer)

5-10 mg/kg q24h PO, SC, IM, IDe

6.6 mg/kg IM q24h, or
11 mg/kg IM q48h

10 mg/kg IM q48h

5 mg/kg PO, IM q24h

10 mg/kg IM q54h

5 mg/kg IM q24-48h

5 mg/kg IM q12-24h

5 mg/kg IM q48h

10 mg/kg IM q24h

Most species/IM administration is painful and may result in tissue necrosis and sterile abscesses; may cause skin discoloration or tissue necrosis if given SC

Pythons/PO (reticulated pythons);
Pseudomonas

Snakes/PO (Burmese pythons);
Pseudomonas

Lizards/PO (green iguanas); marked pharmacokinetic variability with PO administration may make IM more suitable in critically ill animals

Monitors/PO (savannah monitors); preliminary data

Chelonians and most other reptiles/PO (gopher tortoises); hypercalciation, incoordination, diarrhea reported in a Galapagos tortoise

Chelonians/PO (Indian star tortoises);
g12h for Pseudomonas and Citrobacter;
g24h for other bacteria

Sea turtles

Chelonians/PO (Hermann's tortoises)


Sea Turtle PK papers

Pharmacokinetic Studies in Sea Turtles

- Ceftazidime, Florfenicol
  - Stamper et al. 1999, Stamper et al. 2003, Innis et al. 2011
- Fluconazole
  - Mallo et al. 2001, Innis et al. 2011
- Itraconazole
  - Manire et al. 2001
- Praziquantel, Enrofloxacin
- Meloxicam
  - Claus et al. 2007 (Proc IAAAM), Soloperto et al. 2011 (ISTS)
- Oxytetracycline
  - Harms et al. 2004
- Ticarcillin
  - Manire et al. 2005
- Danofloxacin
  - Marin et al. 2005
- Marbofloxacin
- Clindamycin
  - Harms et al. 2011
- Tramadol
  - Norton et al. 2013 (ISTS)

Pitfalls of the Gold Standard

- The hazards of single-dose PK studies
  - E.g., Oxytetracycline
- Is it the right drug for the job?
  - E.g., Fluconazole
NMFS Galveston Laboratory – Best Place to do PK Study!

Ceftazidime

- Stamper et al. 1999, healthy loggerheads; Innis et al. 2011, cold-stunned ridleys, rewarmed
- Third generation cephalosporin, Gram negative infections, parenteral only
- 20 mg/kg IM q 72 h
- Clearance 0.22 ml/min/kg
- Renally excreted in mammals
  - 25 mg/kg IM or SQ q 8 – 12 h in dogs
  - Clearance 3.1 ml/min/kg in dogs
- Relatively non-irritating, few observed side effects
- Resistance issues
Florfenicol

- Stamper et al. 2004, healthy loggerheads
- 30 mg/kg (20 mg/kg q 48 h cattle; q 8 hr dogs)
- MICs 0.25 – 2 µg/ml
- Mixed hepatic and renal excretion in mammals

Oxytetracycline

- Harms et al. 2004, healthy loggerheads
- Validating bone marking, but potential for treating susceptible microbes as well
- Renally excreted unchanged
- VD 18 L/kg (vs 2.1 in small mammals); T1/2 64 h
- MIC 4 µg/ml (but lower for mycoplasmas, chlamydiias)
**SIMULATED** Multiple Dose Regimens

- Versus actual data, courtesy Charlie Innis, Mark Papich
- Kemp’s ridley with mixed mycoplasmal and mycobacterial (*M. chelonae*) tracheitis, high dose option, 3 weeks
- Peak concentration **49 µg/ml**
- Trough concentration **26 µg/ml**
- Appetite decreased
- Tracheitis improved…

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**Fluconazole**

- Mallo et al. 2002, healthy loggerheads
- Antifungal, mainly yeast, +/- *Aspergillus* spp.
- Renally-excreted
- Single dose study 2.5 mg/kg IV and SC
- Multiple dose study 21 mg/kg SC loading dose then 10 mg/kg q 5 d
- BUT….
Fluconazole

- Innis et al. 2011, cold stunned Kemp’s ridleys, rewarmed
- 21 mg/kg SC
- $AUC_{24} = 1921 \, \text{h} \cdot \mu\text{g/ml}$
- Clinical efficacy associated with $AUC_{24}/\text{MIC} > 25$
- MIC < 64 µg/ml susceptible at this dose, but filamentous fungi MICs often higher
- *Beuvaria bassiana* isolates MIC >64 µg/ml (NEAQ)
- *Colletotrichum acutatum* isolate from ridley MIC 64 µg/ml (Manire et al. 2002)

Itraconazole

- Manire et al. 2003, cold-stunned ridleys, multiple doses, steady state (after 30 d of treatment)
- Oral only
- Hepatic metabolism, hydroxyitraconazole also active
- $T_{1/2} = 75$ h (vs 15 – 24 or 21 – 64 h in humans)
- 15 mg/kg q 72 h or 5 mg/kg q 24 h
- 0.5 µg/ml target trough concentration
Clindamycin

- Harms et al. 2011, healthy loggerheads, 10 mg/kg IV, IM, PO
- Anaerobic bacteria
- Mixed hepatic and renal excretion
- CLSI MIC = 0.5 µg/ml

Enrofloxacin

- Jacobson et al. 2005, healthy loggerheads, 10 or 20 mg/kg PO
- Renal and non-renal excretion
- Ciprofloxacin active metabolite
- 20 mg/kg no more than once weekly recommended “until multiple dose studies are conducted”
Danofloxacin

- Marín et al. 2008, healthy loggerheads, 6 mg/kg IV, IM, SC
- Primarily renal excretion in cattle, greater non-renal excretion in some other species
- $T_{1/2} = 15$ h (vs. 3 – 6 h mammals)
- MIC 0.5 µg/ml (50 µg/L)
- q 48 h may be adequate

Marbofloxacin

- Lai et al. 2009, healthy loggerheads, 2 mg/kg IV and IM
- Renal and hepatic excretion
- Only oral form in US
- $T_{1/2} = 15$ h (vs 9 – 13 h dogs & cats)
- MIC 0.5 µg/ml, achievable with q 24 h dosing
Ticarcillin

- Manire et al. 2005, healthy loggerheads, 50 mg/kg IV, 25, 50 or 100 mg/kg IM
- Renally excreted
- T\(\frac{1}{2}\) 5 h (vs 45 – 80 min dogs & cats)
- For MIC < 16 µg/ml, 50 mg/kg q 24 h or 100 mg/kg q 48 h

Praziquantel

- Jacobson et al. 2003, healthy loggerheads, 25 and 50 mg/kg PO, 25 mg/kg PO q 3 h x 3
- Hepatic metabolism, urinary excretion
- Necrotic skin lesions occurred in one turtle at 50 mg/kg
- High variability, uptake slow, elimination slow
- MRT 9 h (vs 4.4 h in humans)
Sea Turtle PK Synopsis

Drugs eliminated primarily unchanged by renal excretion in mammals generally have slow elimination times in sea turtles and may be administered at conveniently long dosing intervals (fluconazole [Mallo et al. 2002], ceftazidime [Stamper et al. 1999], ticarcillin [Manire et al., 2005], oxytetracycline [Harms et al. 2004]), while drugs metabolized primarily by the liver or exhibiting mixed hepatic and urinary excretion in mammals may have either prolonged (enrofloxacin [Jacobson et al., 2005], marbofloxacin [Lai et al., 2009], danofloxacin [Marín et al., 2008]), itraconazole [Manire et al. 2003] praziquantel [Jacobson et al., 2003] or rapid (florfenicol [Stamper et al., 2003], clindamycin [Harms et al., 2011], meloxicam [Clauss et al., 2007]) elimination in sea turtles as compared with mammals.