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Suppressing Coccidioidomycosis in Naturally Infected Dogs by Frequent Dosing of Nikkomycin Z

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68th Annual Coccidioidomycosis Study Group

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Overview – Cocci Treatment in Dogs

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- ▶ Some dogs have poor response to first line drugs (flu, itra)
- ▶ Intolerance to azole drugs can occur
 - Hepatotoxicity, GI intolerance, other adverse effects
- ▶ Nikkomycin Z (NikZ) showed excellent tolerance in dogs (60 days)
 - Plasma concentrations showed short residence time
- ▶ Short NikZ half life can be addressed by repeated small doses
 - Commercial formulation will be sustained-release, daily pill
- ▶ Dosed at 12 to 75 mg/kg/day for 2 to 7 months
- ▶ Dosing here was q 4, 2 or 1 hour, with dose loading at bedtime to bridge overnight sleep

Shubitz, et.al., Med Myc, 2013



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Methods

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- ▶ Canine patients: Compassionate use requests for NikZ
 - Intolerance or failure to respond to oral azole antifungals
- ▶ Screening: histories, routine blood tests, coccidioidal serology, imaging
 - Confirm at least probably coccidioidomycosis
 - Four recent cases disseminated, One early intervention (mild, at first detection)
- ▶ Antifungal treatment solely with NikZ
 - Allowed: Medications for unrelated health problems
- ▶ Depending on severity, dosing at 12 to 75 mg/kg/day
- ▶ Duration: minimum 60 days, mostly 3-4 months,
 - One was treated for 7 months
 - Early intervention – 6 weeks



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Dog 1: 7 YO SF Doberman pinscher, 32 kg

- ▶ Dog had congenital copper storage disease and was treated with d-penicillamine to reduce progression of cirrhosis
- ▶ Developed cocci pneumonia based on clinical signs (mainly gagging cough, lethargy), serum chemistries, CBC, cocci serology (1:8)
- ▶ Dog was not started on fluconazole, ALT 1541, poor appetite
- ▶ Dog was treated with NikZ administered for 3 months, 33 mg/kg/day
 - At 2 months, “doing well, likes to play, walk, but coughing when excited”
- ▶ No azole given, liver enzymes stable, lungs continued to resolve



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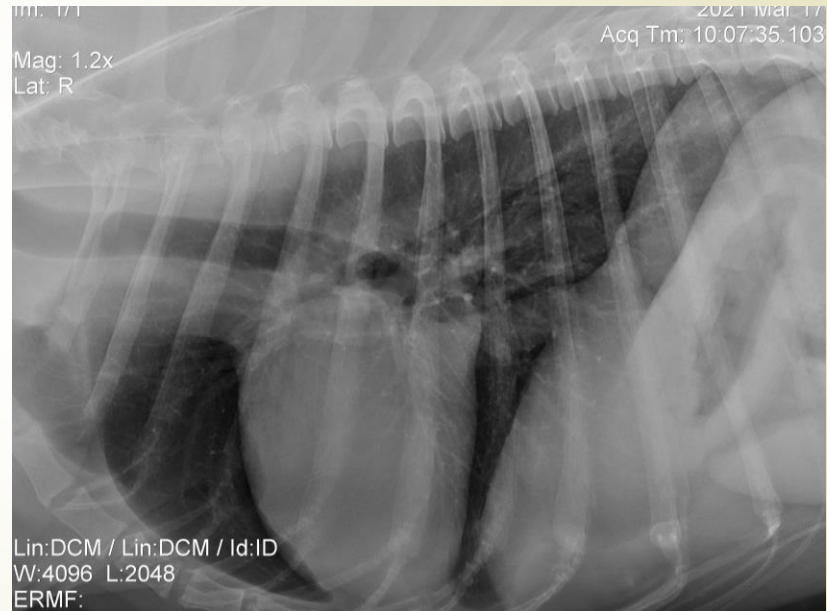
Radiographic progression showing near resolution over 3 months with 2 months NikZ



12/20/20 – at intake



1/21/21 – 1 month



3/17/21 – 3 months



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Dog 2: 15 YO SF 4 kg Shih Tzu

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- ▶ Dog was diagnosed July 2020 by MRI with a cocci brain granuloma, titer 1:2. Clinical signs included left sided weakness. History 6 weeks prior to CNS granuloma of coughing and mild lethargy
 - Dog also had previous history of acute liver injury and hepatopathy
 - Being treated with fluconazole and low dose prednisone for last 12 months
- ▶ At initial VSCOT assessment in July 2021, the dog was experiencing left sided stumbling and knuckling with falling, ALT 869, episodic pancreatitis
 - Poor candidate for anesthesia, can't repeat MRI
- ▶ NikZ for 4 weeks (75 mg/kg/day, q 2 hr): Neurological signs nearly resolved to minimal stumbling on left side, appetite good, attitude bright and happy



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15 YO SF Shih Tzu

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- ▶ NikZ continued (50 mg/kg/day, q 4 hr) to 5 months, then stopped.
- ▶ Returned to fluconazole, hospitalized for acute hepatitis, pancreatitis, comatose, euthanasia was considered but dog recovered
- ▶ Off fluconazole, very mild stumbling and weakness of left side returned
- ▶ At month 7, NikZ resumed for 1 month then stopped due to poor appetite, intermittent diarrhea, weight loss
 - No further antifungal treatment
- ▶ Dog was alive with stable, minimal CNS deficits over one year later at almost 17 yrs of age



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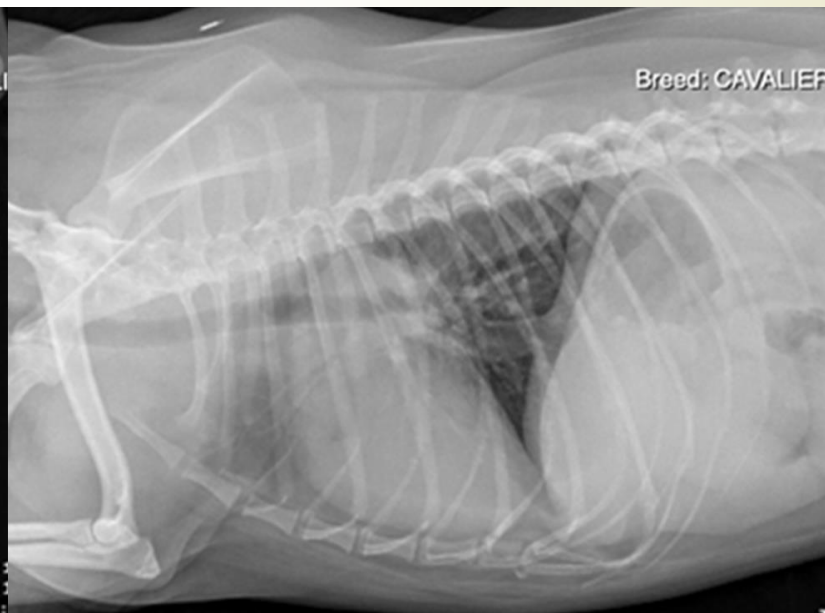
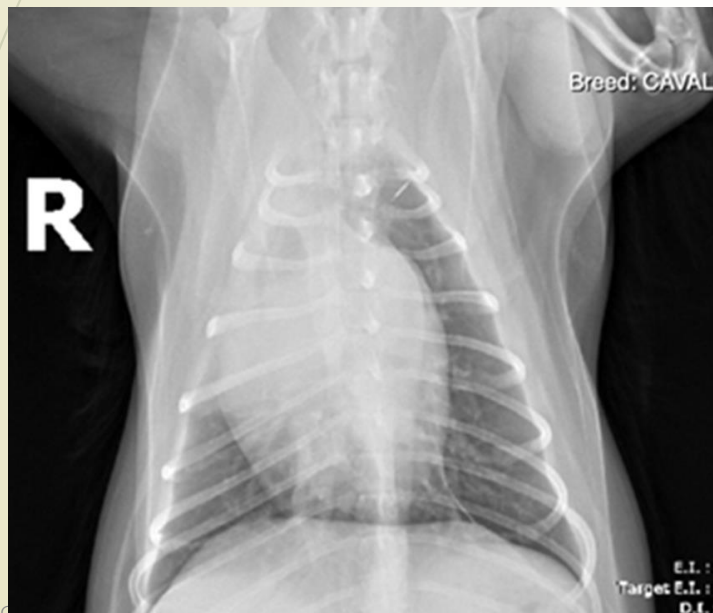


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Dog 3: 6 YO 13 kg CM Cavalier King Charles Spaniel

- Right cranial lung infiltrate and moderate hilar lymphadenopathy
- Treated with fluconazole 12 mg/kg BID from 2/2/21-6/12/21 with modest response

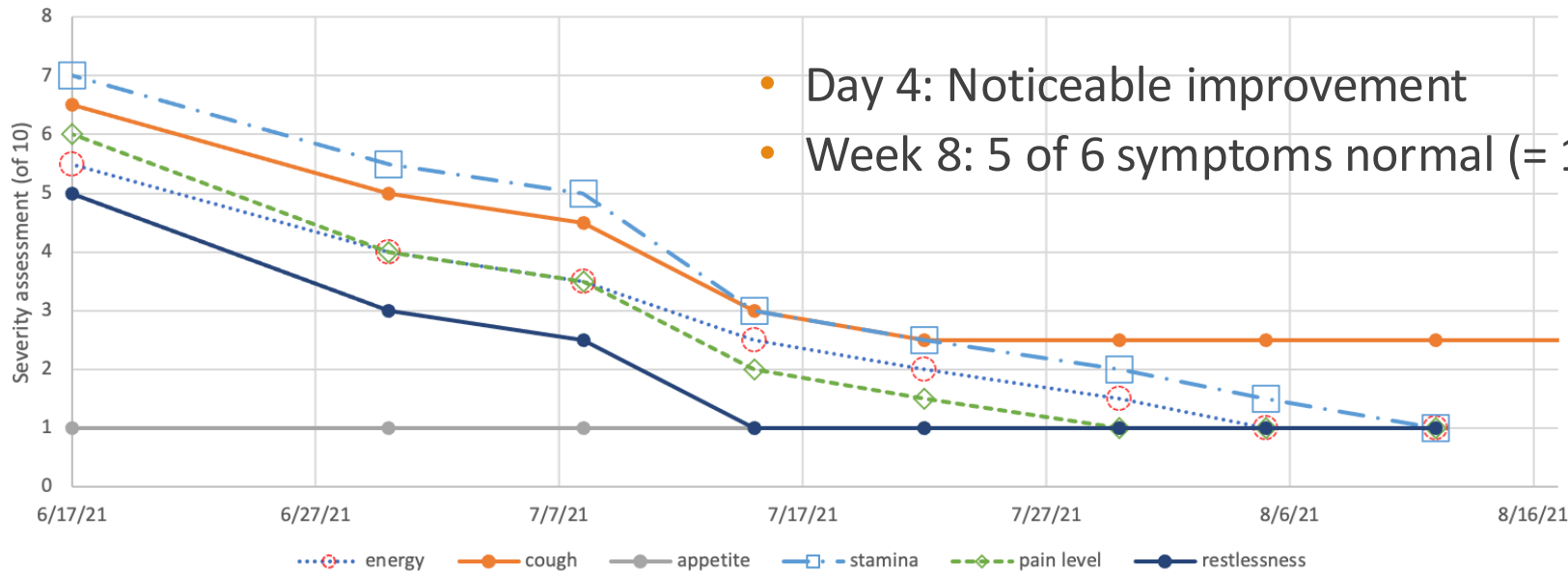


Flu,
60 days



Cavalier: NikZ 12.5 mg/kg/day (match flu) divided by 12, q 2 hours

Cavalier progress PRO scores - 6/12 FCZ (from 2/3, 4.5 months),
6/17 NikZ 12.5 mpkd (to 8/27)



- Day 4: Noticeable improvement
- Week 8: 5 of 6 symptoms normal (= 1)



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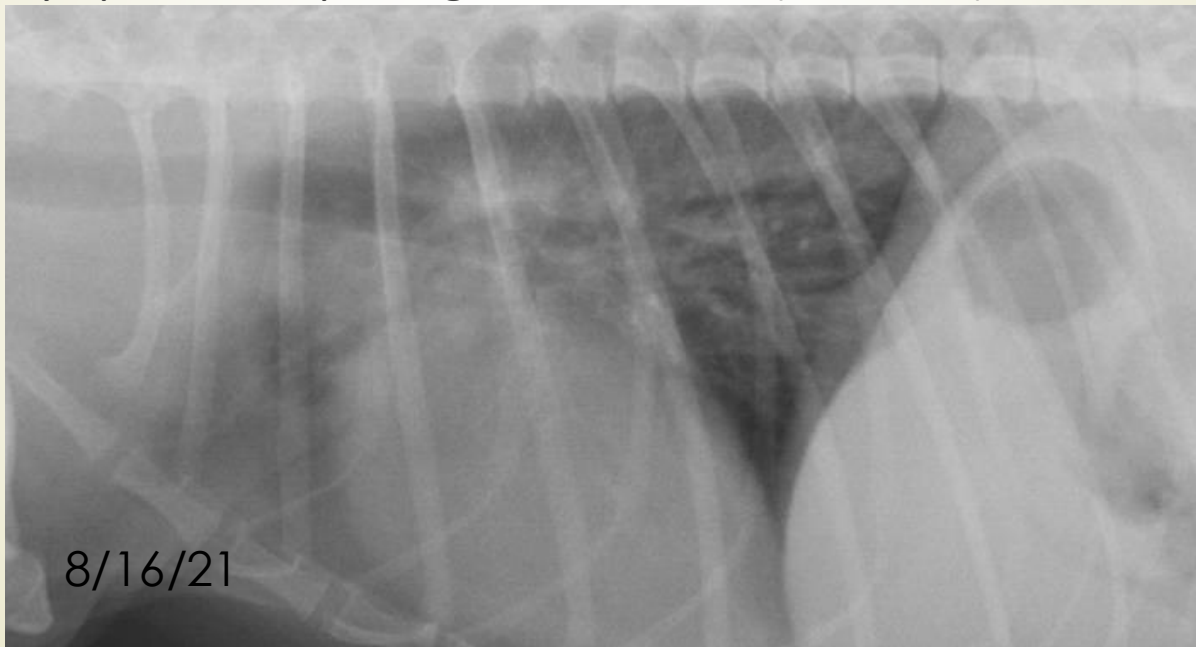


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Cavalier – 8 weeks NikZ – Chest rads

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- ▶ Radiologist review of radiographs 60 days after starting NikZ showed ongoing right cranial lobe infiltrates as well as hilar lymph node enlargement still present
- ▶ No symptoms except cough, BUT titer 1:8 (increased)



8/16/21
NikZ 60 d

Cavalier – symptoms down, titer up

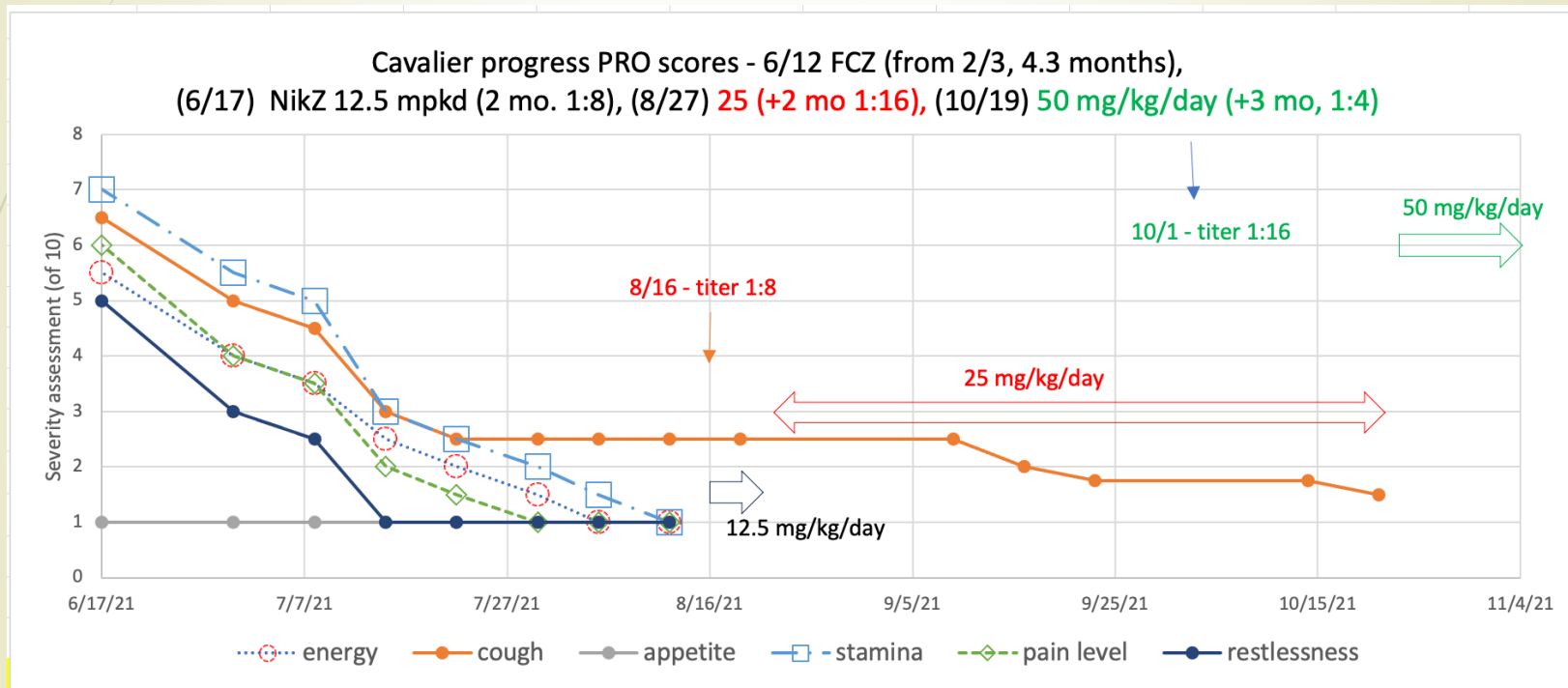
Dose step to 50 mg/kg/day was enough



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➤ Dose doubled 8/27, again 10/19, titer finally to 1:4 at 1/28 (7.3 months)

6 YO Cavalier – Week 14 CT Scan, double dose Week 33: Clear, no recurrence



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- ▶ Week 10: for a moderate, persistent cough, dose doubled to 25, q 1 hour
- ▶ Week 14 – CT showed significant abnormalities, titer 1:16 (getting worse), disease still active
- ▶ Week 16 - Dose doubled again to 50 mg/kg/day, q 1 hr (final dose level)
- ▶ Week 33 (7.3 months), titer dropped to 1:4, asymptomatic, stopped therapy
- ▶ Week 68 follow up - titer 1:2, dog healthy, asymptomatic
- ▶ Year 2.2 follow up, still happy, symptom free
- ▶ Future: consider starting at a medium-high dose, such as 30-50 mg/kg/day for 4 to 6 weeks,
 - then maintenance at about 50% to 4 to 6 months

Dog 4: 2 YO 31 kg F Golden Retriever – Early Intervention

- ▶ Pulmonary coccidioidomycosis at initial diagnosis, titer 1:16, lack of energy
- ▶ First NikZ dose 9 days after diagnosis
- ▶ Dosed 30 mg/kg/day q 2 hr for 4 weeks, then 15 mg/kg/day q 4 hr for 4 weeks
- ▶ 3 weeks “much better” (films look normal)
- ▶ 8 weeks - last dose
- ▶ 6 months: New litter of puppies Nov ‘23
- ▶ 10 months “doing fine”



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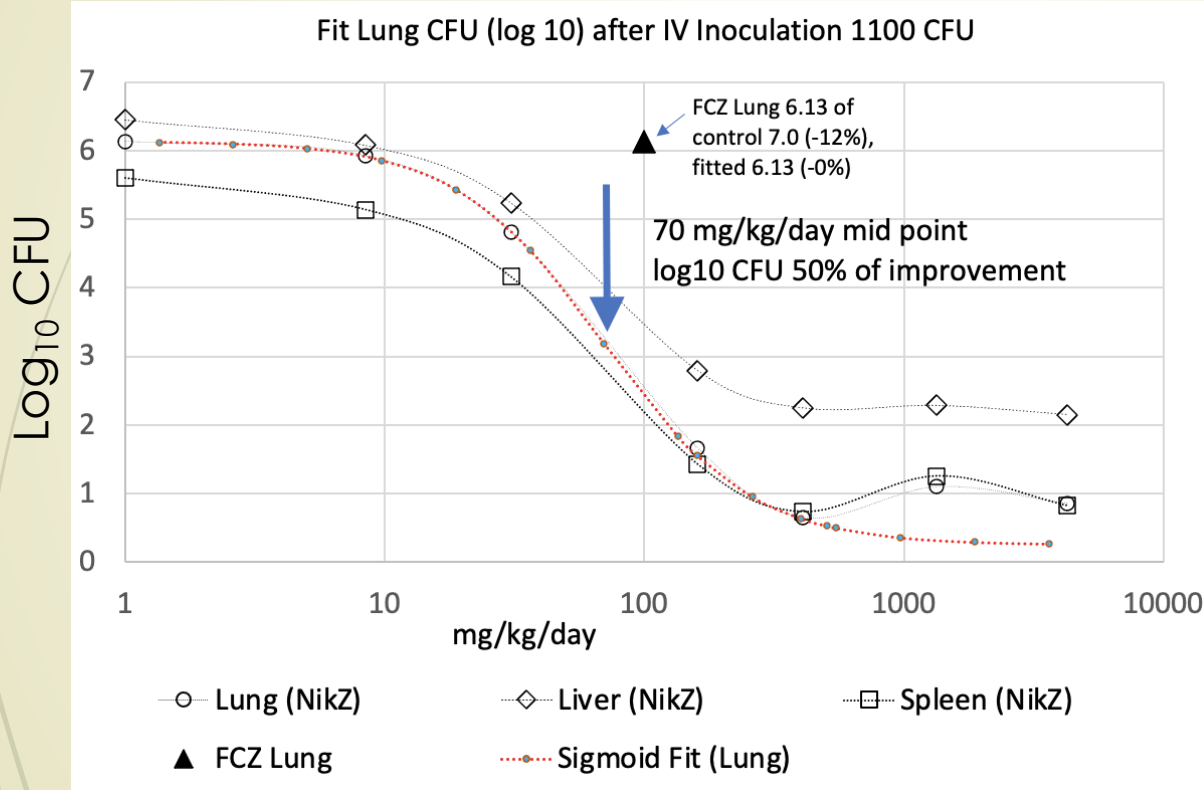
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NikZ levels: mice, IV disseminated model CFU suppression (log)

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- Survival 70% at 8 mg/kg/day (mpkd), 100% at 160, 400 (11 days)
- 8 mpkd NikZ superior to 100 mpkd FCZ (fluconazole)
- Fluconazole only fungistatic, NikZ fungicidal (other experiments)
- Isolate NikZ MIC: 2 µg/mL

Conclusions



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- ▶ NikZ oral therapy at 2-4 hour intervals during waking hours resulted in improvement or resolution of clinical disease in three dogs with persistent natural infection and inadequate response or intolerance to azole therapy.
- ▶ Liver issues contraindicating fluconazole (2 dogs) – no liver toxicity
- ▶ Known CNS disease (1 dog) improved substantially, stable with no antifungal medication > 1 year after NikZ therapy for 6 months
- ▶ Pulmonary disease – resolution in 2 dogs (2, 7 months therapy)
- ▶ Early intervention suppressed disease in ≤ 6 weeks (1 dog)
- ▶ Planned future sustained-release formulation should be efficacious, with convenient QD dosing

Thank you

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 - Critical support over time



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