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 CARE  
Managing the  
Immunosuppressed Patient

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PRACTICE LIMITED INTERNAL MEDICINE (SAIM)

11 / 09 / 2019

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**Immune-Mediated Diseases in Veterinary Medicine**

- **Most common immune-mediated hematologic disorders**
  - immune-mediated hemolytic anemia (IMHA)
  - immune-mediated thrombocytopenia (ITP)
- **Most common gastrointestinal immune-mediated disorder**
  - inflammatory bowel disease (IBD)
- **Treatment**
  - immunosuppressive drugs
    - glucocorticoid therapy +/- a 2<sup>nd</sup> line drug

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## Drug Therapy

- **IMHA/ITP**
  - Glucocorticoid
  - Cyclosporine
  - Azathioprine
  - Mycophenolate
  - Chlorambucil
- **IBD**
  - Glucocorticoid
  - Cyclosporine
  - Chlorambucil
  - Mycophenolate



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## Glucocorticoids

- **Mainstay for immune-mediate disease (IMHA, ITP, IBD)**
- **Prednisone at a dose of 2 mg/kg/day (dog) or 2-4 mg/kg/day (cat), given orally**
- **If using alone, a second drug should be considered if glucocorticoid therapy is noted to be ineffective**
  - worsening clinical signs, worsening hematologic changes
- **Dexamethasone can be given intravenously at 0.2 mg/kg/day**
  - equivalent to approximately a 2 mg/kg/day dose of prednisone
- **Budesonide can also be used, especially in those patients that are prednisone-sensitive**
  - acts locally within the GI tract.
  - doses can range from 9 mg/kg/day or 3 mg/m<sup>2</sup>, \$\$\$



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## Cyclosporine

- **Common second-line drug**
- **Potent immunosuppressive agent that suppresses T-cell function**
  - patients should be closely monitored for secondary infections
- **Dose ranges from 5-10 mg/kg, twice daily, given orally**
- **It is important to ensure the formulations are microemulsified, which provides better GI absorption**
- **Cyclosporine can be quite expensive, therefore concurrent use with ketoconazole could be used to allow for a decrease in cyclosporine administration**
- **Side-effects of cyclosporine include gingival hyperplasia, hepatotoxicity, and renal toxicity**



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## Azathioprine

- Purine analogue- very effective in combination with glucocorticoids
- Doses commonly start at 2 mg/kg orally (dogs)
- Azathioprine is a relatively inexpensive drug
  - side-effects include hepatotoxicity, pancreatitis, and myelosuppression
- This drug is not well tolerated in cats and not recommended for use



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## Chlorambucil

- Cell cycle non-specific alkylating agent- very effective in combination with glucocorticoids
- Doses starting at 0.1-0.2 mg/kg/day (4-6 mg/m<sup>2</sup>)
  - come in 2 mg tablets
- Well tolerated, side-effects including myelosuppression and GI upset
- Although the cost of chlorambucil can be expensive, with its small tablet size it can be an ideal choice for our smaller dogs and cats
  - Compounding pharmacies



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## Mycophenolate

- Inhibits enzymes needed for purine synthesis- very effective in combination with glucocorticoids
- Starting doses range from 10-20 mg/kg, twice daily, given orally
- It is relatively inexpensive with the most common side-effect including severe GI upset (diarrhea, vomiting)
- This drug should be used with caution in cats, and since it inhibits purine synthesis, it should not be used in conjunction with azathioprine



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## Leflunomide

- Inhibitor of pyrimidine synthesis- very effective in combination with glucocorticoids
  - inhibits B and T cell function, suppresses antibody production and has anti-inflammatory effects
- It has not been well documented in using this drug with IMHA and IMT but has been used in some refractory cases
- Most common dose is 2-4 mg/kg, once daily, given orally
- Leflunomide is commonly well tolerated but side-effects can include myelosuppression and hepatotoxicity.



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## Drug Monitoring

- Cyclosporine assays (qRT-PCR)
  - Whole blood used
  - Offered through MSU Pharmacodynamic Laboratory,
  - Can help in adjusting oral cyclosporine doses in dogs to optimize systemic immunosuppressive effects
    - Mild, moderate, or complete suppression
  - Cyclosporine has been shown to have much the same effect on T cell cytokine production in cats as it does in dogs
    - Feline assay in the works



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## Drug Monitoring

- Leflunomide- levels to Auburn Veterinary Teaching Hospital
- Drug will accumulate 50% with a 24 hr dosing interval
- Sampling times:
  - recommend a single trough sample



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## Secondary Infections

- **Significant immunosuppression is desired when treating severe life-threatening diseases**
  - This comes with significant associated risk to predisposing our patients to infection
  - Seen even more so when multiple immunosuppressive drugs are used
- **Infections**
  - Mycobacteriosis
  - Noncardiosis
  - Generalized demodecosis
  - Systemic fungal infections
  - Toxoplasmosis
  - Hemotropic mycoplasmas



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## Secondary Infections

- **Avoid using powerful immunosuppressive therapy to treat minor diseases that are not life-threatening**
  - save the "big guns" for more severe illnesses
- **Use the lowest effective drug dose possible**
- **Avoid using combinations of multiple different immunosuppressive agents unless absolutely necessary**
- **Screen patients very carefully for underlying infectious disease before commencing immunosuppressive therapy, especially when infection can mimic immune-mediated disease (*Babesia gibsoni* masquerading as IMHA)**
- **Watch patients on immunosuppressive therapy closely for signs of new infection**



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## Immune Mediated Hemolytic Anemia

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## Meet Lucy

- 5 yo FS English Cocker Spaniel- presented for lethargy, melena, mild anemia
- PE: HR: 156 bpm , RR: 32 bpm, T:102.9F
  - pale mucous membranes
  - slight yellow/icteric color to her sclera
- Macro-agglutination noted on blood draw




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## Diagnostics

WBC	11.9	Ku/L	7.0 - 22.0
WBC	1.92	L/MuL	4.30 - 8.27
HGB	5.0	L/g/dl	11.0 - 19.0
HCT	14.0	L %	24.0 - 39.0
MCV	72.5	fL	69.0 - 77.0
MCH	29.8	pg	18.0 - 29.0
MCHC	39.6	g/dl	32.0 - 37.0
RDW	14.6	%	No Ref Interval
Platelets	139	L/KuL	160 - 690
Tech Instrument: Heather Cunningham, MT (ASCP)			
PCV	14.0	L %	24.0 - 39.0
SP	7.8	g/dl	5.0 - 10.0
Sigma %	89	H %	80 - 77
Sigma	10591	fL	3500 - 14200
Lymph %	9	L %	12 - 30
Lymph	1071	L/fL	1200 - 6900
Mono %	2	L %	3 - 10
Mono	298	fL	178 - 1700
Platelet Estimator	Accuracy Decreased		
Plt. Est. Number	112		
Platelet Morphology	Occasional Mega Platelets		



RBC Morphology: Slight Polychromasia, 1+ Anisocytes, 2+ Poikilocytes, Occasional / 1+ Blastocytes, Few / 2+ Keratocytes/ Helmet Cells, 1+ Occasional Eosinophils  
 Application: Sample Condition: 2+ Hemolysis, 1+ Icteric

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## Diagnostics

- Chemistry: Tbili: 4.9 mg/dl
- 4DX: negative
- PT/PTT: WNL
- AXR: NSF
- TXR: NSF




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## Hospitalization

- **Transfusion- pRBC's**
- **Immunosuppression**
  - dexamethasone 0.2 mg/kg IV SID
  - cyclosporine 7.5 mg/kg BID
- **Acute increase in RR- PTE suspected**
- **Antiplatelet/clotting**
  - enoxaparin, aspirin, clopidogrel



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## Hospitalization

- **Day 2: PCV dropped to 14%- 2<sup>nd</sup> transfusion (post PCV:23%)**
- **Day 4: PCV dropped to 16%- 3<sup>rd</sup> transfusion (post PCV: 25%)**
- **Day 5: PCV dropped to 13%- 4<sup>th</sup> transfusion (post PCV: 22%)**
  - cyclosporine dose increased to 10 mg/kg BID
- **Day 7: PCV dropped to 14%- 5<sup>th</sup> transfusion (post PCV 23%)**



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## Hospitalization

- **Day 8: no macro/micro-agglutination noted**
- **Day 9: PCV 20%**
- **Day 10: PCV 20%**
  - Reticulocyte count: 2.1% (poorly regenerative)
- **Lucy discharged**



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## TGH Medications

- Cyclosporine 100mg BID- 10 mg/kg
- Prednisolone 20mg SID- 2 mg/kg
- Cerenia 24 mg SID- 2.4 mg/kg
- Omeprazole 10mg SID- 1 mg/kg
- Clopidogrel 12 mg SID- 1.1 mg/kg
- Aspirin 20 mg SID- 2 mg/kg



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## Follow Up

- 1<sup>st</sup> recheck**
- 2 weeks from discharge
  - PCV 25 %
  - Reticulocyte count 4.2%
  - All medication left the same

- 2<sup>nd</sup> recheck**
- 4 weeks from discharge
  - PCV 30%
  - All medication left the same



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## Follow Up

- 3<sup>rd</sup> recheck**
- 6 weeks from discharge
  - PCV 39%
  - 25% decrease in prednisone dose- 1.5 mg/kg SID
    - cyclosporine remained the same

- 4<sup>th</sup> recheck**
- 8 weeks from discharge
  - PCV 42 %
  - Doses kept the same



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## Follow Up

### 5<sup>th</sup> recheck

- 10 weeks from discharge
  - PCV 40%
  - 25% decrease in prednisone dose-
- 1 mg/kg SID
- cyclosporine remained the same

### 6<sup>th</sup> recheck

- 12 weeks from discharge
- PCV 45 %
- Doses kept the same



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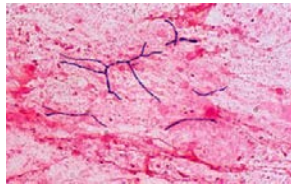
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## Follow Up

### 7<sup>th</sup> recheck

- 12 weeks from discharge
- PCV 41%
- Small, draining wound on the right front shoulder
- Impression smear:
  - acid fast positive = nocardia
- Kept prednisone at 1 mg/kg SID
- IMMEDIATELY discontinue cyclosporine
- Initiated TMS therapy (STT)
  - Cleaned and lavaged wound



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## Follow Up

### 8<sup>th</sup> recheck

- 14 weeks from discharge (2 weeks since nocardia)
- PCV 35% (no agglutination)
- Wound much improved
- Kept prednisone at 1 mg/kg SID

### 9<sup>th</sup> recheck

- 17 weeks from discharge (5 weeks since nocardia)
- PCV 43%
- Wound completely healed- palpates normally
- Decrease prednisone to 0.75 mg/kg SID



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## Follow Up

### 10<sup>th</sup> recheck

- 19 weeks from discharge (7 weeks since nocardia)
- PCV 45%
- Decrease prednisone to 0.5 mg/kg SID
- TMS discontinued



### 11<sup>th</sup> recheck

- 21 weeks from discharge (9 weeks since nocardia)
- PCV 43%
- Continue prednisone on same dose



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## Follow Up

### 12<sup>th</sup> recheck

- 23 weeks from discharge (11 weeks since nocardia)
- PCV 42%
- Decrease prednisone to 0.25 mg/kg SID

### 13<sup>th</sup> recheck

- 25 weeks from discharge (13 weeks since nocardia)
- PCV 45%
- Continue prednisone on same dose



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## Follow Up

### 14<sup>th</sup> recheck

- 27 weeks from discharge (15 weeks since nocardia)
- PCV 40%
- prednisone at 0.25 mg/kg EOD for 7 days and then d/c

### 15<sup>th</sup> recheck

- 29 weeks from discharge (17 weeks since nocardia)
- PCV 43 %
- NO MEDICATIONS



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## Immune Mediated Thrombocytopenia

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### Meet Mik

- 8-year-old male neutered mixed breed
- presented for a persistent draining tract
- Nine months previously a stick was removed from Mik's left pharyngeal region
  - Multiple surgeries, an abscess formed with persistent draining tracts
  - CT revealed foreign material still present within the neck.
- Current medications:
  - amoxicillin 500mg twice daily
  - cephalexin 500mg twice daily
- Snap test positive for Ehrlichia canis/ewingii
- Platelet count of 2,000
- Physical Exam: Pale pink gums, covered in ticks and fleas, oozing serosanguinous fluid from multiple draining tracts around the left cervical region

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## Diagnostic Plan

- **Diagnosis: Immune-mediated thrombocytopenia (ITP)**
- **Other testing**
  - Chest Rads- WNL
  - Abdominal Rads-WNL
  - Abdominal Ultrasound
    - Enlarged spleen with hypoechoic areas
  - Cervical CT with fistulogram
    - Foreign body present within the abscess



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## Day 4

- **CBC:**
  - PLT: 1.36 K/ul (160-650)
  - Eosinophils: 3135 /ul (120-1330)
  - HCT: 39.9%
  - Manual platelet count: 40 K/ul
  - Morphology: mild megaplatelets seen
- **D-Dimer: negative**



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## Initial Therapy

- **Doxycycline (5 mg/kg BID)**
- **Metronidazole (7.5 mg/kg BID)**
- **Cerenia**
- **Famotidine**



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## Home on Day 16



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## TGH Medications

- Prednisone 40 mg SID – 2 mg/kg
- Doxycycline 200 mg BID – 10 mg/kg
- Metronidazole 200 mg BID -10 mg/kg
- Tylenol 4 30 mg TID – 1.5 mg/kg
- Famotidine 10 mg BID- 0.5 mg/kg



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## 1<sup>st</sup> Recheck

- Recheck 2 weeks later-
  - Mik is doing great- healing appropriately at his surgical site
  - CBC:
    - Manual PLT count:
      - 360,000 /ul (160-650)
- Staples removed
- Kept prednisone dose the same



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## 2<sup>nd</sup> Recheck

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- Recheck 2 weeks later
- Mik is doing well, incision still healed appropriately
- Prednisone still at 2 mg/kg/d
  - 40 mg
- Reduce the dose?? Keep the same??



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## 2<sup>nd</sup> Recheck

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- Prednisone reduced to 30 mg total
  - 20 mg tab, 1.5 tab SID
- Plan to recheck in 1 week after dose reduction



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## 3<sup>rd</sup> Recheck

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- 1 week after 1<sup>st</sup> taper
- CBC:
  - Manual PLT count: 321,000 K/ul
- Recheck in 2 weeks



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## 4<sup>th</sup> Recheck

- 3 weeks later...
- The owner had decided to taper on his own schedule
  - Dropped to 20 mg SID- 1mg/kg
- CBC  
Manual PLT count: 378,000 /ul
- What to do???



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## 5<sup>th</sup> Recheck

- 2 weeks later
  - CBC: Manual PLT count: 322,000 /ul
  - Tapered pred to 0.5 mg/kg SID
- 3 weeks later
  - CBC: Manual PLT count: 451,000 /ul
  - d/c pred
- 4 weeks later
  - CBC: Manual PLT count: 451,000 /ul
  - No medications needed!!!



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## Inflammatory Bowel Disease

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## Meet "Memphis"



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## History

- 3 year old MN mixed terrier breed
- 1.5 weeks of diarrhea and ascites
- Hypoalbuminemia
- Currently on: Cerenia (anti-nausea), Provable (probiotic), metronidazole
- Eats z/d due to sensitive skin
- Lifelong history of "sensitive stomach"



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## Physical Exam

- Normal TPR
- Abdominal distension



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## Diagnosics

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- **CBC: normal**
- **Serum chemistry**
  - Marked hypoalbuminemia (1.1 g/dl; 2.1-4.3 )
  - Mild hypocalcemia (7.5 mmol/L; 8.8-11.2)
- **Urinalysis**
  - Proteinuria
  - Urine specific gravity 1.055
- **Urine protein:creatinine ratio**
  - 2.3 (0-2)



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## Diagnosics

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- **Abdominal ultrasound (quick peek in ICU)**
  - Free fluid in abdomen



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## Problem List

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- **Diarrhea**
  - Small bowel
  - Acute onset??
- **History of sensitive stomach**
- **Ascites**
- **Hypoalbuminemia**
- **Proteinuria**
- **Hypocalcemia**



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## Proteinuria Hypocalcemia

- Fecal flotation
- Liver function test
- Urine culture
- Abdominal radiographs
- Abdominal ultrasound
- Baseline cortisol
- GI panel



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## Diagnostics

- **Abdominocentesis**
  - Pure transudate
- **Fecal flotation**
  - No parasites seen
- **Abdominal ultrasound**
  - Corrugated duodenum



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## Diagnostics

- **Urine culture**
  - No growth at 48 hours
- **Baseline cortisol**
  - >2 µg/dl
- **GI panel (pending)**
  - Cobalamin/folate
  - qPLI
  - TLI



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## Endoscopy

- Granular appearance to mucosa
- Severe mucosal hyperemia



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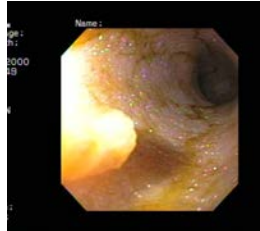
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## Endoscopy

- Granular appearance to mucosa
- Severe mucosal hyperemia



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## Biopsy Reports

- Stomach and duodenum
  - Moderate lymphoplasmacytic and severe eosinophilic enteritis
  - Normal lacteals
  - Crypt abscesses
  - Villous blunting



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## Treatment

- Metronidazole continued
- Cerenia
- Omeprazole
- Famotidine
- Hetastarch 20 ml/kg/day
- Dexamethasone 0.25 mg/kg IV
- Fenbendazole trial



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## Response- Day 3

- Albumin: 1.2 g/dl
- Worsening ascites
- Poor appetite
- Soft stool
- Cyclosporine added at 5 mg/kg PO BID



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## Response- Day 4

- Eating better
- Ascites improved
- Albumin 1.7 g/dl
- Discharged
  - Cyclosporine
  - Prednisone 2mg/kg daily
  - Cerenia
  - Metronidazole 10 mg/kg BID



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## Treatment Take 2

- Returned on 5 days later
- Trembling
- Albumin 1.0 g/dl
- Suspected adverse reaction to metronidazole
- Metronidazole discontinued
- Hetastarch restarted
- No improvement in trembling in 48 hours



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## Treatment Take 2

- Rare reports of trembling with cyclosporine noted
- Cyclosporine discontinued
- Mycophenolate started 2 days later
- Severe GI pain, collapse, melena
- Worsening ascites
- GI protectants started
- Discontinued Hetastarch



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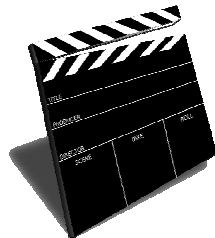
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## Treatment Take 3

- Chlorambucil started at 4 mg/m2 daily
- Ascites improved off of Hetastarch
- Melena resolved
- Tremors decreased daily
- GI panel
  - Low normal cobalamin
  - Decreased folate



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## Outcome

- 6 days after 2<sup>nd</sup> presentation
- Liver function test normal
- Albumin 1.1 g/dl
- Discharged
  - Prednisone 3 mg/kg daily
  - Chlorambucil 4 mg/m<sup>2</sup> daily
  - Tylosin
  - Fortiflora
  - Omeprazole
  - Cerenia



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## Follow Up

- 4/27: Albumin 1.5 g/dl
- 5/11: Albumin 1.9 g/dl
- 5/18: Albumin 1.5 g/dl
- 6/23: Albumin 2.1 g/dl
- 7/21: Albumin 2.4 g/dl
  - Decreased pred by 25%



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## Follow Up

- 9/9: Albumin 2.6 g/dl
  - Chlorambucil tapered to M, W, F regimen
- 12/28: Albumin 2.5 g/dl
  - Decreased pred by another 25%
  - 1 mg/kg daily
- 1/15: Albumin 2.8 g/dl
  - Decreased pred (chlorambucil still M,W,F)
  - 0.5 mg/kg daily



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## Follow Up

- 2/9: Albumin 2.8 g/dl
  - Prednisone d/c
- 2/28: Albumin 3.0 g/dl
  - Chlorambucil M,Th
- 3/15: Albumin 3.2 g/dl
  - d/c chlorambucil
- 4/02: Albumin 2.1 g/dl
  - Memphis had started having loose stool
  - Placed back on chlorambucil M,Th
- 4/16: Albumin 2.8 g/dl
  - Continued indefinitely



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## Recap

- Let your patient help you
- IMHA/ITP, PLE's can require aggressive immunosuppression
- Be patient with treatment responses
- Every patient is different
  - Medication side effects
  - Response



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## Questions???



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