UCI University of California, Irvine

Take My Breath Away

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Disclosures

- None

HPI

[redacted] year old [redacted] with history of hepatic steatosis, LTBI on INH/B6 (started 6/2023), Ph Like Pre-B ALL (s/p HyperCVAD) admitted for haploidentical stem cell transplant (from [redacted]) in July 2023.

Conditioning: Fludarabine/Melphalan with Total Body Irradiation

ID consulted on Day 6 of stem cell infusion due to acute hypoxemic respiratory failure with *Klebsiella pneumoniae* bacteremia.

HPI

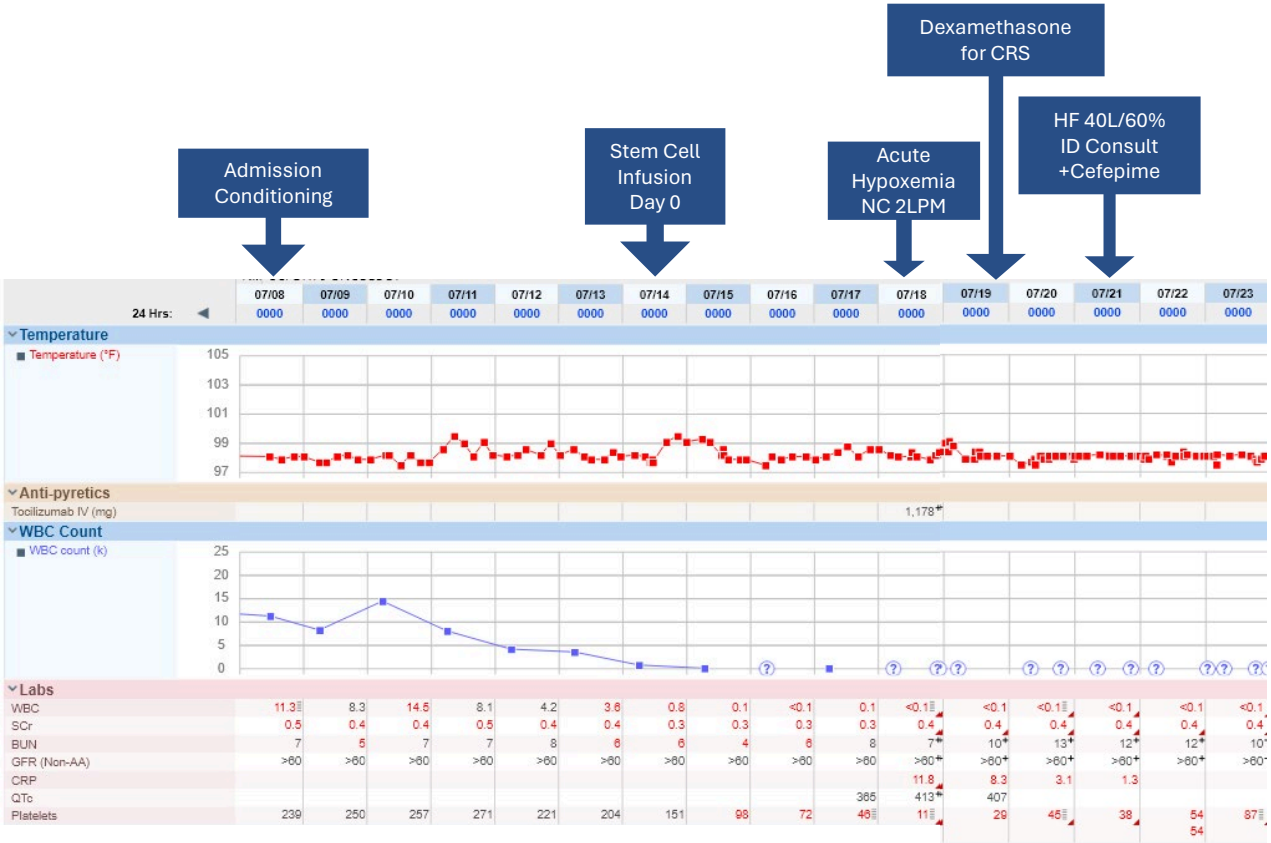
Prior to transplantation, patient has had intermittent postprandial epigastric pain for 6 months.

Pre-transplant workup with EGD and CT Abdomen/Pelvis was negative for obvious etiology.

- **Day 3:** Fatigue, weakness, progressive shortness of breath, and new productive cough. Worsening abdominal discomfort and bloating after meals. Notes feeling of chest heaviness and discomfort with swallowing liquids, throat pain, as well as few loose stools.
- **Day 5:** Started on tocilizumab and dexamethasone due to concern for cytokine release syndrome.
- **Day 6:** Started on cefepime for bacteremia.

Social History

- Born in Mexico, moved to the US several decades prior
- Lives in [redacted], CA
- Previously worked as a truck driver for a shipping company in CA and has been in "every state in the US"
- No known active TB contacts


Admission Conditioning
Stem Cell Infusion Day 0
Acute Hypoxemia NC 2LPM
Dexamethasone for CRS
HF 40L/60% ID Consult +Cefepime
24 Hrs:
07/08 0000
07/09 0000
07/10 0000
07/11 0000
07/12 0000
07/13 0000
07/14 0000
07/15 0000
07/16 0000
07/17 0000
07/18 0000
07/19 0000
07/20 0000
07/21 0000
07/22 0000
07/23 0000
Temperature
Temperature (°F)
105
103
101
99
97
Anti-pyretics
Tocilizumab IV (mg)
1,178
WBC Count
WBC count (k)
25
20
15
10
5
0
Labs
WBC 11.3 8.3 14.5 8.1 4.2 3.6 0.8 0.1 <0.1 0.1 <0.1 <0.1 <0.1 <0.1 <0.1 <0.1
SCr 0.5 0.4 0.4 0.5 0.4 0.4 0.3 0.3 0.3 0.3 0.4 0.4 0.4 0.4 0.4 0.4
BUN 7 5 7 7 8 6 6 4 6 8 7 10 13 12 12 10
GFR (Non-AA) >60 >60 >60 >60 >60 >60 >60 >60 >60 >60 >60 >60 >60 >60 >60 >60
CRP 11.8 8.3 3.1 1.3
QTc 365 413 407
Platelets 239 250 257 271 221 204 151 98 72 46 11 29 45 38 54 54 87

Physical Exam

Temp 97.5 HR 108 RR 24 BP 143/106
SpO2 95% on HFNC 40L/60% FiO2

General: tachypneic

HEENT: neck supple, no LAD, no oral lesions

Heart: tachycardic, no murmurs

Lungs: diffuse crackles, no wheezing

Abdomen: mild epigastric tenderness, nondistended

Extremities: no edema, PICC s/p removal, site clean

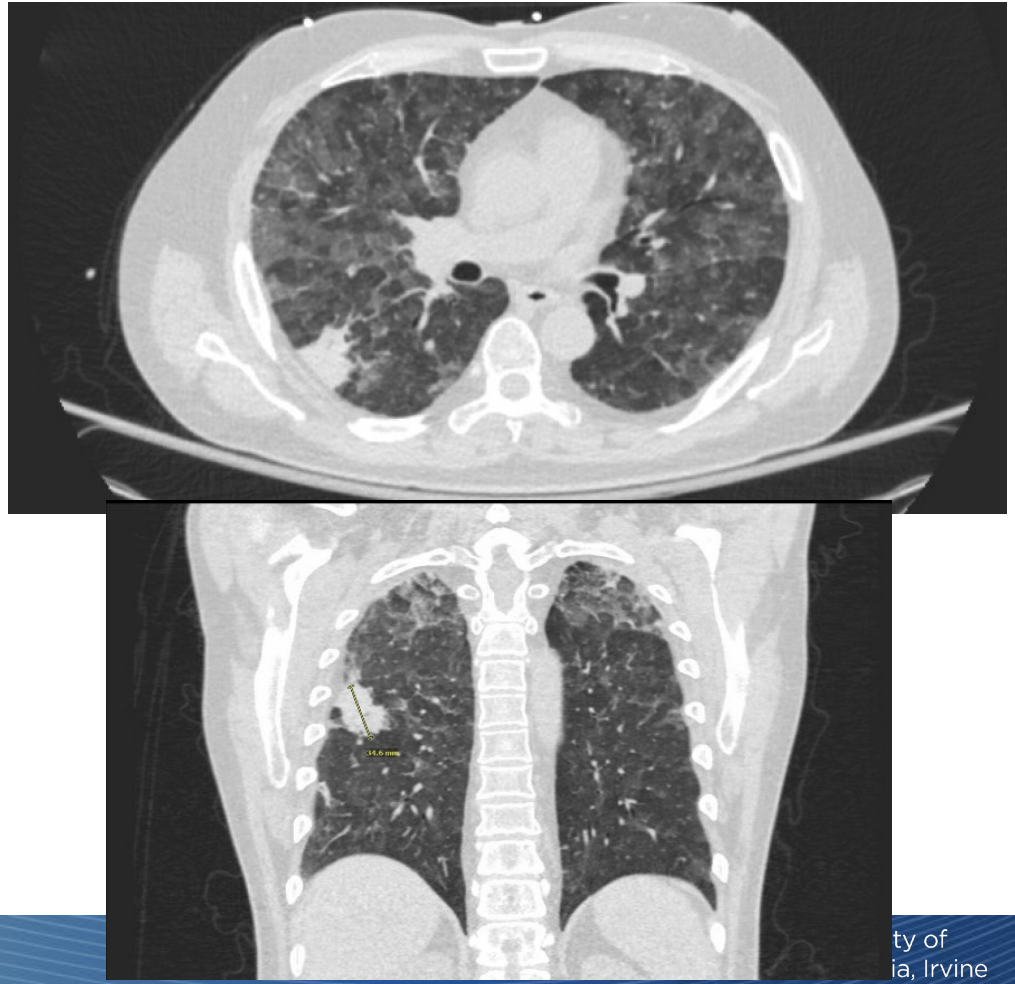
Neuro: grossly intact, alert, and oriented

Skin: no rashes

Imaging

CT Chest (Day 6) Bilateral multiple patchy confluent ground-glass opacities, interlobular septal wall thickening, and few scattered patchy consolidations. Features suggest pulmonary edema with a possible underlying coexistent infectious process.

CT abdomen (Day 6) Mild circumferential mural thickening of the duodenum and proximal jejunum with fluid-filled small and large bowel suggestive of enteritis and rapid transit state.



Pre-Transplant Serologies

- HSV-1 IgG positive / HSV-2 IgG negative
- VZV IgG positive
- Toxoplasma IgG positive
- CMV Donor positive / Recipient negative
- Strongyloides IgG negative
- Coccidiomycoses IgM/IgG negative
- HTLV-1 IgG negative
- HBV surface antibody, surface antigen, core antibody: negative
- HCV antibody: negative
- H pylori Stool Ag: negative
- Quantiferon-TB Gold+ positive (NIL 0.02, TB1-NIL 0.91, TB2-NIL 0.67, Mitogen-NIL 9.98) AFB x3 negative, TB NAAT x1 negative, started on INH/B6 1 mo ago

Labs

WBC < 0.1 Hgb 7.2 Platelets 14 Creatinine 0.4

- Respiratory Viral Panel: +Enterovirus/Rhinovirus
- Blood cultures (Day 5): *Klebsiella pneumoniae* (2/2)
- Stool C difficile PCR w/ reflex to toxin: negative
- Stool Multiplex Panel: negative
- Sputum culture: 2+ normal flora
- Other negatives: Toxoplasma PCR blood, CMV quantitative PCR (serum), HHV-6 Quantitative RT-PCR (serum), HSV Quantitative RT-PCR (serum), Aspergillus Galactomannan, Histoplasma Urinary Antigen, β-D glucan, Legionella Urinary Antigen, AFB sputum w/ TB PCR, Coccidioides serum antibodies and CF, Cryptococcal antigen

Summary

[redacted] year old [redacted] originally from Mexico being treated for LTBI (INH/B6 ~1 mo) who received a stem cell transplant 6 days ago, now with worsening hypoxemic respiratory failure, multifocal pneumonia, enteritis, and *Klebsiella pneumoniae* bacteremia.

[redacted] also has sore throat and dysphagia/odynophagia.

[redacted] received tocilizumab, systemic steroids as well as enteral budesonide.

Microbial Cell Free DNA Reveals the Diagnosis

- Does your institution have any policies or ID restrictions regarding when to send cfDNA testing?
- Would you have sent cfDNA in this scenario?
- What other additional tests would you have sent?

Labs

WBC < 0.1 Hgb 7.2 Platelets 14 Creatinine 0.4

- Respiratory Viral Panel: +Enterovirus/Rhinovirus
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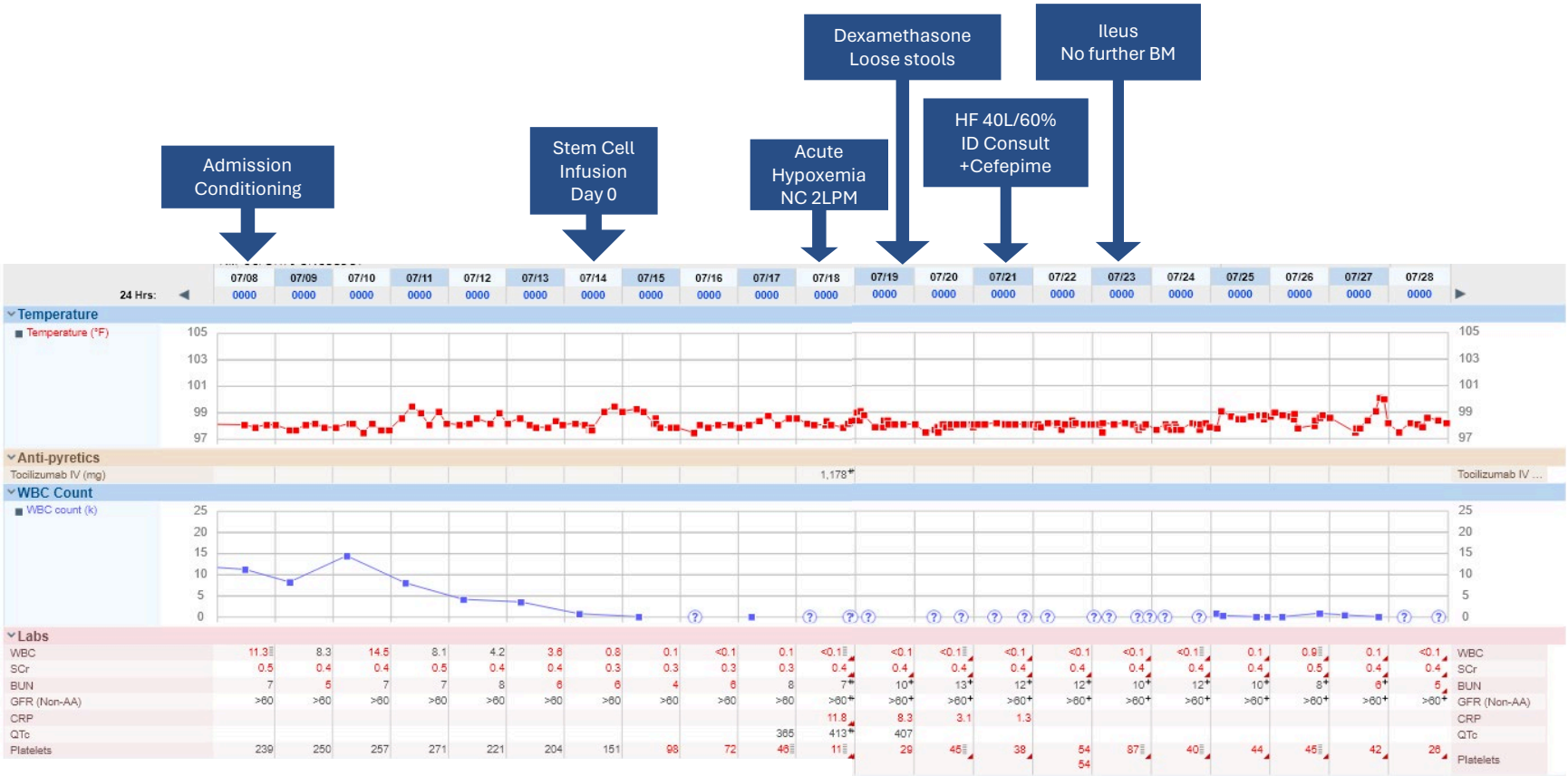
Admission Conditioning
Stem Cell Infusion Day 0
Acute Hypoxemia NC 2LPM
Dexamethasone Loose stools
HF 40L/60% ID Consult +Cefepime
Ileus No further BM
07/08 07/09 07/10 07/11 07/12 07/13 07/14 07/15 07/16 07/17 07/18 07/19 07/20 07/21 07/22 07/23 07/24 07/25 07/26 07/27 07/28
24 Hrs:
Temperature
Temperature (°F)
Anti-pyretics
Tocilizumab IV (mg)
1,178
WBC Count
WBC count (k)
Labs
WBC
SCr
BUN
GFR (Non-AA)
CRP
QTc
Platelets

Microbial Cell Free DNA Reveals the Diagnosis

Pulmonary consultation:

The patient is too hypoxic to undergo bronchoscopy/BAL.

The patient stops having BM with increasing abdominal discomfort.

- Thoughts?

Microbial Cell Free DNA Reveals the Diagnosis

TEST RESULTS

MICROORGANISM DETECTED	DNA MOLECULES PER MICROLITER (MPM)*	REFERENCE INTERVAL (MPM)**
Enterococcus faecium	16,150	< 10
Strongyloides stercoralis	892	< 10
Klebsiella pneumoniae	852	< 10

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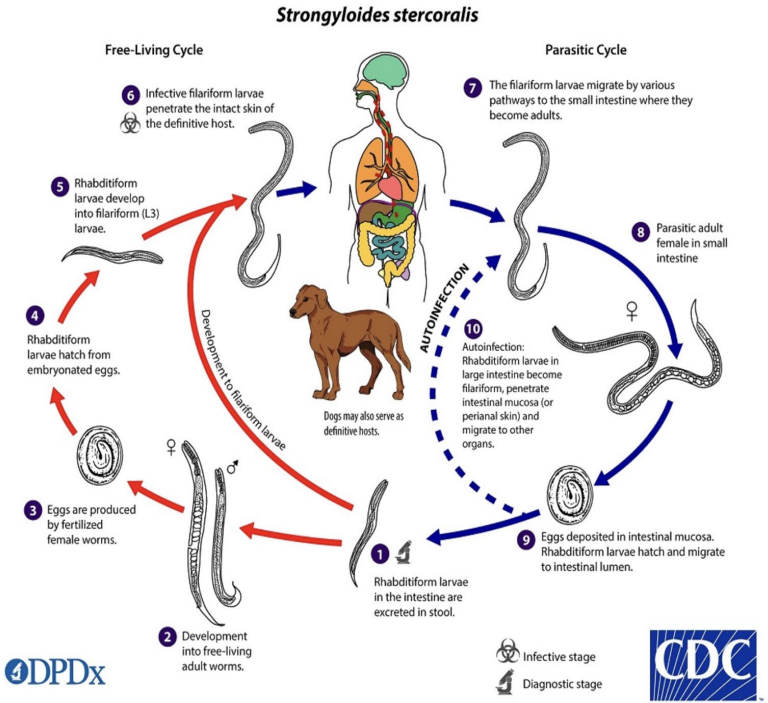
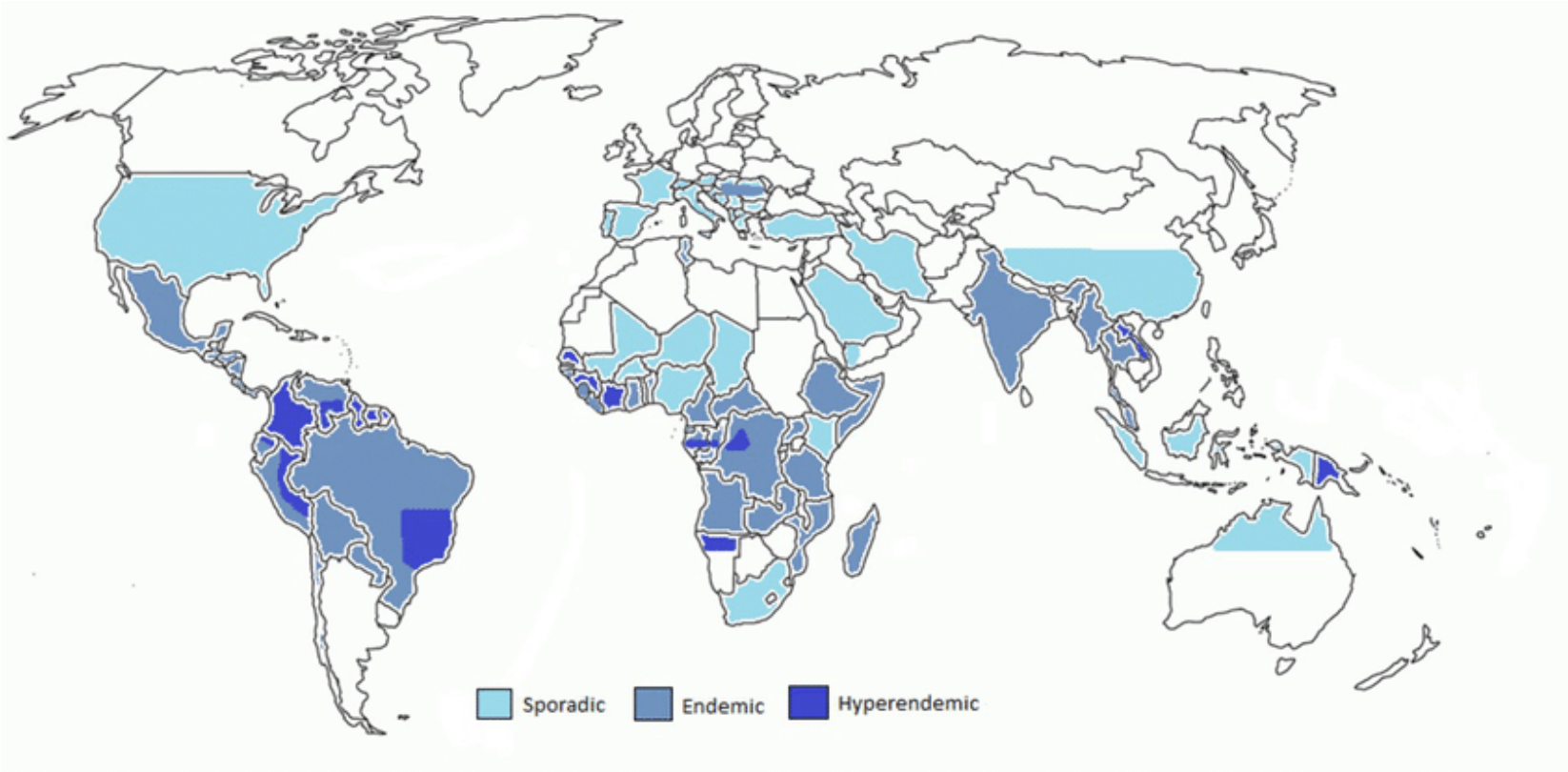
Strongyloides stercoralis Hyperinfection Syndrome

Strongyloidiasis





Longo et al. Neurorad Brain (2015).

Strongyloidiasis Seroprevalence

Disclaimer: Current serological assays cross-react with other nematode infections such as filarial parasites, schistosomes, and Ascaris lumbricoides and likely overestimate the burden of disease

- US
  - Maryland Migrant Farm Workers 4%
  - Tennessee Johnson City Residents 4%
  - Seattle Asian Refugees 2.5%
  - Miami, Florida deceased donors 3.9%
- **Mexico 1.6 – 5.7%**
- Brazil 13%
- Thailand 23.7%
- Okinawa, Japan 5.2%
- China 11.7%
- Australia Aboriginal Communities 35-60%
- Canadian refugees 9-77%
- Spain Migrants 17.2%

- Roxby et al (2009). CID 49(9): 1411-1423.
- Lichtenberger et al (2015). Inf Disease Antimicrobial Agents. http://www.antimicrobe.org/new/t31_dw.html#ref

How good is our judgment on who is at risk for Strongyloides?

38 year-old patient who immigrated from Southeast Asia 5 years prior presents with wheezing and respiratory distress. The patient's peripheral eosinophil count was 900 cells/μL (9%) with normal chest radiograph.

- A survey of 363 residents found that only 9% of US-trained physicians could recognize a case presentation of a person in need of screening for strongyloidiasis
  - Compared with 56% of foreign-trained physicians (Brazil, Singapore, Thailand)
- 23% of US-trained physicians advocated for empiric steroids

- Boulware et al. Am J Med. 2007 Jun; 120(6): 545.e1–545.e8.

Strongyloides Screening Pre-Transplant

- Does your institution have any guidelines for Strongyloides screening before transplantation?
    - Yes, universal screening
    - Yes, if clinical symptoms (wheezing, abdominal pain) or eosinophilia
    - Yes, if from endemic area
        - How do you define endemic areas?
    - No guidelines for Strongyloides screening

How good are Strongyloides Diagnostics?

Method	Chronic Intestinal Strongyloidiasis	Hyperinfection Syndrome
Stool O&P	1 sample with SN 15-30% 7 samples SN ~100%	Larvae easily seen
Stool Culture	SN ~70-90%; not widely available	Not applicable
Eosinophilia	Intermittent	Rare
Serological Testing	Sensitivity ~90% but potential false-positive results	False negative results in immunocompromised patients
Upper GI Endoscopy with Aspirate or Biopsy	Sensitive but invasive	Sensitive but invasive
Skin biopsy of larva currens rash	Insensitive, but helpful if larvae seen	Insensitive, but helpful if larvae seen
Body Fluid Wet Mount	Not applicable	Larvae easily seen

Immunity against Strongyloidiasis

- B lymphocytes are essential to develop resistance to larval *S. stercoralis*
  - IgM and IgG antibodies are protective against autoinfection larvae
  - Increased IgG4 antibodies are associated with albendazole resistance
- Both eosinophils and neutrophils are required for protective innate immune response
  - Eosinophil levels may play key roles in preventing *S. stercoralis* infection
- Only neutrophils are necessary for the protective adaptive immune response

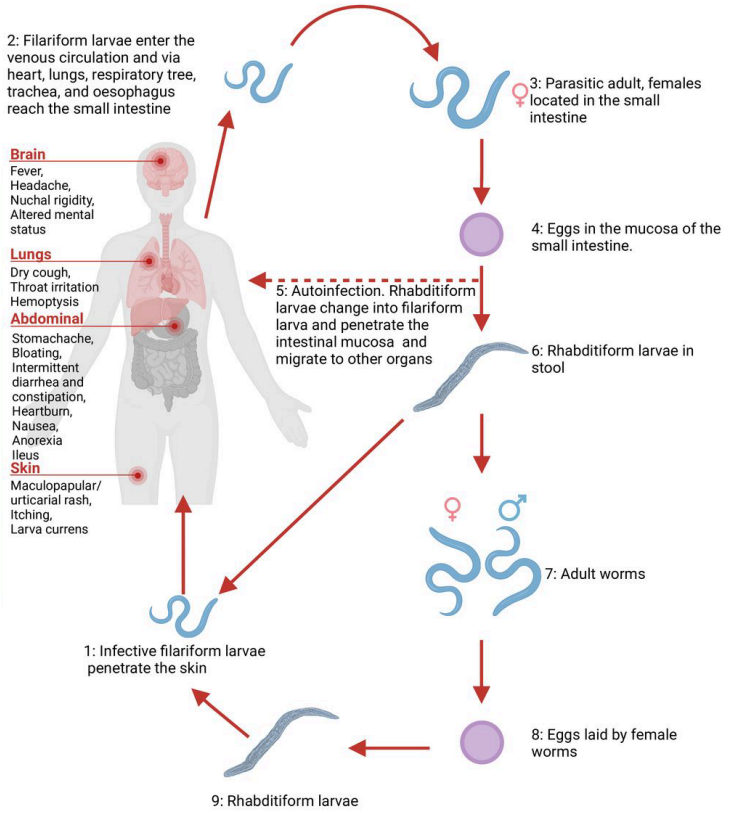
Strongyloides Serology in Immunocompromised

- **Inclusion Criteria:**
  - Corticosteroids
  - Immunosuppressive drugs
  - Chemotherapy
  - Hematological malignancies
  - Solid organ transplantation
  - HIV-infected patients who were symptomatic with opportunistic infections and/or had $CD4^+$ cells < $200/mm^3$
- **Only 42.9% sensitive (positive predictive value)** but 96.3% specific (negative predictive value)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4973189/.

Strongyloidiasis Hyperinfection Syndrome

- Extensive larval proliferation leads to systemic sepsis and multi-organ failure: Shock, disseminated intravascular coagulation, bowel obstruction/perforation, meningitis, renal failure and respiratory failure.



- Roxby et al (2009). CID 49(9): 1411-1423.
- Iriemenam et al (2010). Parasitology International 59(1): 9-14.

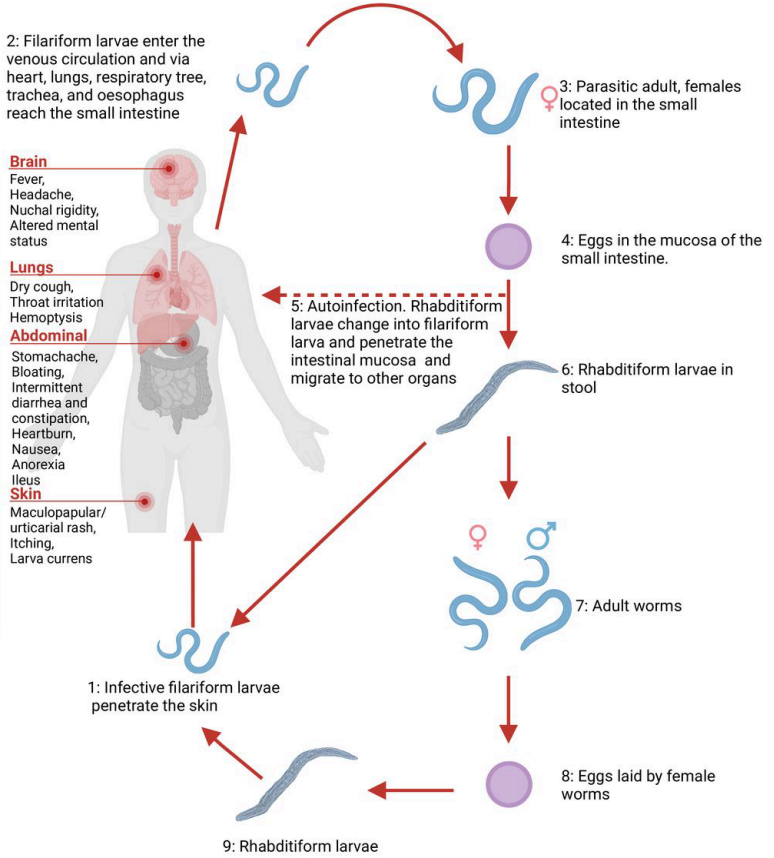
Strongyloidiasis Hyperinfection Syndrome

- Can be seen with steroid use, hypogammaglobulinemia, HTLV-1 infection, and post-transplant immunosuppression
  - **HTLV-1** infects T cells and leads to total serum IgE, IL-5 responses; decreased IgG4 can reduce therapeutic efficacy
  - In contrast, although HS is seen in advanced HIV, HIV infection alone does not obviously augment the odds of systemic infection
  - **Steroids** can act directly act on parthenogenic females to hasten transform into filiariform larvae and increase oviposition

- Roxby et al (2009). CID 49(9): 1411-1423.
- Iriemenam et al (2010). Parasitology International 59(1): 9-14.

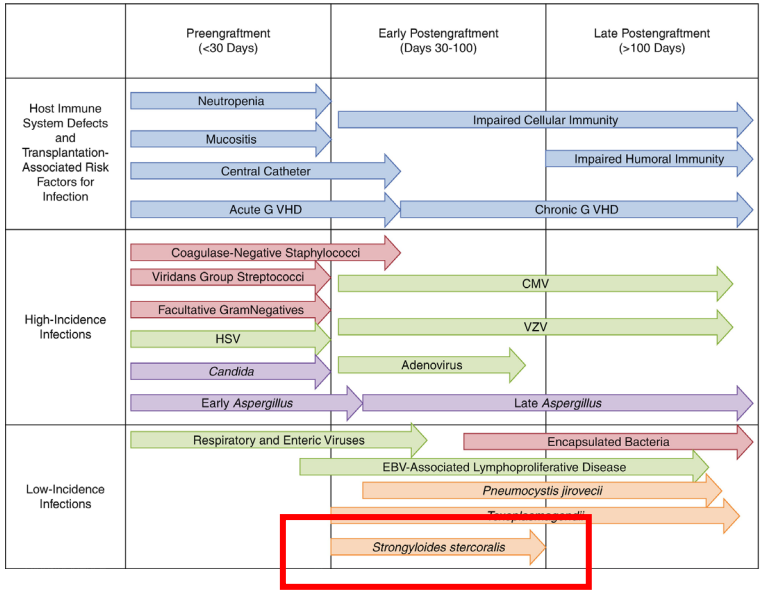
Strongyloidiasis Disseminated Infection

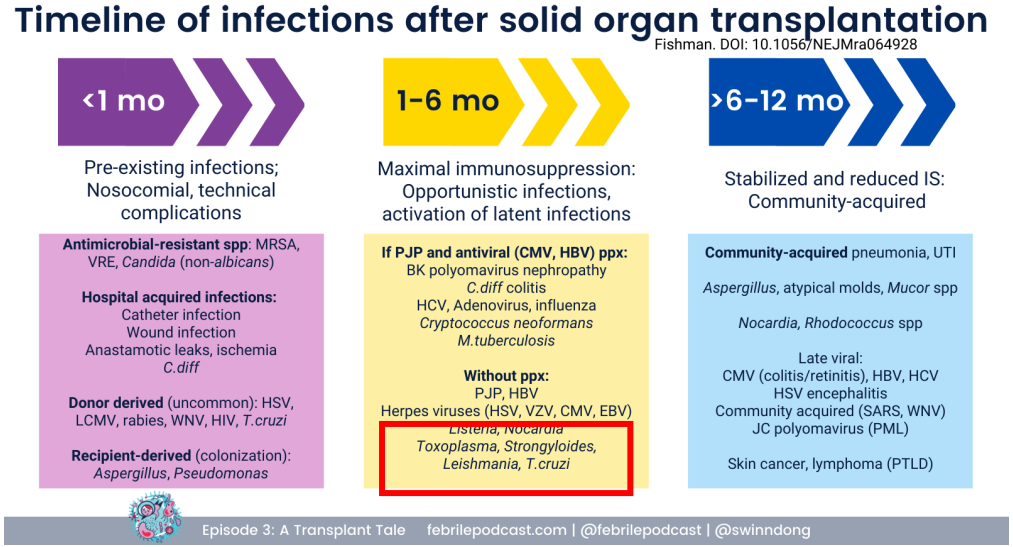
- Normally, the larvae are present in the traditional life cycle sites such as the skin, gastrointestinal tract or lungs.
- Disseminated Disease is when larvae are found in alternative sites such as heart, brain, muscle, etc.,



Pedersen et al (2022). BMJ Case Reports 15(9): e247032

Strongyloidiasis Timeline in Transplant





- Fishman (2007). NEJM 357 (25):2601-14.
- Pereira et al (2019). Principles and Practice of Transplant Infectious Diseases. Chapter 10: Infections in Allogeneic Stem Cell Transplant.

Strongyloidiasis in Transplantation

Characteristics	Total (n=108)	SOT (n=91)	HCT (n=15)
Median time to clinical presentation from day of transplant, in weeks (range)		**10.8 (.14–417)**	**8.8 (0–208)**
Initial presenting symptoms, *n*	108 (100)	93 (100)	15 (100)
GI	49 (45.4)	40 (43)	9 (60)
Respiratory	14 (12.9)	13 (13.9)	1 (6.7)
Other[e]	10 (9.3)	9 (9.7)	1 (6.7)
GI + respiratory	9 (8.3)	8 (8.6)	1 (6.7)
Respiratory + other	4 (3.7)	3 (3.2)	1 (6.7)
GI + respiratory + other	9 (8.3)	7 (7.5)	2 (13.2)
Asymptomatic	2 (1.9)	2 (2.2)	–
NR	2 (1.9)	2 (2.2)	–
Fever, Y	31/103 (30)	26/88 (29.5)	5/15 (33.3)
Rash, Y	22/108 (20.4)	22/93 (23.7)	0/15 (0)

Abad et al (2022). Clin Transplant 36(11): 314795.

Strongyloides in Transplantation

- *Strongyloides* hyperinfection clinical diagnosis is often delayed at a mean of 5 days after hospital presentation
- Mortality:
  - Hospitalization required: 16.7%
  - Hematopoietic stem cell transplant recipients: 50-85% [Wirk et al (2009) Transpl Infect Dis 11:243-9].
  - Renal transplant recipients: up to 50% [De Vault et al (1990) Rev Infect Dis 12:653-71, Turner et al (2005), Am J Trop Med Hyg 73:991-4].
- Prognosis appears to be improved for patients with elevated eosinophil counts and for patients whose corticosteroid treatment is rapidly tapered

Strongyloidiasis in Transplantation

Characteristics	Total (n=108) (%)	SOT (n=91) (%)	HCT (n=15) (%)
Peripheral eosinophilia, Y	41/77 (53.2)	34/67 (50.7)	7/10 (70)
Prior to transplant	11 (26.8)	7 (20.6)	4 (57.1)
Prior and during illness	1 (2.4)	1 (2.9)	–
Prior to transplant, on retrospective review	3 (7.3)	2 (5.9)	1 (14.3)
***Strongyloides* disease spectrum**	108 (100)	93 (100)	15 (100)
Hyperinfection Syndrome	97 (89.8)	84 (90.3)	13 (86.7)
Disseminated Strongyloidiasis	11 (10.2)	9 (9.7)	2 (13.3)
Outcome			
Graft loss	5/108 (4.6)	5/93~ (5.4)	0/15 (0)
Death, Y	48/107 (44.9)	40/92 (43.5)	8/15 (53.3)
Attributable mortality	32/48 (66.7)	27/40 (67.5)	5/8 (62.5)

Abad et al (2022). Clin Transplant 36(11): 314795.

Strongyloides Treatment Pre-Transplant

- Does your institution have any guidelines that recommend pre-transplant treatment for Strongyloides regardless of serological studies?
  - Yes, universal prophylaxis
  - Yes, if patient is from an endemic region
  - Yes, if HTLV-1/2 IgG positive
  - Yes, based on symptoms pre-transplant
  - No
  - Other

Treatment of Strongyloidiasis Pre-Transplant

- Current clinical guidelines recommend **empirical treatment** for strongyloidiasis before hematopoietic stem cell transplantation and solid-organ transplantation for patients with **exposure to areas of endemicity**, even if results of diagnostic testing are negative
    - How are areas of endemicity defined?

Roxby et al (2010). CID 49(9): 1411-1423.

Food for Thought: From Dr Morris (UMiami)

"We had the same sad experience with false negative testing at Miami, with some terrible outcomes. Our Strongyloides IgG positivity rate in the solid organ population was close to 12% when we analyzed it 7 years ago. [...] Since we consider Miami an endemic area, **we now treat 100% of our transplant candidates pre-transplant.** This is the protocol used in Brazil and many other South American transplant centers."

- Cellular therapy patients (SCT & CAR-T) are given 2 days of ivermectin on admission with repeat dosing 2 weeks later. If already treated at the initiation of their cancer, doses are still repeated.
- HTLV-1 patients are re-treated monthly during the time of maximum immunosuppression, as relapses have still been seen with dissemination after adequate treatment.
- All solid organ transplant donors are screened with recipients re-treated if the donor is either from a high-risk area or Strongyloides screen positive.
- OPO gives a dose of ivermectin (NG) in local positive deceased donors.

Strongyloides Hyperifection Treatment

- Do you have experience utilizing any of the alternative regimens for treatment of Strongyloides hyperinfection (multiple answers)?
  - Ivermectin po
  - Albendazole po
  - Ivermectin + Albendazole po
  - Ivermectin Subcutaneous
  - Ivermectin Enema

	Chronic intestinal strongyloidiasis		Disseminated strongyloidiasis or hyperinfection syndrome	
Drug	Treatment regimen	Notes	Treatment regimen	Notes
First choice: ivermectin	200 µg/kg orally once a day for 2 days; consider a repeat dose after 2 weeks	Verify cure. Immunocompromised hosts may require longer duration and/or suppressive therapy.	200 µg/kg orally once a day, until larvae are not detected at any site; repeat 1 dose at 2 weeks after clearance of larvae	Consider intravenous ivermectin in severe cases or rectal or subcutaneous ivermectin (not FDA approved). Consider combination therapy with albendazole.
Second choice				
Albendazole (not FDA approved)	400 mg orally twice a day for 3 days	Verify cure or consider a repeat dose after 2 weeks. Immunocompromised hosts may require longer duration and/or suppressive therapy	400 mg orally twice a day, until larvae are not detected at any site	Consider combination therapy with ivermectin
Thiabendazole	25 mg/kg orally twice a day for 3 days	Verify cure or consider a repeat dose after 2 weeks. Immunocompromised hosts may require longer duration and/or suppressive therapy	25 mg/kg orally twice a day, until larvae are not detected at any site	Consider combination therapy with ivermectin

- Roxby et al (2009). CID 49(9): 1411-1423.

Our Patient

- All steroids stopped immediately
  - 20% eosinophils noted on only one CBC pretransplant (in setting of leukopenia, low absolute counts)
  - Eventually Stool O+P was collected Day 14, but both negative
- Started on po ivermectin and albendazole on Day 9 with gradual improvement → continued until engraftment
- Cefepime and Daptomycin
- Doing well at follow up but with occasional recurrence of post-prandial abdominal pain (every other month or so) with resolution following re-treatment

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Thank you!