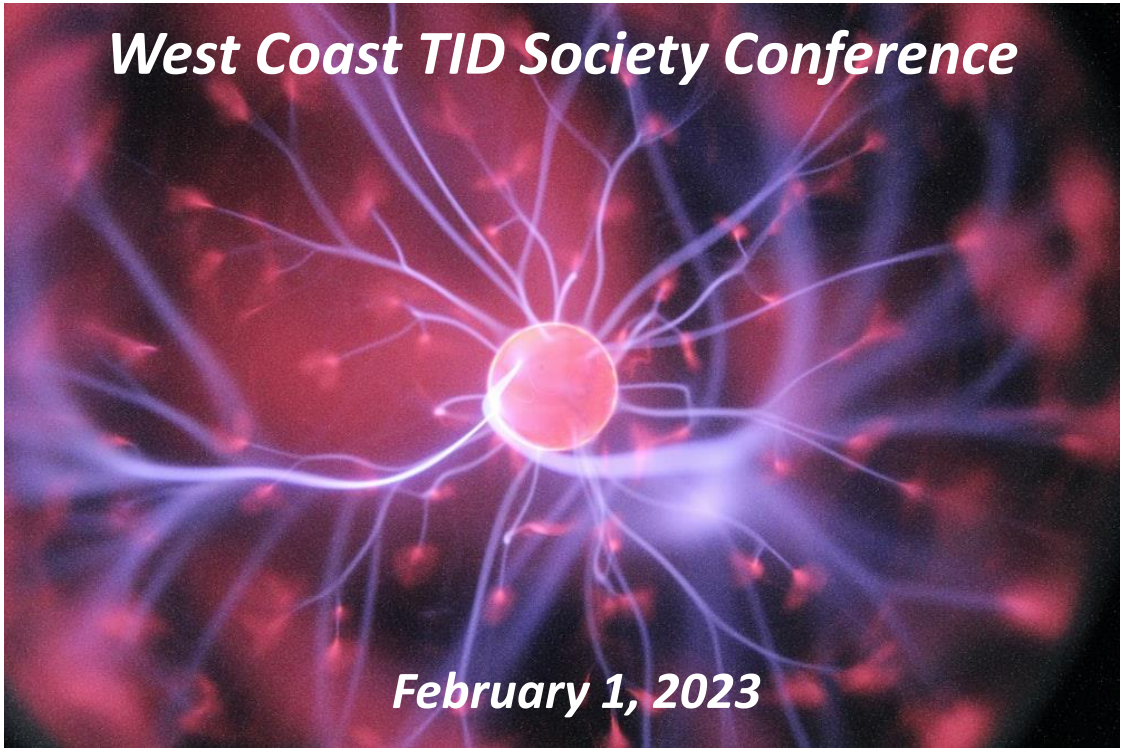
An Unusual Cause of Encephalopathy post allo-SCT



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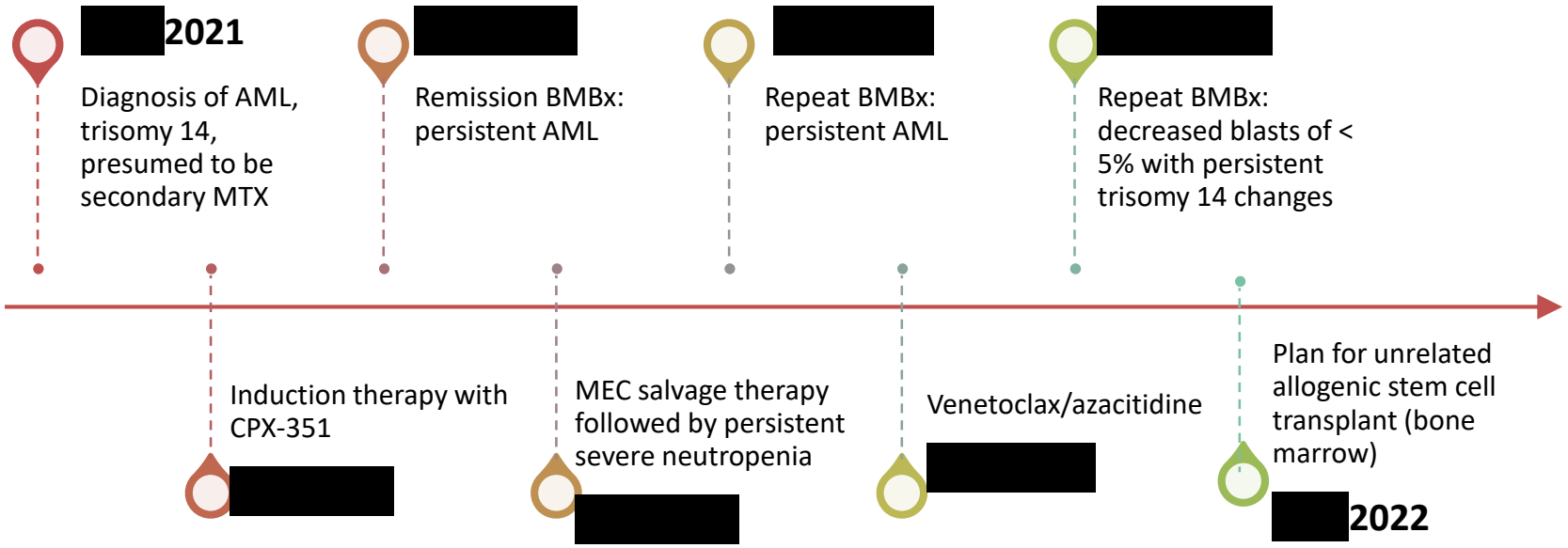
Vancouver CoastalHealth

Case

- A [redacted] in [redacted] with the following past medical history:
  - Psoriasis treated with methotrexate
  - HTN
  - [redacted]
  - Latent TB infection (untreated)

Hematological diagnosis



Case

Pre-transplant course

- **Febrile prior** to starting **conditioning chemotherapy**
  - Started on meropenem (piperacillin-tazobactam and ceftazidime drug eruptions)

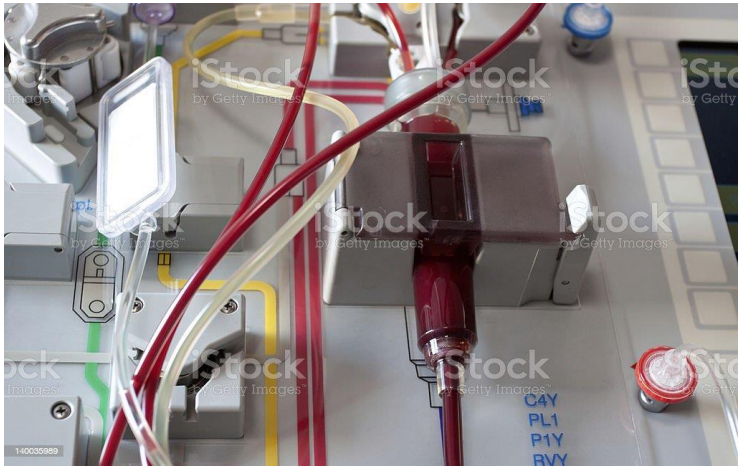
- CT chest:
  - **Left upper lobe cavitating consolidation** with surrounding GGO
  - Bronchoscopy: **Fungal organisms** seen on **cytology**; fungal culture grew ***Aspergillus fumigatus*** within 7 days (serum galactomannan negative)
  - Started on liposomal amphotericin B (L-AmB)
    - ✓ Defervesced with radiographic improvement at 2 weeks

- **Transplant delayed** by 3 weeks

Case

Transplant details

- ❑ Type: 10/10 matched unrelated donor
- ❑ Conditioning chemotherapy: MA Busulfan, fludarabine, ATG
- ❑ GVHD prophylaxis: Cyclosporine + MTX
- ❑Serologies: EBV/HSV-1/VZV **seropositive**, CMV/Toxoplasma **seronegative**



Case

Post-transplant course

- Course complicated by:
  - **Severe mucositis** with bleeding (large clot in the oropharynx)
  - D+9 transferred to **ICU** for airway protection and to facilitate removal of the clot
  - **Dexamethasone** 10 mg bid x 3 days
  - D+11 extubated

- Antimicrobials:
  - Acyclovir IV (prophylaxis)
  - Antibiotics: Meropenem (empirical) continued post febrile neutropenia
  - Antifungals: L-AmB for invasive pulmonary aspergillosis

Case

Post-transplant course

- D+13: **Re-intubated for ↓ LOC**, agitation and re-bleeding

- *En* route to CT head, witnessed **generalized tonic-clonic seizure**
  - Aborted with propofol, midazolam and diazepam
  - Loaded on levetiracetam
  - Refractory **status epilepticus**:
    - ✓ Propofol, midazolam, ketamine, levetiracetam, lacosamide
    - ✓ EEG confirms **ongoing seizure activity** despite multiple antiepileptics

Case

- **Laboratory investigations**
  - WBC < 0.1 x 10^9/L
  - INR 1.3, fibrinogen > 9 g/L
  - pCO2 29-40 mmHg
  - Peripheral blood smear: **No microangiopathic features**
  - Total bilirubin **86 µmol/L (5.3 mg/dL),** ↓ from 112 µmol/L (6.5 mg/dL)
    - ✓ Direct 71 µmol/L (4.2 mg/dL)
    - ✓ ALT 18 U/L, AST 6 U/L, alkaline phosphatase 130 U/L

Case

- **Laboratory investigations (cont'd)**
  - Cyclosporine level: 210 µg/L
  - Creatinine **129 µmol/L (1.46 mg/dL)**
    - ✓ **Baseline** pre-L-AmB **30 µmol/L (0.34 mg/dL)**
  - Na+ 140 mmol/L, calcium 2.5 mmol/L (adjusted to albumin)
  - Glucose **37.4 mmol/L/673.8 mg/dL** [(3.6-11.0 mmol/L/65-198 mg/L)]
  - CMV < 35 IU/mL and EBV < 1000 copies/mL

Case

Post-transplant course

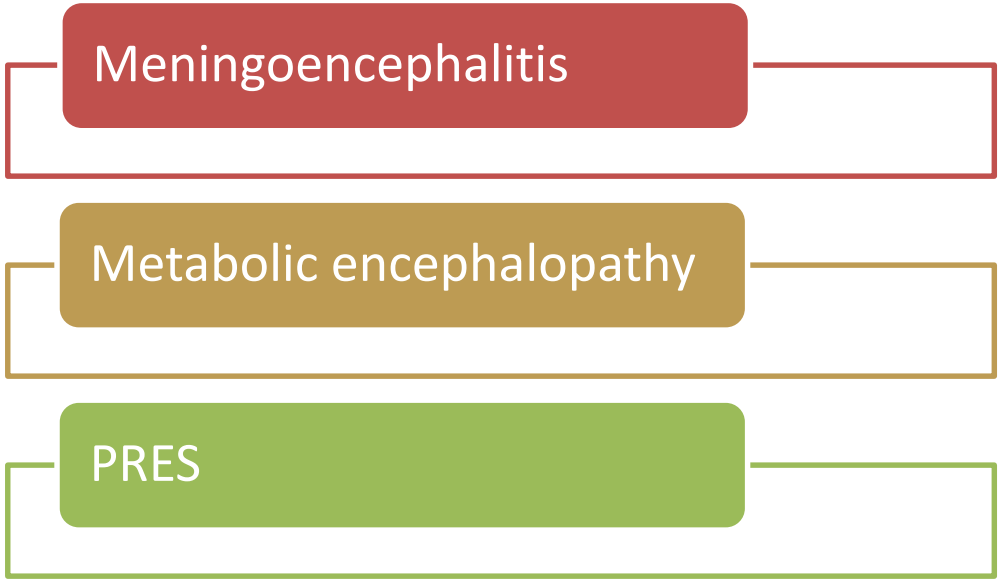
- **AKI** 2nd L-AmB
  - Switched to Posaconazole
- **Hyperbilirubinemia**
  - Presumed to be 2nd to TPN and MTX
- **CT head** (non-contrast): **No** definitive **acute intracranial pathology**

Question 1

What do you think is the most likely cause of the status epilepticus?
(Please add free text)

Case

Differential Diagnoses?



Case

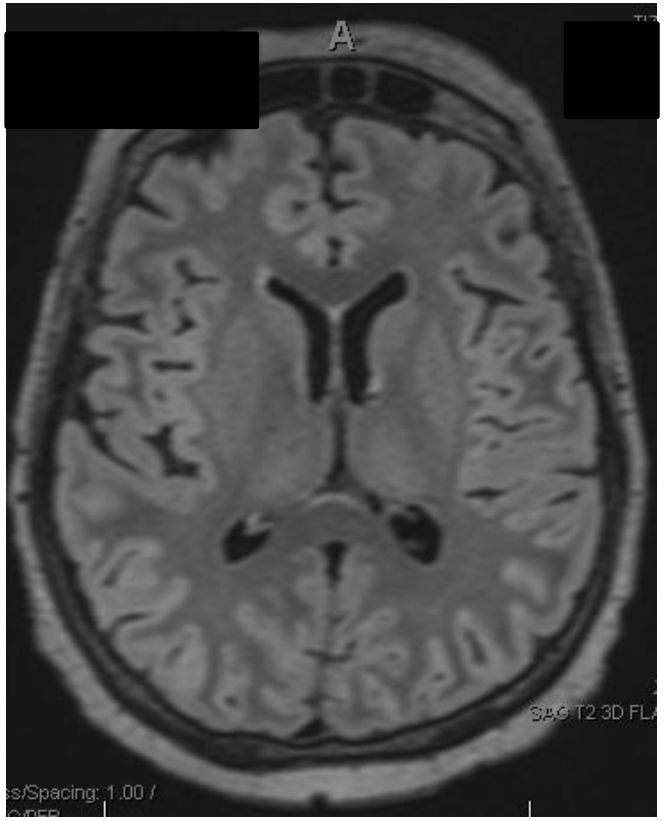
- **Cerebrospinal fluid (CSF) part 1**
  - ✓ WBC < 1 x 10^6/L
  - ✓ Glucose 9 mmol/L (162 mg/dL) [(2.3-4.1 mmol/L/41-74 mg/L)]
  - ✓ Protein 0.6 g/L (< 0.45 g/L)
  - ✓ Bacterial and fungal cultures: **negative**
  - ✓ HSV, VZV and enteroviral NAT: **negative**
  - ✓ CSF CrAg: **negative**

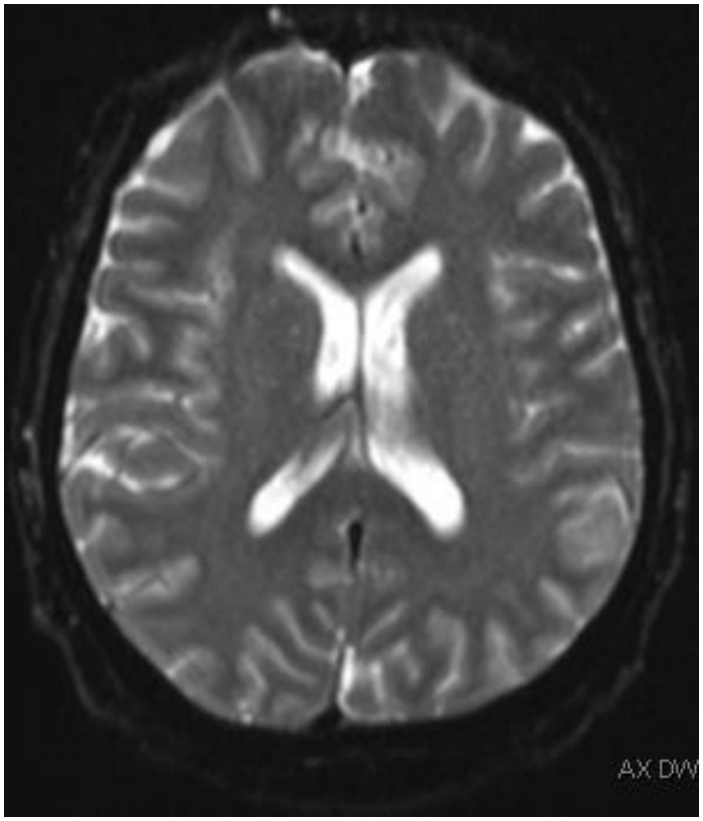
Case

- **Cerebrospinal fluid (CSF) part 2**
  - Multiplex NAT:
    - ✓ *N. meningitidis, S. pneumoniae, H.influenzae, E. coli* K1 NAT: **negative**
    - ✓ *Listeria monocytogenes* NAT: **negative**
    - ✓ CMV, HHV-6, VZV, HSV, enterovirus, parechovirus NAT: **negative**
    - ✓ *Cryptococcus neoformans/gattii* NAT: **negative**

Case

- **MRI brain**



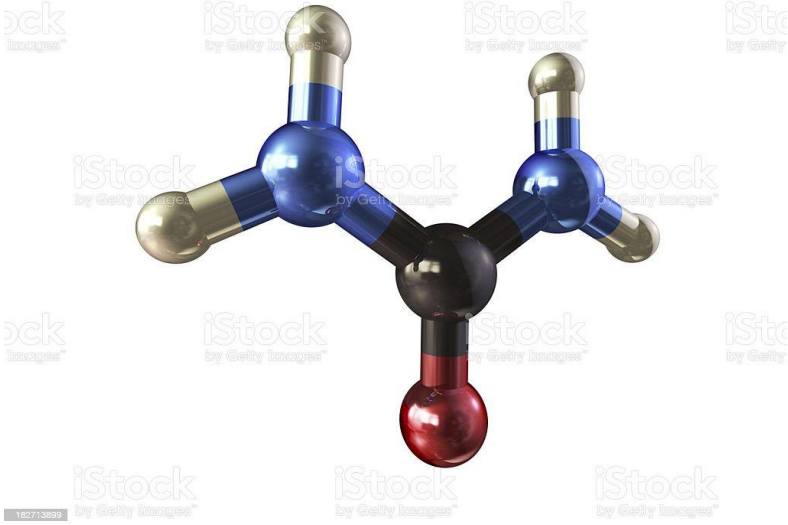


- **Extensive cortical restricted diffusion/cytotoxic edema**, with additional cytotoxic edema in the thalami bilaterally
- **No white matter abnormality**

Case

❑ Laboratory investigations (cont'd)

- **Ammonia 339 µmol/L** (reference range: < 35 µmol/L)



- Metabolic testing: No primary amino acid or urea cycle disorder

Question 2

What other diagnostics would you add?

1. Send CSF for 16S

2. Microbial cell-free DNA (Karius®)

3. Send urine, plasma and CSF for *Mycoplasma* and *Ureaplasma spp*. culture

4. Send urine, plasma and CSF for *Mycoplasma* and *Ureaplasma spp*. PCR

5. Other (please comment on chat)

Question 3

What immediate treatment would you recommend?

1. Start levofloxacin and azithromycin
2. Start moxifloxacin and doxycycline
3. Start moxifloxacin, doxycycline and azithromycin
4. Start moxifloxacin, doxycycline, lactulose and rifaximin
5. Start moxifloxacin, doxycycline, metronidazole, lactulose and rifaximin

Case

- **Treatment course**
  - Doxycycline & moxifloxacin
  - Rifaximin and lactulose
  - D+15: Neutrophil engraftment
  - D+20: Poor neurological status, goals of care changed to comfort measures
    - ✓ Passed away shortly after coming off the ventilator

Case

Additional investigations (resulted post-mortem)

- Urine: ***Ureaplasma parvum*** **DNA detected by PCR**
- CSF: 16S negative

Question 4

Have you ever seen a patient with *Ureaplasma/M.hominis* hyperammonemia syndrome following allogeneic-SCT?

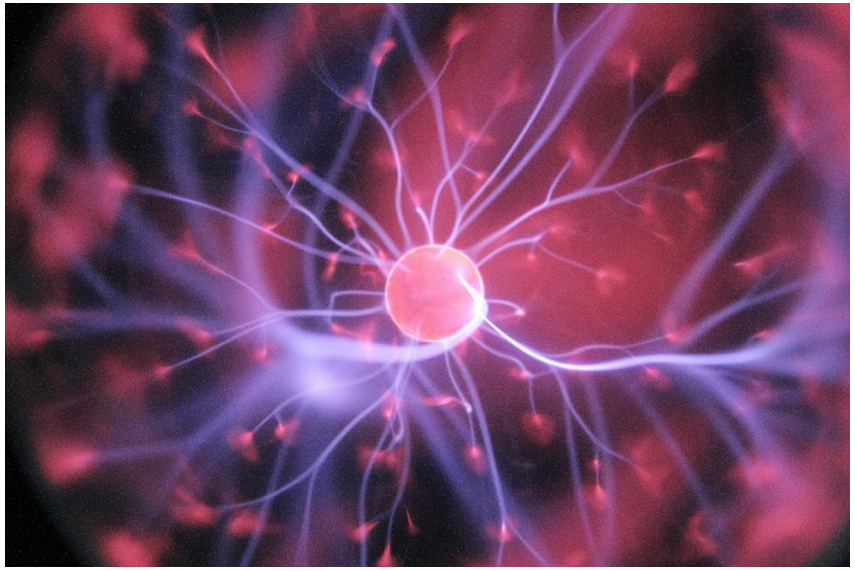
1. Yes
2. No

Review

Hyperammonemia Syndrome (HS)

- Frequently fatal syndrome characterized by ↑ serum ammonia levels and progressive neurologic dysfunction in the absence of liver dysfunction
  - Ranges from confusion or lethargy to cerebral edema, seizures (including status epilepticus) and brain herniation

Roberts SC et al. Curr Opin Infect Dis. 2022
Tantengco OAG et al. Clin Transplant. 2021



Review

Hyperammonemia Syndrome (HS)

- First cases HS (idiopathic) reported in 3 patients with acute leukemia by Watson in 1985
  - Lichtenstein reported the 1st case following lung transplantation (LT) in 1997

Lichtenstein GR et al. Gastroenterology. 1997
Watson AJ et al. Lancet. 1985

- HS was previously hypothesized to be related to unmasking of an inborn error of metabolism induced by the introduction of CNIs post-transplantation

- Experimental immunocompromised murine models later demonstrated that *Ureaplasma urealyticum and Ureaplama parvum* cause hyperammonemia

Kurihara C et al. Transplantation. 2021
Wang X et al. PLoS One. 2016
Wang X et al. Eur J Clin Microbiol Infect Dis. 2017

Review

Ureaplasma & *M. hominis* pathogenesis and disease

- *Ureaplasma spp.* contain highly active ureases
  - *Ureaplasma spp.*
    - ✓ Hydrolyzes urea into CO_2 and ammonia to obtain free energy

- *Mycoplasma hominis*
  - ✓ Uses arginine during energy production which may increase subsequent ammonia level as a byproduct

Kurihara C et al. Transplantation. 2021
Nowbakht C et al. Open Forum Infect Dis. 2019

Ureaplasma & M. hominis pathogenesis and disease

- *M. hominis* and *Ureaplasma spp*. has been found in 21%-53% and 40-80% in the lower genital tract of adult women, respectively
  - Lower rates of colonization in men
  - Association with GU infections (PID and NGU)
  - Extragenital: Septic arthritis & osteomyelitis, wound infections, pneumonia, endocarditis, meningoencephalitis

Glanville AR et al. Transplantation. 2021
Taylor-Robinson D. Clin Infect Dis. 1996
Madoff S et al. Rev Infect Dis. 1988

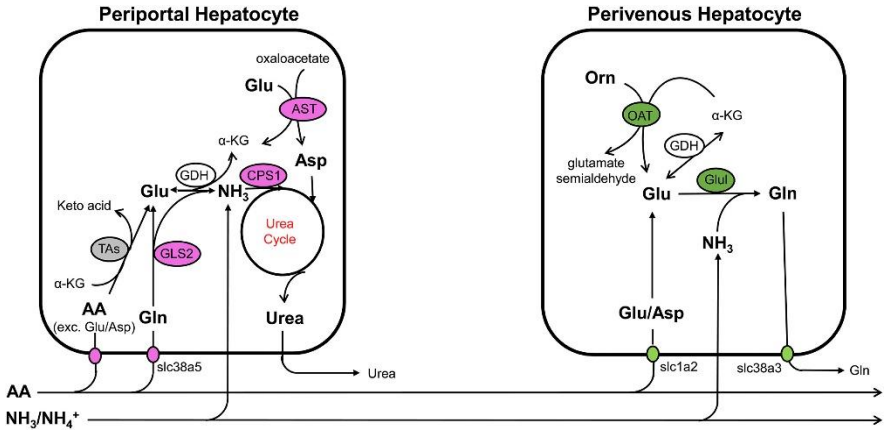
Hyperammonemia Syndrome (HS)

- Causality between systemic infection with *Ureaplasma spp. (U.parvum and U.urealyticum)* and *Mycoplasma hominis* and HS in immunocompromised hosts was later established

Bharat A et al. Sci Transl Med. 2015

- Studies have identified substantial hepatic glutamine synthetase deficiency
  - Transient downregulation?

Kamel AY et al. Transpl Int. 2022



Zhou Y et al. Neurochem Int. 2020

Review

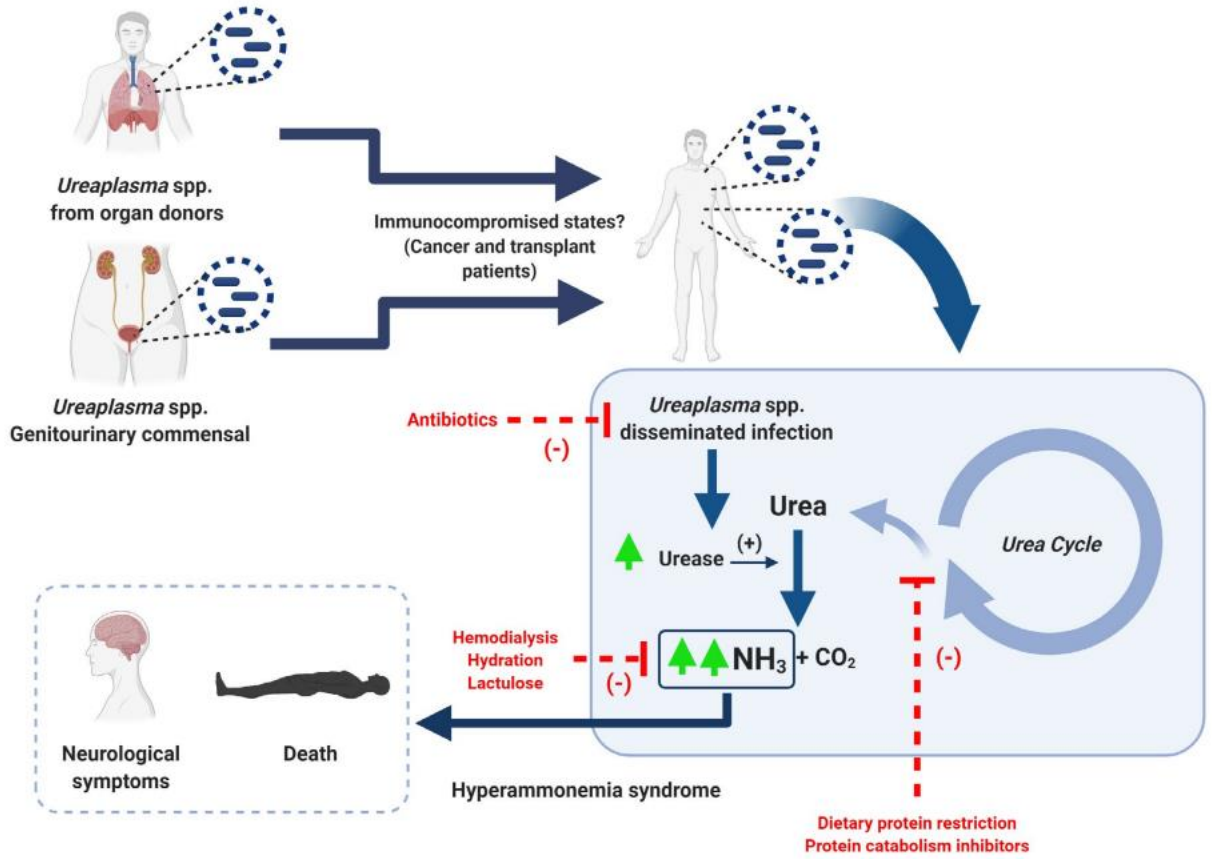


FIGURE 3 Schematic representation of the proposed pathophysiology of hyperammonemia syndrome (HS) caused by Ureaplasma spp. infections and the mechanism of action of therapeutic strategies for HS

Tantengco OAG et al. Clin Transplant. 2021

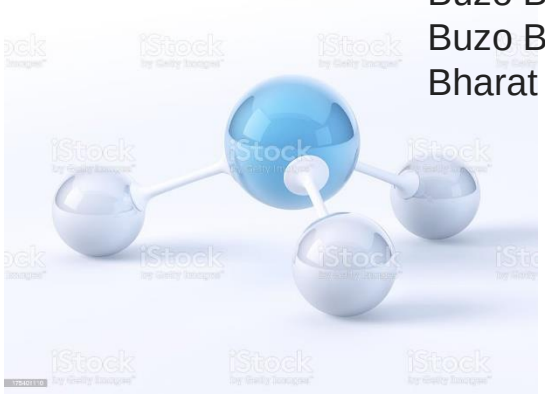
Review

Hyperammonemia Syndrome (HS)

- Well recognized complication after lung transplant (LT)
  - Frequencies from 1 to 4%, mortality up to 75%
  - Often in the first 2 weeks of transplant (mean 11 days)
  - Likely acquired through donor airway colonization/infection

- Also reported after kidney, liver, heart, intestinal, islet transplants as well as hematologic malignancies including following allogeneic SCT and CAR T-cell therapy

Roberts SC et al. Curr Opin Infect Dis. 2022
Tantengco OAG et al. Clin Transplant. 2021
Buzo BF et al. Transpl Infect Dis. 2022
Buzo BF. Am J Transplant. 2021
Bharat A et al. Sci Transl Med. 2015



Review

Hyperammonemia Syndrome (HS)

- A study showed U. *urealyticum* and U. *parvum* produce more ammonia under uremic conditions in LT recipients
  - Plausible contributing factor to *Ureaplasma*-induced HS

Fleming D et al. Microbiol Spectr. 2022

- SR assessing 49 LT cases with HS
  - The mean serum ammonia level at diagnosis was 326 umol/L
  - 36.6% had different grades of cerebral edema
  - 88% positive for *Mycoplasma/Ureaplasma spp*.
    - ✓ *U. urealyticum* 56%, *U. parvum* 31.2% and *M. hominis* 31.2%
    - ✓ 18.7% co-infected
  - Fatality rate 59.1%
    - ✓ 91.6% of those with any grade of cerebral edema and 60% of those with seizures

Buzo BF et al. Transpl Infect Dis. 2022

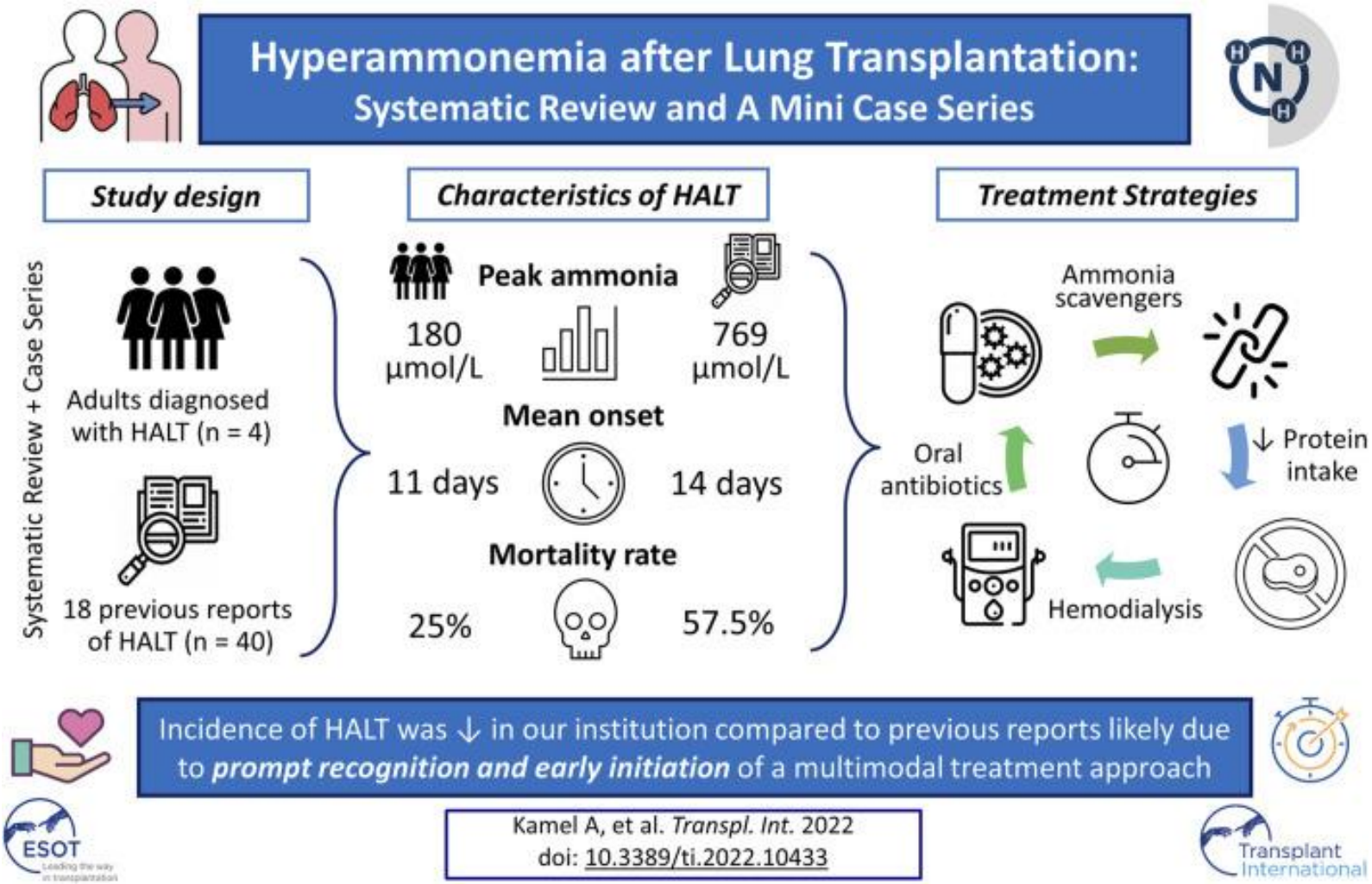
Review

Hyperammonemia Syndrome (HS)

- Single-center study, 159 LT adult patients underwent prospective early surveillance with a *Mycoplasmataceae* 16S rRNA gene detection PCR (2017-2019)
  - 42 (26.4)% had a *Ureaplasma* or *Mycoplasma* airway positive PCR
    - ✓ *M. salivarum* 59%, *U. parvum* 15.9%, *U. urealyticum* 11.3%, *M. hominis* 6.8% and *M. pneumoniae* 4.5%
    - ✓ 4.7% co-infected
    - ✓ HS in 3 (*U. parvum*, *U. urealyticum* and *M. hominis*, 2 co-infected), 1 death
  - ***M. salivarium*** and ***M. pneumoniae*** **not associated** with HS
  - Mean peak ammonia levels were higher in those colonized with *Ureaplasma spp. (p*=0.04*)*
  - On multivariate regression, *Ureaplasma spp*. positivity was associated with younger and female donors

Buzo BF. Am J Transplant. 2021

Review


Hyperammonemia after Lung Transplantation:
Systematic Review and A Mini Case Series
Study design
Systematic Review + Case Series
Adults diagnosed with HALT (n = 4)
18 previous reports of HALT (n = 40)
Characteristics of HALT
Peak ammonia
180 µmol/L
769 µmol/L
Mean onset
11 days
14 days
Mortality rate
25%
57.5%
Treatment Strategies
Ammonia scavengers
Oral antibiotics
↓ Protein intake
Hemodialysis
Incidence of HALT was ↓ in our institution compared to previous reports likely due to prompt recognition and early initiation of a multimodal treatment approach
Kamel A, et al. Transpl. Int. 2022
doi: 10.3389/ti.2022.10433
ESOT
Transplant International

Review

Data in allogeneic-SCT

- Largest study to date is a 21-year BMT database of 2358 patients:
  - 12 patients (0.5%) with HS, ages 19 to 46
  - 14 to 106 days after transplant (median, 25 days)
  - Most common presentation:
    - ✓ Metabolic encephalopathy, with lethargy and confusion evolving into unresponsiveness, metabolic coma
    - ✓ Seizures in 8 cases
  - 10 of 12 patients died 1 to 9 days (median 3.5 days) after diagnosis
  - Main limitation: No microbiological or antibiotic data, reported as idiopathic

Davies SM et al. Bone Marrow Transplant. 1996

Review

Case Reports > Am J Hematol. 1991 Oct;38(2):140-1. doi: 10.1002/ajh.2830380213.

Hyperammonemia following allogeneic bone marrow transplantation

N Tse [1], S Cederbaum, J A Glaspy

Affiliations + expand

PMID: 1951305 DOI: 10.1002/ajh.2830380213

Case Reports > Transpl Infect Dis. 2018 Apr;20(2):e12839. doi: 10.1111/tid.12839. Epub 2018 Feb 12.

Successful resolution of hyperammonemia following hematopoietic cell transplantation with directed treatment of Ureaplasma parvum infection

Riley Graetz [1 2], Robyn Meyer [1 2], Kareem Shehab [1 2], Emmanuel Katsanis [1 2 3]

> Bone Marrow Transplant. 2022 Jun;57(6):1028-1030. doi: 10.1038/s41409-022-01669-8. Epub 2022 Apr 11.

Infective hyperammonaemic encephalopathy after allogeneic stem cell transplant

Michael J Shipton [1], Paul M Kinsella [2], Thomas Davis [1], Francesca Azzato [3], George Taiaroa [4],

Case Reports > BMJ Case Rep. 2022 Nov 9;15(11):e250852. doi: 10.1136/bcr-2022-250852.

Hyperammonaemia syndrome in disseminated *Ureaplasma parvum* infection

Nadiya Brell [1 2], Kristen Overton [3 2], Milton J Micallef [2], Siobhan Hurley [2]

Affiliations + expand

PMID: 36351675 PMCID: PMC9664287 (available on 2024-11-09)

DOI: 10.1136/bcr-2022-250852

Case Reports > Bone Marrow Transplant. 1997 Dec;20(11):1007-8. doi: 10.1038/sj.bmt.1701003.

Idiopathic hyperammonaemia syndrome following allogeneic peripheral blood progenitor cell transplantation (allo-PBPCT)

A Y Ho [1], A Mijovic, A Pagliuca, G J Mufti

Case Reports > Rinsho Ketsueki. 2000 Dec;41(12):1285-8.

[Idiopathic hyperammonemia following allogeneic bone marrow transplantation for refractory lymphoma]

[Article in Japanese]

T Watanabe [1], S Okamoto, A Asahi, T Mori, N Takayama, Y Ikeda

Case Reports > Pediatr Transplant. 2015 Jun;19(4):E104-5. doi: 10.1111/petr.12467. Epub 2015 Mar 29.

Idiopathic hyperammonemia after hematopoietic stem cell transplantation: A case report

Vedat Uygun [1], Gülsün Karasu, Hayriye Daloğlu, Volkan Hazar, Akif Yeşilipek

Affiliations + expand

PMID: 25819322 DOI: 10.1111/petr.12467

Case Reports > Bone Marrow Transplant. 2000 Aug;26(3):343-5. doi: 10.1038/sj.bmt.1702485.

Hyperammonemia after high-dose chemotherapy and stem cell transplantation

P Frere [1], J L Canivet, C Gennigens, J P Rebeix, G Fillet, Y Beguin

Affiliations + expand

PMID: 10967577 DOI: 10.1038/sj.bmt.1702485

Review

Antimicrobial Therapy

- *Ureaplasma spp.* and *M. hominis* are resistant to β-lactams

- *Ureaplasma spp*. generally susceptible to fluroquinolones (FQs) and macrolides
  - Variable resistance to tetracyclines reported
  - Reported azithromycin-resistance of *Ureaplasma*-associated HS during treatment

Meygret A et al. J Antimicrob Chemother. 2018
Fernández J et al. Antimicrob Agents Chemother. 2016
Beeton ML et al. J Antimicrob Chemother 2017

- *Mycoplasma hominis*
  - Increasing resistance to FQs
  - Intrinsic resistance to azithromycin, clarithromycin and erythromycin

Lee JY at al. Antimicrob Agents Chemother. 2020

- Suggested approach:
  - Combination therapy with at least 2 classes
    - ✓ Tetracycline or macrolide plus FQ
      - ❖ *Mycoplasma hominis*: tetracycline and FQ

- Optimal duration unknown: 10-14 days?

Review

Other Therapies

- Goal: ↓NH_3 production and ↑ NH_3 clearance

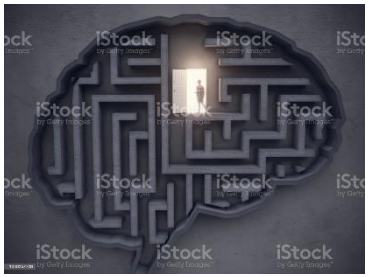
- ↑ NH_3 clearance strategies:
  - Renal replacement therapy
  - Nitrogen scavengers
    - ✓ Sodium benzoate, sodium phenylacetate and arginine

- ↓ NH_3 production strategies:
  - Bowel decontamination
    - ✓ Lactulose, metronidazole, rifaximin, neomycin
  - Dietary modifications (low protein)

Kamel AY et al. Transpl Int. 2022
Gupta S et al. Clin J Am Soc Nephrol. 2016

Discussion & key takeaways

- *Ureaplasma spp. & Mycoplasma hominis* infection can cause HS in immunocompromised hosts
- Well recognized complication post-lung transplant, frequently donor-derived
- Rarely described in allo-SCT, frequency 0.5% in remote cohort (idiopathic)
- Uremia may be a contributing factor
- Seizures likely portend poor prognosis



- Early recognition and management is key but mortality still high
  - Optimal antibiotic therapy and duration unknown
    - ✓ Combination with 2 class-agents (FQ and tetracyclines)

Acknowlegdements

- Thuraya Albusaidi (BC Leukemia/BMT program)
- Linda Hoang (BCCDC)

All images obtained from https://unsplash.com/ unless indicated otherwise