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Pearls & Oy-sters: Status Epilepticus and Cerebral Edema From Hyperammonemia Due to Disseminated Ureaplasma and Mycoplasma Species

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Abstract
Non-hepatic hyperammonemia syndrome is a rare cause of neurologic dysfunction and cerebral edema and has most commonly been reported in post-transplant patients. Only recently has opportunistic infection with *Ureaplasma* species and *Mycloplasma hominis* been found to be key to the pathogenesis. We describe the cases of three immunosuppressed patients who developed hyperammonemia syndrome with new onset refractory status epilepticus and diffuse cerebral edema. PCR was positive for *Mycloplasma hominis* in one patient and *Ureaplasma parvum* in the other two. Despite of early diagnostic suspicion and aggressive management with empirical antibiotics, seizure control, hypertonic saline, and ammonia elimination, none of our patients survived this life-threatening infection. Non-hepatic hyperammonemia and new onset seizures can be presenting features of disseminated *Ureaplasma* species and *Mycoplasma hominis* infections in post-transplant patients. Immunosuppression in the absence of organ transplantation is likely sufficient to trigger this entity, as was the case in our third patient. When suspected, empiric combination antibiotics should be used due to high likelihood of resistance. The diagnostic test of choice is PCR. Patients with hyperammonemia syndrome associated with these infections typically have a poor prognosis. Early recognition and aggressive multimodal interventions may be key to ameliorating the high mortality and severe neurologic sequelae from this entity.

Pearls
- Non-hepatic hyperammonemia and seizures can be presenting features of disseminated *Ureaplasma* and *Mycoplasma* infections.
- The diagnostic test of choice is PCR.

Oysters
- *Ureaplasma* and *Mycoplasma* infections may be underdiagnosed in immunosuppressed patients presenting with encephalopathy, seizures, cerebral edema, and hyperammonemia.
- Empiric combination antibiotics is recommended as there is high likelihood of resistance to a single agent.

Case Presentations
Patient 1:
A 56-year-old man underwent bilateral orthotopic lung transplantation 7 days earlier. He then developed encephalopathy and gaze deviation concerning for seizure. He was on immunosuppression with tacrolimus, mycophenolate, and prednisone. Evaluation revealed elevated ammonia level of 432 umol/L (Reference range 18-72 umol/L; ammonia level 3 weeks prior was 36 umol/L). He had no history of liver dysfunction and liver function tests (LFTs) were normal. Initial head CT was unremarkable. He was afebrile with no leukocytosis. Continuous venovenous hemodiafiltration (CVVHD) and lactulose were initiated for hyperammonemia management. There was concern for opportunistic infection with *Mycoplasma* and/or *Ureaplasma* spp. and serum PCR tests were sent. Antibiotic treatment with azithromycin was initiated empirically. The next day, he had recurrence of seizures. Despite treatment with lorazepam, levetiracetam, and lacosamide, he progressed to refractory status epilepticus (eFigure 1) requiring midazolam and ketamine infusions. Antibiotics were broadened to doxycycline and levofloxacin 24 hours post-presentation. Approximately 38 hours post-presentation, he had dramatic worsening. His neurologic exam was notable for unresponsiveness and absence of all brainstem reflexes. A repeat head CT

revealed diffuse cerebral edema with complete loss of gray-white differentiation and obliteration of the basal cisterns. Despite hyperosmolar therapy and correction of ammonia level to less than 90 umol/L, his neurologic exam remained poor with absence of all brainstem reflexes except initiation of spontaneous breaths. Following discussions with family, he was transitioned to comfort measures and died shortly after. PCR testing later resulted positive for *Mycoplasma hominis*.

Patient 2:
A 59-year-old man status post orthotopic heart transplantation 7 weeks earlier developed acute encephalopathy. He was on immunosuppression with tacrolimus and prednisone. He was afebrile but had a leukocytosis attributed to pneumonia. Laboratory workup revealed an ammonia level of 810 umol/L (ammonia level 3 days prior was 65 umol/L). Initial head CT was normal. He subsequently developed seizures with left facial twitching and head jerking. He progressed to refractory status epilepticus (eFigure 1) requiring midazolam infusion. CVVHD, arginine, levocarnitine, lactulose, and rifaximin were initiated for ammonia clearance. There was concern for opportunistic infection with *Mycoplasma* and/or *Ureaplasma* spp. and serum PCR tests were sent. Antibiotic treatment with doxycycline was initiated empirically. Thirty-six hours post-presentation, he was noted with bilateral dilated and nonreactive pupils. A repeat head CT showed diffuse cerebral edema with sulcal effacement and crowding of the basal cisterns. Hyperosmolar therapy was initiated. His exam remained poor. Later that evening, he suffered a cardiac arrest and died. PCR testing resulted the following day confirming *Ureaplasma parvum* infection.

Patient 3:
A 57-year-old man with dermatomyositis, seronegative rheumatoid arthritis, and interstitial lung disease on immunosuppression with methotrexate, leflunomide, prednisone, mycophenolate mofetil, and rituximab, was admitted for septic arthritis. On day 4, he became acutely obtunded requiring intubation. Non-contrast head CT and CT angiogram was unrevealing. He had low grade fevers and a mild leukocytosis attributed to septic arthritis. Ammonia level returned markedly elevated at 1477 umol/L. He had no prior history of liver dysfunction, normal LFTs, and an ammonia level about a month earlier was 15 umol/L. CVVHD, lactulose, and rifaximin were initiated. There was concern for opportunistic infection with *Mycoplasma* and/or *Ureaplasma* spp. and serum PCR tests were sent. Antibiotic treatment with doxycycline was initiated empirically. Later that day, he developed seizures which progressed to refractory status epilepticus (eFigure 1) requiring midazolam and ketamine infusions. A repeat head CT revealed diffuse cerebral edema. He was initiated on hyperosmolar therapy in addition to ongoing efforts for ammonia clearance. Ammonia levels fell to less than 90 umol/L by day 8. PCR testing for *Ureaplasma parvum* later resulted positive. He completed an 8-day course of doxycycline. Although seizures resolved, he remained severely encephalopathic. Brain MRI obtained on day 14 showed diffuse cortical diffusion restriction (Figure 1). Somatosensory evoked potentials revealed presence of bilateral cortical N20 peaks. Family elected to allow time for neurologic recovery. His clinical course however was complicated by development of bowel ischemia and sepsis with multiorgan failure, and he died on day 26.

Discussion

Here we describe three immunosuppressed patients, two of whom were post solid organ transplantation, who developed encephalopathy, status epilepticus, and cerebral edema. They were then found with hyperammonemia in the absence of significant liver dysfunction. Non-hepatic hyperammonemia/hyperammonemia syndrome, is a rare and often fatal cause of neurologic dysfunction and cerebral edema. The differential is broad and includes gastrointestinal bleeding, multiple myeloma, urea cycle disorders, and the adverse effects of certain medications [1]. It has been reported most commonly in post-transplant patients, especially after lung transplantation [2-9]. Only recently has opportunistic infection with *Ureaplasma* spp. and *Mycoplasma hominis* been found to be key to the pathogenesis [5,6].

Ureaplasma spp. and *M hominis* are known benign, commensal urogenital organisms. Ammonia is generated as a consequence of their metabolic processes. While this production is benign under normal circumstances, ammonia clearance becomes problematic when these organisms become widely disseminated. Such dissemination can occur in immunocompromised post-transplantation patients [4-7]. Lung transplant patients are most frequently affected. This is postulated to be due to transmission of bacteria through donor lungs as additional respiratory tract colonization by these organisms has been described [2,7]. *Ureaplasma* spp. utilize the urease enzyme to generate ATP via hydrolysis of urea into carbon dioxide and ammonia [5] (Figure 2). *Mycoplasma hominis* produces energy through arginine degradation, which as well generates ammonia as a by-product [10]. There are additionally data showing that *Ureaplasma* spp. may disrupt the blood brain barrier (BBB). This is hypothesized to be the mechanism by which *Ureaplasma* directly invade the central nervous system in neonatal meningitis [11]. Meningitis was considered in all our cases. However, a lumbar puncture was determined to be risky given the rapid development of cerebral edema and signs of elevated intracranial pressure. Whether breakdown of the BBB contributes to the rapid development of malignant cerebral edema remains unknown**.**

Diagnosis of these infections through serum PCR testing is preferable as this typically yields faster results [5,6,10]. Lung transplantation patients may also have PCR of bronchioalveolar lavage or pleural fluid sent [7]. Obtaining culture provides important information regarding antimicrobial susceptibility [5]. However, culture is difficult to obtain as these are known fastidious organisms requiring use of specific enriched media [5,7,10]. The ongoing ammonia generation by these organisms is postulated to make typical strategies aimed at ammonia clearance ineffective or insufficient. Additional use of antibiotics to cull the infections have been shown to be an important factor [5,9,10]. While *Ureaplasma* spp. are generally susceptible to fluoroquinolones, macrolides, and tetracyclines, resistance to each of these classes have also been reported [5,10]. *Mycoplasma hominis* notably has known resistance to macrolides [10]. As such, combination antimicrobial therapy (i.e., tetracycline plus fluoroquinolone) is recommended as empiric treatment while awaiting sensitivity data from culture [10]. All three of our patients were initially treated with a single antibiotic. Though our first patient was quickly broadened to a combination regimen, that was not the case for the other two.

Typical MRI findings of hyperammonemia in adults have been reported as restricted diffusion and T2 FLAIR hyperintensity in the insular and cingulate cortices [12]. Other cortical areas may be involved to a variable degree. Only our third patient underwent MRI, which showed extensive diffuse cortical restricted diffusion and FLAIR hyperintensities (Figure 1). This cortical injury has been shown to be potentially reversible [12]. Sadly, all three of our patients had poor outcomes. Unfortunately, patients with hyperammonemia syndrome associated with these infections typically have a poor prognosis. A recently published systematic review and meta-analysis [7], found a five-fold increased mortality rate among immunocompromised patients and transplant recipients with hyperammonemia syndrome associated with *Ureaplasma* spp. Early recognition and aggressive intervention to include combination antimicrobial therapy may nevertheless be key to ameliorating the high mortality and severe neurologic sequelae from this entity. For hyperammonemia, we recommend an early, aggressive, multimodal approach similar to that proposed by Krutsinger et al. [8], which includes bowel decontamination, use of nitrogen scavengers, and intensive high-dose renal replacement therapy. Further, we emphasize early aggressive management of neurologic sequelae of seizures and cerebral edema [13,14].

These infections may be underdiagnosed in patients presenting with encephalopathy, seizures, cerebral edema, and hyperammonemia in the setting of organ transplantation or immunosuppression. Indeed, prior to discovery of the unique pathophysiologic contribution of these organisms, many cases likely went undiagnosed. Underdiagnosis may be particularly common in cases of immunosuppression without organ transplantation, as was the case in our third patient [15]. A key clue is noting marked hyperammonemia in the absence of significant liver dysfunction. We hope these cases raise awareness of this entity and recommend early initiation of empiric multimodal interventions. These should include empiric combination antimicrobial therapy, multimodal therapies aimed at ammonia clearance, and aggressive management of neurologic sequelae. We recommend PCR testing for prompt diagnosis. Culture data may also be pursued but should be expected to yield delayed results.

http://links.lww.com/WNL/C574

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FIGURES

Figure 1
Title: MRI brain
Legend: MRI brain diffusion weighted imaging (DWI) showing diffuse cortical diffusion restriction (A and B), with apparent diffusion coefficient (ADC) correlate (C and D). Patient 3.

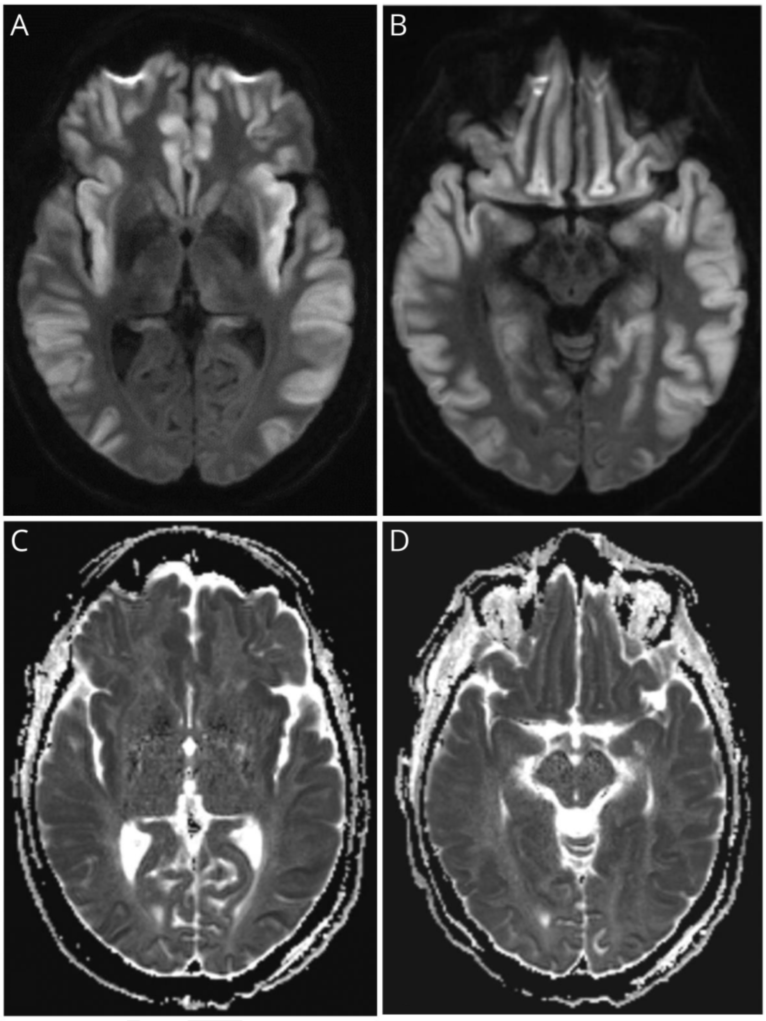
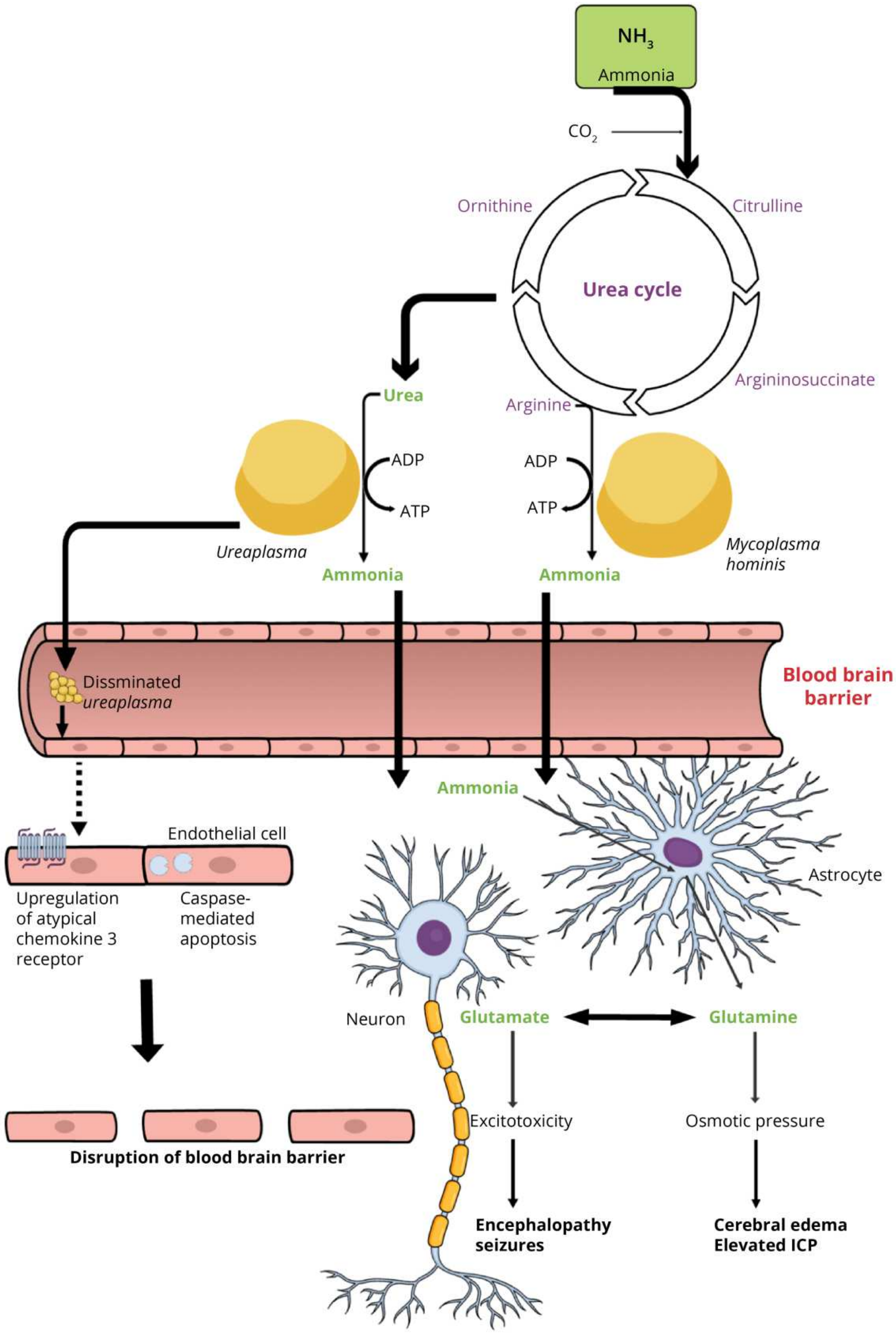


Figure 2
Title: Representation of mechanisms of ammonia generation by Ureaplasma spp. and Mycoplasma hominis and pathophysiologic consequences.
Legend: Original work.



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