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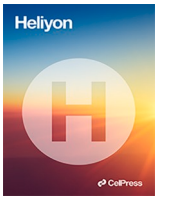

Case report

A late-onset hyperammonemia syndrome caused by *Ureaplasma parvum* infection after kidney transplantation

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ABSTRACT

Hyperammonemia syndrome has a high mortality rate in the immunosuppressed population due to its association with mental status changes. Recently studies have shown that *Ureaplasma* organisms' infection can lead to hyperammonemia in post-transplant patients. Symptoms typically occur within 30 days postoperatively. However, the late-onset hyperammonemia caused by *Ureaplasma parvum* infection after kidney transplantation has never been reported. In this case study, a 64-year-old Chinese male presented with symptoms such as nausea, vomiting, trouble sleeping, and deteriorating mental status 81 days after kidney transplantation. His plasma ammonia level was significantly elevated, and there was no evidence of liver synthetic dysfunction. Although common methods for ammonia clearance, such as haemodialysis and oral lactulose were initiated, his serum ammonia levels remained high. Metagenomic sequencing of serum determined *Ureaplasma parvum* infection. Levofloxacin and minocycline were administered respectively, which resulted in a decrease in ammonia levels, but normalization was not achieved. The computed tomographic scan revealed the presence of cerebral edema. Unfortunately, the patient eventually became brain dead with multiple organ failure. This case highlights that *Ureaplasma parvum* can cause late-onset hyperammonemia in kidney transplant patients. Once the mental status changes are identified, immediate empiric treatments should be initiated without waiting for a confirmed diagnosis of *Ureaplasma* spp. infection.

1. Background

Hyperammonemia syndrome (HS) is an uncommon and life threatening complication in immunosuppressed patients, characterized by a high serum ammonia level and abnormal neurological signs [1]. It was first discovered after an allogeneic bone marrow transplant in 1991 [2]. Over the past decade, HS has been observed after solid organ transplantation (SOT), primarily in lung transplant recipients [3]. The exact reasons why HS is seen in these populations are not fully understood. *Ureaplasma* infection has been reported as a cause of HS in post-transplant patients [1,4–6]. *Ureaplasma* spp. are common, fastidious, commensal organisms that colonized the urogenital tracts of healthy individuals. The hydrolysis of urea into ammonia and CO_2 by *Ureaplasma* organisms is inconsequential to the host [4]. However, disseminated infection threatens ammonia excretion in people with SOT [4]. The difficulty in culturing *Ureaplasma* spp. using routine laboratory methods results in a low detection rate for these species [7]. We present a case who developed HS 81 days after a kidney transplant due to *Ureaplasma parvum* infection and the patient died unfortunately because of the delayed diagnosis and

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treatment.

2. Case presentation

A 64-year-old Chinese male with a medical history of focal sclerosing glomerulonephritis and end-stage renal failure underwent right kidney transplantation at Beijing Hospital. The kidney was from a deceased donor. Induction immunosuppression included basiliximab 20 mg and methylprednisolone 500 mg. His immunosuppression maintenance regimen was comprised of cyclosporine, methylprednisolone, and enteric-coated mycophenolate sodium (EC-MPS). Routine blood and urine cultures were negative, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) DNA polymerase chain reaction (PCR) tests were below the limit of detection (<500 copies/ml), and he did not have immediate post-operative complications. Therefore, he was discharged on post-operative day (POD) 15 with a plasmatic cyclosporine concentration of 179 ng/ml (trough) and 733.5 ng/ml (peak).

Routine follow-up visits (weekly) lasted for a month, and there were no vital signs of abnormality. In addition, the double J ureteral stent was successfully removed on POD 34. On POD 40, he presented with hypodynamia, anorexia, and difficulty walking without any noticeable causes. Deep venous thrombosis of the lower right extremity was suspected based on an ultrasound imaging test. Aspirin, clopidogrel, and enoxaparin sodium were given to anticoagulate the blood. CMV infection (16500 copies/ml) was detected on POD 42, and ganciclovir was given intravenously. He was discharged again on POD 48, with the CMV DNA reduced to 8650 copies/ml. After 10 days of continuous oral ganciclovir treatment, the viral load was reduced below the detection limit (<500 copies/ml).

On POD 81, he experienced nausea, vomiting, trouble sleeping, and a deterioration in mental status. He was admitted to the emergency room, where he was intubated for airway protection and given intravenous latamoxef sodium and esomeprazole sodium. After a neurologic examination, which revealed loss of consciousness, he was transferred to the intensive care unit. Upon arrival, his serum creatinine and blood urea nitrogen (BUN) levels were 190 mmol/L and 14.68 mmol/L, respectively. A routine blood test showed a leukopenia of 1.88×10^9/L with 84.1 % neutrophils. His liver synthetic function tests were unremarkable (total bilirubin 10.4 mmol/L, aspartate aminotransferase 13 U/L, alanine aminotransferase 10 U/L). His maintenance immunosuppression agents were adjusted to EC-MPS and prednisone. On the next day, he developed multiple epileptic seizure activity. Propofol, midazolam, and sodium valproate were given to control the condition but were not effective. Cisatracurium besilate was added. A computed tomography (CT) scan of the head (Fig. 1A and B and C) showed lacunar infarction and demyelination of cerebral white matter. Intravenous mannitol was administered (125ml q8h for 4 days). Intermittent attacks of cardiac arrhythmia were also detected, and amiodarone hydrochloride was continuing venous pump in. His serum ammonia (normal 18–72 μmol/L) was elevated to 1225 μmol/L compared to 653 μmol/L at admission (Fig. 2). Haemodialysis and lactulose were initiated to remove ammonia. The ammonia concentration decreased to 288

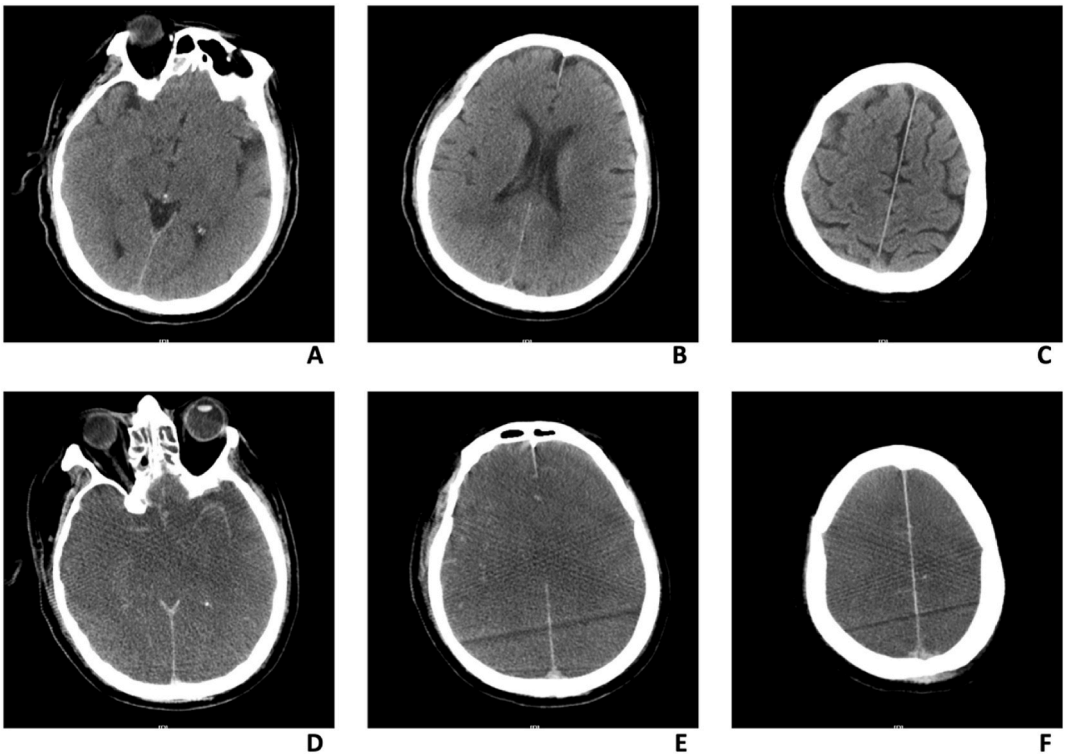

Fig. 1. Computed tomography scans of the head were conducted on day 1 (A, B and C) and day 6 (D, E and F). Images A, B and C reveal scattered subcortical white matter hypodensity, as well as enlargement of sulci and cisterns. Images D, E and F illustrate a diffuse loss of grey-white differentiation due to edema. The brain exhibited significant swelling, resulting in the effacement of sulci and ventricles.

μmol/L on hospital day 4 but did not normalize (Fig. 2). Considering that he had been in a coma since admission, blood transfusion (200ml AB Rh + per day for 5 days) was started to raise his blood volume and hooked up to the ventilator. The Leukocyte count continued to decrease (1.01×10^9/L), and the neutrophil count was 0.84×10^9/L. A urine test was performed for *Ureaplasma* by PCR and the result was negative. Examination of plasma and cerebrospinal fluid (CSF) using metagenomic Next Generation Sequencing (mNGS) was performed. The plasma was positive for CMV (1544 reads per ten million, RPTM), EBV (326 RPTM), and *Ureaplasma parvum* (31 RPTM), while the CSF was positive for EBV (273 RPTM). Levofloxacin, human granulocyte colony-stimulating factor, and ganciclovir were initiated for the treatment of systemic infection (Fig. 2). The immunosuppression agent EC-MPS was halved. His liver function was normal, and ornithine aspartate and L-glutathione reduced were empirically given for liver protection. On hospital day 6, a tracheotomy operation was performed to prevent respiratory infections. Despite ongoing haemodialysis and lactulose administration, his serum ammonia levels remained high (Fig. 2), and the antimicrobial medication was changed from levofloxacin to minocycline. In addition, methylprednisolone (40mg qd) was initiated for the treatment of EBV infection in the central nervous system. The second CT scan of the head (Fig. 1D and E and F) demonstrated cerebral edema and the absence of cerebral sulci and gyri, indicating suspected subarachnoid space bleeding. These findings were consistent with hypoxic-ischemic encephalopathy (HIE). Despite the lifesaving efforts administered by medical staffs but were unsuccessful. Unfortunately, the patient was determined to be brain dead with multiple organ failure the following day.

3. Discussion

Here, we describe a case who developed HS 81 days after kidney transplantation, possibly related to *Ureaplasma parvum* infection. The previous meta-analysis of patients with HS after SOT showed that the median length of time for signs or symptoms suggestive of HS to occur was 9 days postoperatively [8]. However, our patient did not experience mental deterioration in the early post-transplant period. Renal transplant function was normal, with no complications or noticed infections. Although CMV infection was observed on POD 42, it was promptly managed with antiviral treatment.

The occurrence of HS is mainly attributed to liver dysfunction, portosystemic shunt, and urea cycle disorder [9]. In our case, no evidence of these common causative factors for HS was found. Previous studies have reported the development of HS after SOT due to *Ureaplasma* spp. infection [5,10,11], with a higher risk observed in post-lung transplantation [4,12]. The reasons for *Ureaplasma* spp. infection in SOT are still unknown, the prevailing hypothesis being donor-derived infection [13]. The immunosuppression status of the recipient is also considered a contributing factor to the predilection for *Ureaplasma* spp. infections in SOT patients [14]. Unfortunately, *Ureaplasma* spp. are not included in the blood tests performed on the donor before procurement, as they are commensal organisms in

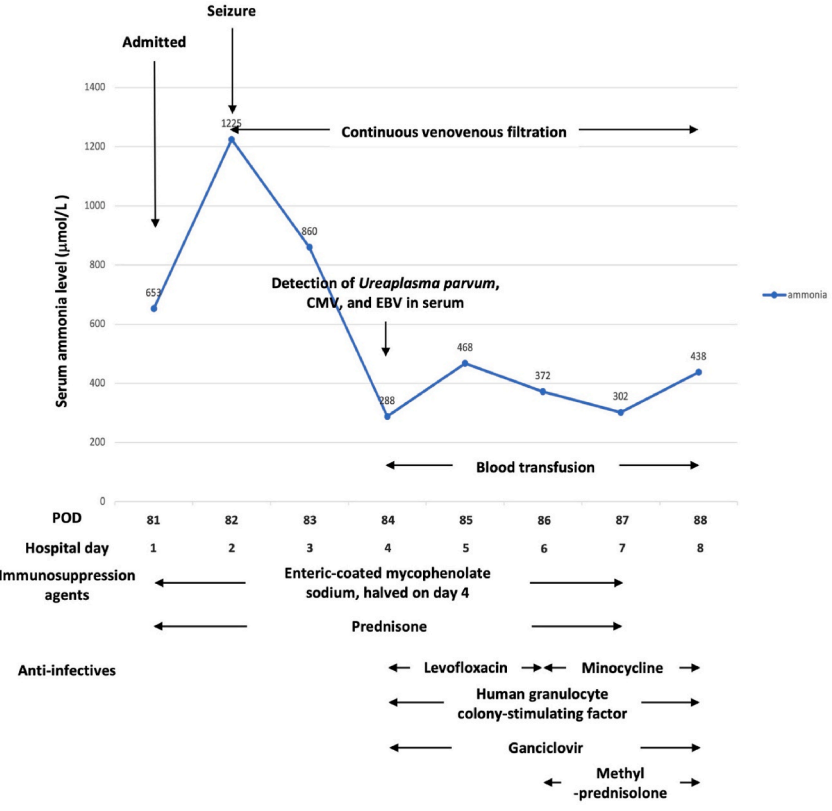

Fig. 2. Timeline of notable symptoms, ammonia level, and treatment regimens throughout the patient's hospitalization.

healthy populations. The mNGS test suggested a *Ureaplasma parvum* infection in the serum of our case. However, attempts to test for *Ureaplasma* spp. in the donor for our patient after transplantation were not possible as specimens were not available.

At the same time, CMV and EBV were detected in the serum, and EBV was positive in the CSF. The result of the mNGS sheds some light on the abnormally elevated ammonia levels in our patient. However, the presence of virus re-infection complicated the treatment strategy to some extent. It is well-known that EBV can affect the central nervous system in immunocompromised populations [15]. Unlike the development of HS caused by disseminated *Ureaplasma* spp. infection, which can lead to neurotoxic effects, the understanding of its impact is limited [16]. Therefore, in our case, antiviral treatments took precedence over antimicrobial treatments. It has been noted that valproic acid can induce hyperammonemia, although most cases present asymptomatically [17]. The hospital consultation determined that seizure control was a priority, and thus sodium valproate injection was administered on days 1, 2, 3 and 5. As shown in Fig. 2, the ammonia level increased rapidly after the first administration (from day 1 to day 2). Fortunately, the ammonia levels did not worsen after subsequent administration, which may be attributed to the continuous venovenous filtration, discontinuation of sodium valproate, and lactulose treatment [17]. Additionally, the administration of sodium valproate effectively reduced seizures. Ammonia levels remained abnormal throughout the patient's hospitalization. Although levofloxacin or minocycline were given to slightly reduce the ammonia levels, a single class of antibiotics is ineffective against disseminated infection of *Ureaplasma parvum* (Fig. 2) [12].

The ineffectiveness of the treatment applied to the patients resulted in a poor prognosis. Eventually, our case with poorly controlled ammonia levels developed HIE, which was the main cause of death. The high mortality of HS has hindered the study of its underlying pathophysiology and potential therapies [1,4]. *Ureaplasma* organisms can generate urease, which hydrolyses urea into CO_2 and ammonia, producing ATP in the process [4]. The released ammonia can then be metabolized into urea in the liver or into glutamine in muscle cells and cerebral astrocytes through ATP utilization [18,19]. The positive feedback loop of urea hydrolysis and hepatic urea generation leads to the accumulation of ammonia in the human body [4]. This mechanism greatly affects the excretion of ammonia, which is why haemodialysis was ineffective in clearing ammonia in our case.

One of the reasons for the failure to decrease the ammonia level in our case is the delayed diagnosis of *Ureaplasma parvum* infection. Early diagnosis of *Ureaplasma* spp. infection is crucial for the prognosis of patients, however, it can be challenging [12]. Standard bacterial culture methods are unable to grow *Ureaplasma* due to their fastidious nature, and Gram stain is also unable to identify them as they lack a cell wall [20]. Molecular methods such as PCR tests and mNGS are powerful tools for detecting the bacterium. The mNGS is an unbiased, hypothesis-free diagnostic method, also known as shotgun sequencing. In our case, total RNA was extracted from the patient's serum and CSF using the QIAamp Viral RNA Mini Kit (Qiagen, Germany). Sequencing was performed on an Illumina Nextseq using a single-end mode (1 x 75bp). Clean reads were aligned against the reference databases (IDseq^{TM} Ultra, China) [21]. However, due to limitations in resource settings, molecular-based techniques are not widely available in clinical microbiology laboratories. Therefore, the development of a novel testing method that is fast, inexpensive, and specific for detecting *Ureaplasma* spp. infection in transplant recipients is urgently needed.

The hypothesis for the late development of HS in our case is related to the antirejection and antimicrobial therapy during the peritransplantation. It is possible that *Ureaplasma parvum* from the donor entered a state of reduced activity, due to exposure to a new environment (the recipient) [22]. However, the mechanism of this kind of state formation in our case is unclear. Prolonged courses of methylprednisolone and prednisone increase susceptibility to infections, and the clinical presentation of infections may be atypical [23]. In our case, the early stage of *Ureaplasma parvum* infection went undetected due to mild or absent of HS clinical symptoms. It has been reported that kidney recipients with *Ureaplasma* spp. bacteraemia can have no clinical manifestations related to HS [24].

Successful management of HS in SOT recipients due to *Ureaplasma* spp. infection has been reported [4,6,19,20,25,26]. The treatment for *Ureaplasma* spp. infection involves combining two antimicrobials from different classes, such as fluoroquinolones (e.g. levofloxacin and moxifloxacin), macrolides (e.g. azithromycin), or tetracyclines (e.g. doxycycline) [12]. β-lactam and carbapenems are ineffective against *Ureaplasma* spp. since these antibiotics inhibit cell wall synthesis, whereas *Ureaplasma* spp. lack a cell wall [27]. Despite the utilization of levofloxacin or minocycline in our case, the efficiency of ammonia clearance remained low. This underscores the importance of dual therapy with antimicrobials, even though the optimal treatment is not well defined [4,28]. This is an important issue for future research.

Our study had several limitations. First, we did not perform the *Ureaplasma* spp. test on the donor since the samples and additional details were not able to be obtained. The absence of another method, such as PCR, to confirm the presence of *Ureaplasma parvum* in our case is another limitation. However, we have confidence in the reliability of mNGS. Finally, the diagnosis of *Ureaplasma parvum* was not prompt, which failed to decrease the ammonia level in this patient. It is desirable to establish a process that examines *Ureaplasma* spp. with a more rapid turnaround time.

4. Conclusion

In this case study, the most interesting finding is that HS caused by *Ureaplasma parvum* infection can occur several months after transplantation. This finding contradicts previous studies that suggested HS occurs with a median of 9 days postoperatively [8]. This intriguing observation may be linked to the continued use of antibiotics and immunosuppressive medications after kidney transplantation. Another possible explanation is that the transmission of *Ureaplasma parvum* is not donor-derived. However, caution should be exercised, as the absence of donor blood and urine tests for *Ureaplasma parvum* limits the interpretation of these findings. We tend to believe the infection is donor-derived since there is no evidence supporting that *Ureaplasma parvum* originates from the recipient. Therefore, donor screening for *Ureaplasma* spp. appears to be an effective and simple method to reduce the risk of developing HS in SOT patients. With the observations in this study, we should pay more attention in our future clinical practice. It is crucial to monitor

mental status changes and ammonia levels in the transplant population, even several months after the transplantation surgery.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient relative(s) for anonymized patient information to be published in this article.

Availability of data and materials

The datasets analysed or generated during the study are available from the corresponding author upon reasonable request.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Jing Wu: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Yunjian Hu:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

ATP	adenosine triphosphate
BUN	blood urea nitrogen
CMV	cytomegalovirus
CSF	cerebrospinal fluid
CT	computed tomography
EBV	Epstein-Barr virus
EC-MPS	enteric-coated mycophenolate sodium
HIE	hypoxic-ischemic encephalopathy
HS	hyperammonemia syndrome
mNGS	metagenomic Next Generation Sequencing
PCR	polymerase chain reaction
POD	post-operative day
RPTM	reads per ten million
SOT	Solid organ transplantation
TMP/SMX	trimethoprim/sulfamethoxazole

References

[1] G.R. Lichtenstein, Y.X. Yang, F.A. Nunes, J.D. Lewis, M. Tuchman, G. Tino, et al., Fatal hyperammonemia after orthotopic lung transplantation, Ann. Intern. Med. 132 (2000) 283–287.

[2] N. Tse, S. Cederbaum, J.A. Glaspy, Hyperammonemia following allogeneic bone marrow transplantation, Am. J. Hematol. 38 (1991) 140–141.
[3] S.D. Moffatt-Bruce, T. Pesavento, J. Von Viger, D. Nunley, A. Pope-Harman, S. Martin, et al., Successful management of immunosuppression in a patient with severe hyperammonemia after lung transplantation, J. Heart Lung Transplant. 27 (2008) 801–803.
[4] A. Bharat, S.A. Cunningham, G.R. Scott Budinger, D. Kreisel, C.J. DeWet, A.E. Gelman, et al., Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans, Sci. Transl. Med. 7 (2015) 284re3.
[5] R.K. Kiberenge, H. Lam, Fatal hyperammonemia after repeat renal transplantation, J. Clin. Anesth. 27 (2015) 164–167.
[6] R. Graetz, R. Meyer, K. Shehab, E. Katsanis, Successful resolution of hyperammonemia following hematopoietic cell transplantation with directed treatment of Ureaplasma parvum infection, Transpl. Infect. Dis. 20 (2018) e12839.
[7] K.B. Waites, B. Katz, R.L. Schelonka, Mycoplasmas and ureaplasmas as neonatal pathogens, Clin. Microbiol. Rev. 18 (2005) 757–789.
[8] S.C. Roberts, W. Malik, M.G. Ison, Hyperammonemia syndrome in immunosuppressed individuals, Curr. Opin. Infect. Dis. 35 (2022) 262–268.
[9] A.S. Clay, B.E. Hainline, Hyperammonemia in the ICU, Chest 132 (2007) 1368–1378.
[10] D. Bezinover, L. Douthitt, P.M. McQuillan, A. Khan, P. Dalal, J. Stene, et al., Fatal hyperammonemia after renal transplant due to late-onset urea cycle deficiency: a case report, Transplant. Proc. 42 (2010) 1982–1985.
[11] M. Albersen, S. Joniau, H. Van Poppel, P.-J. Cuyle, D.C. Knockaert, W. Meersseman, Urea-splitting urinary tract infection contributing to hyperammonemic encephalopathy, Nat. Clin. Pract. Urol. 4 (2007) 455–458.
[12] Tantengco Oag, F.C.C. De Jesus, E.F.S. Gampoy, E.D.B. Ornos, M.S. Vidal, C.L.R. Abad, Hyperammonemia syndrome associated with Ureaplasma spp. Infections in immunocompromised patients and transplant recipients: a systematic review and meta-analysis, Clin. Transplant. 35 (2021) e14334.
[13] R. Fernandez, A. Ratliff, D. Crabb, K.B. Waites, A. Bharat, Ureaplasma transmitted from donor lungs is pathogenic after lung transplantation, Ann. Thorac. Surg. 103 (2017) 670–671.
[14] X. Wang, M.J. Karau, K.E. Greenwood-Quaintance, D.R. Block, J.N. Mandrekar, S.A. Cunningham, et al., Ureaplasma urealyticum causes hyperammonemia in an experimental immunocompromised murine model, PLoS One 11 (2016) e0161214.
[15] J. Han, Z. Kang, Y. Xie, H. Li, H. Yan, X. Song, Acute diffuse edematous-hemorrhagic Epstein–Barr virus meningoencephalitis, Medicine (Baltim.) 98 (2019) e18070.
[16] R. Ali, S. Nagalli, Hyperammonemia, in: StatPearls. Treasure Island (FL), StatPearls Publishing, 2024.
[17] E. Baddour, A. Tewksbury, N. Stauner, Valproic acid–induced hyperammonemia: incidence, clinical significance, and treatment management, Ment Health Clin 8 (2018) 73–77.
[18] V. Walker, Ammonia metabolism and hyperammonemic disorders, Adv. Clin. Chem. 67 (2014) 73–150.
[19] C. Legouy, A. Hu, F. Mochel, N. Weiss, A. Collin, S. Pereyre, et al., Ureaplasma parvum causes hyperammonemia presenting as refractory status epilepticus after kidney transplant, J. Crit. Care 57 (2020) 79–83.
[20] C.A. Cannon, M.A. Corcorran, K.W. Shaw, M. Montenovo, L. Sibulesky, J.D. Reyes, et al., Hyperammonemia syndrome due to Ureaplasma infection after liver-kidney transplant, Transpl. Infect. Dis. 22 (2020) e13298.
[21] Ai J-W, Zhang Y, Zhang H-C, Xu T, Zhang W-H. Era of molecular diagnosis for pathogen identification of unexplained pneumonia, lessons to be learned. Emerg. Microb. Infect. 9:597–600.
[22] M.D. McDonald, C. Owusu-Ansah, J.B. Ellenbogen, Z.D. Malone, M.P. Ricketts, S.E. Frolking, et al., What is microbial dormancy? Trends Microbiol. 32 (2024) 142–150.
[23] Methylprednisolone | Drugs | BNF content published by NICE. https://bnf.nice.org.uk/drugs/methylprednisolone/. (Accessed 6 March 2024).
[24] C. Wigston, M. Lavender, R. Long, D. Sankhesara, D. Ching, G. Weaire-Buchanan, et al., Mycoplasma and Ureaplasma donor-derived infection and hyperammonemia syndrome in 4 solid organ transplant recipients from a single donor, Open Forum Infect. Dis. 10 (2023) ofad263.
[25] C. Nowbakht, A.R. Edwards, D.F. Rodriguez-Buritica, A.M. Luce, P.B. Doshi, A. De Golovine, et al., Two cases of fatal hyperammonemia syndrome due to mycoplasma hominis and Ureaplasma urealyticum in immunocompromised patients outside lung transplant recipients, Open Forum Infect. Dis. 6 (2019) ofz033.
[26] A.B. Higgins, D. Farmakiotis, R. Rogers, A.J. Osband, A. Seo, B. Chen, et al., Hyperammonemia syndrome due to Ureaplasma urealyticum in a kidney transplant recipient: a case of disseminated disease from a fluoroquinolone-resistant isolate, Transpl. Infect. Dis. 22 (2020) e13328.
[27] M.L. Beeton, O.B. Spiller, Antibiotic resistance among Ureaplasma spp. isolates: cause for concern? J. Antimicrob. Chemother. 72 (2017) 330–337.
[28] F. Cheema, H.L. Kutzler, A.S. Olowofela, B.T. Maneckshana, C. Rochon, P.A. Sheiner, et al., Successful management of noncirrhotic hyperammonemia syndrome after kidney transplantation from putative Ureaplasma infection, Transpl. Infect. Dis. 22 (2020) e13332.