Immunocompromised teenager with meningitis caused by Ureaplasma parvum

Ehrnström, Birgitta; Haugan, Maria Schei; Andreasen, Jo Bønding; Ellingsen, Asbjørn

Published in:
BMJ Case Reports

DOI (link to publication from Publisher):
10.1136/bcr-2023-257261

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

OPEN ACCESS

Immunocompromised teenager with meningitis caused by *Ureaplasma parvum*

Birgitta Ehrnström ,[1,2] Maria Schei Haugan,[3] Jo Bønding Andreasen ,[2,4] Asbjørn Ellingsen[1]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bcr-2023-257261).

[1]Department of Infectious Diseases, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[2]Clinic of Anaesthesia and Intensive Care, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[3]Department of Medical Microbiology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[4]Thoracic Intensive Care Unit, Aalborg Universitetshospital, Aalborg, Denmark

Correspondence to
Dr Birgitta Ehrnström;
birgitta.ehrnstrom@stolav.no

Accepted 29 February 2024

To cite: Ehrnström B, Haugan MS, Andreasen JB, *et al*. *BMJ Case Rep* 2024;**17**:e257261. doi:10.1136/bcr-2023-257261

SUMMARY

Infection in the immunocompromised patient is often challenging on multiple levels. It can be difficult to distinguish between manifestations of the underlying disease, infection or malignancy. Symptoms may be vague or even absent, deviations in the common inflammatory parameters discrete, imaging findings scarce and the causative microbe may be a true pathogen as well as opportunistic. Here, we report an immunosuppressed female in her late teens with a purulent meningitis due to *Ureaplasma parvum*—a very rare cause of infection in the central nervous system of adults. We wish to highlight the relevance of intracellular pathogens and the need to actively search for these microbes, especially when response to broad-spectrum antibiotic treatment is absent. Furthermore, we emphasise the need for adequate molecular microbial diagnostics in search of microbes that are difficult to identify by culture and where serology and antigen tests may be absent or unreliable due to immune suppression.

BACKGROUND

Ureaplasma species are intracellular bacteria that lack cell wall and are therefore resistant to cell wall-targeting antibiotics, such as beta-lactams. Within the genus, two human-associated species exist: *Ureaplasma parvum* and *Ureaplasma urealyticum*. These are hard to detect since they do not grow on routine media or appear on Gram stain. Identification is mainly dependent on special growth medium or PCR.

The role of *Ureaplasma* spp. in human disease has had a controversial history due to the high urogenital colonisation rate among healthy individuals.[1–4] *Ureaplasma* has been associated with urogenital infections, infertility, chorioamnionitis and preterm birth, and infections in neonates are described, including meningitis.[5–9] In adults, *Ureaplasma* as a cause of infection outside the genitourinary tract is uncommon, regardless of immune status. We have found only five previously published cases of adult *Ureaplasma* meningitis.[10–14] Although rare, several recent case reports on serious infections with *Ureaplasma* in immunocompromised patients indicate that this may be a relevant and probably underdiagnosed pathogen that should be considered, especially in this patient population. Patients with humoral immunodeficiency—both primary and acquired—seem particularly at risk. In the past three decades, seven cases of invasive *Ureaplasma* disease have been reported in patients with common variable immunodeficiency/agammaglobulinaemia, in 1 patient with the immunodeficiency disorder Good's syndrome[14–20] and in at least 19 cases of patients receiving B-cell depletion therapy with rituximab.[12 21–38] Hypogammaglobulinaemia is frequently observed in patients treated with rituximab.[39 40]

CASE PRESENTATION

The patient was a female who developed generalised palpable purpura, kidney failure and joint pain in early adolescence. This was followed by breathing difficulties and stridor, caused by an inflammatory subglottic stenosis. CT sinuses revealed pronounced thickening and destruction of the mucoperiosteum, and a biopsy showed ulcerations and pronounced inflammation. Antineutrophil cytoplasmic antibodies (C-ANCA IgG) and proteinase 3 antibodies (PR3 IgG) were positive, confirming the diagnosis granulomatosis with polyangiitis (GPA). Two years later, she began to suffer from persistent headache and discharge from both ears. Prior to the current admission of this case report, the treatment regime consisted of prednisolone 10 mg daily, methotrexate 20 mg weekly and rituximab every 6 months, the last dose administered 3 months earlier.

She was now admitted to the local hospital due to acute onset of intense headache, photophobia, nausea and neck pain. The initial symptom was pain behind the left ear. On admission, she had a fever of 38.2°C but displayed stable vital signs and no focal neurological deficits. A lumbar puncture was performed, notable for marked pleocytosis 2566 × 10^6/L (76% polymorphonuclear leucocytes (PMN)), increased protein 1.16 g/L, cerebrospinal fluid (CSF)/plasma glucose index 0.43 and lactate 3.3 mmol/L. The CSF opening pressure was not measured, neither here nor on later lumbar punctures. Blood samples revealed leucocytosis 19.1 × 10^9/L and C-reactive protein (CRP) 13 mg/L. Infectious meningitis was suspected, and treatment with meropenem, aciclovir and dexamethasone was commenced. Cerebral CT showed liquid-filled ethmoidal sinuses and thickening of mucosa in other sinuses, otherwise normal findings. There was no bacterial growth in either blood or CSF. Multiplex PCR for common bacterial, viral and fungal meningitis/encephalitis pathogens (Biofire FilmArray) on CSF was negative. An otolaryngologist consult was performed. There were no obvious signs of increased activity in GPA and serum ANCA was negative. The patient's condition improved and bacterial meningitis was assumed to be the correct diagnosis. At day 4, she was discharged from the

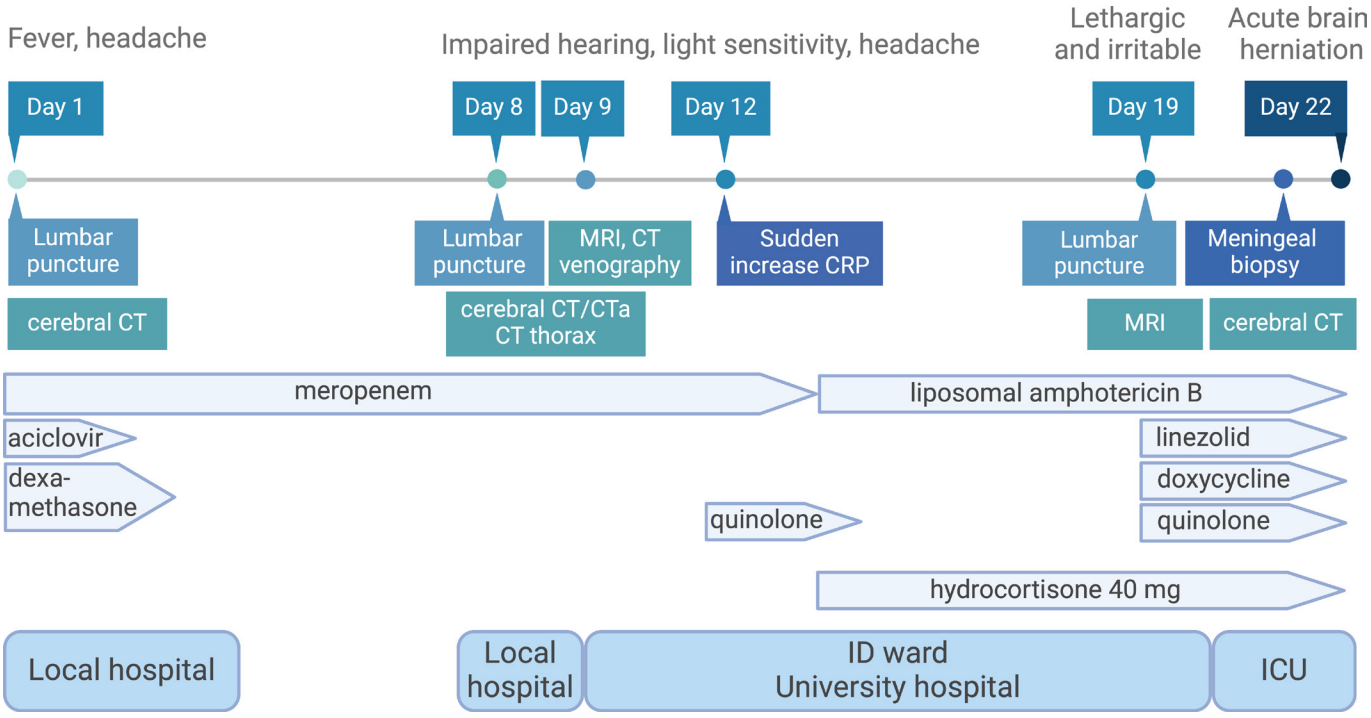

Figure 1 Graphical summary of the clinical course. Author Birgitta Ehrnström. ICU, intensive care unit.

hospital, against medical advice, with a plan to complete meropenem treatment under management by the local health service.

At day 8, she returned to the local hospital because of increasing earache, photophobia and nausea (figure 1). A new lumbar puncture revealed leucocytes 2087 × 10^6/L (58% PMN), protein 1.73 g/L, CSF/plasma glucose index 0.11, lactate 6.4 mmol/L, IgG 95 mg/L and no oligoclonal bands (online supplemental table S1). Clinical examination was normal. Peripheral blood: leucocytes 20.5 × 10^9/L, CRP 18 mg/L and hypogammaglobulinaemia (total IgG 4.5, IgM 0.1 and IgA 0.8 g/L). Repeated cultures of CSF and blood on standard media, alongside multiplex PCR of the CSF, remained negative. Cerebral CT with intravenous contrast and thoracic CT was performed, both with unremarkable findings. As her condition was serious and no diagnosis had yet been established, she was transferred to the department of infectious diseases at the university hospital. Here, cerebral MRI showed normal meninges and brain parenchyma but a possible contrast defect in the left internal jugular vein. CT of the temporal bone and cerebral venography was without signs of venous sinus thrombosis, but a small, new bone destruction at the left jugular foramen was detected.

Significant CSF pleocytosis, and particularly low glucose and high lactate in the CSF, is indicative of infection, yet no causative agent had been identified. We discussed the possibility of fungal or mycobacterial infection and harvested samples for extended microbiological analysis of the CSF, including broad-range PCR for the detection of bacterial DNA (targeting the 16S rRNA gene; a universal barcode for bacteria[41 42]) and fungal DNA (targeting the internal transcribed spacer and D1D2 regions; universal barcodes for fungi), respectively. Tularaemia, endemic in this area, was considered possible, although meningitis is a very rare manifestation. Ciprofloxacin was administered for 2 days, until serology for *Francisella tularensis* came back negative. Meropenem was continued, awaiting further results and clinical development.

Over the next days, impaired hearing was noticed and the headache and photophobia persisted. Repeated culture and PCR analyses of the CSF targeting a broad range of bacterial, viral and fungal pathogens, using both commercial kit and in-house techniques, remained negative. Interferon-gamma release assay (IGRA) for tuberculosis and multiple serology tests (HBV, HCV, *Toxoplasma gondii*, HIV, Borrelia, *Treponema pallidum*, Puumala virus) were negative. We now waited for results of prolonged incubation of the CSF, as well as bacterial 16S rRNA PCR and fungal PCR results from the reference laboratory, which later came back negative (online supplemental table S1).

On day 12, there was a sudden increase in CRP to 199 mg/L. It was uncertain whether this was due to a flare of her underlying GPA or infection, and in the latter case, what microbiological agent could be the cause. The otolaryngologist consultant perceived the clinical and radiological findings most likely as signs of GPA activity, but the lesions described were inaccessible for biopsy. Rheumatology consultants advised against additional immunosuppressive therapy, as an infectious cause was considered more likely than ANCA-associated vasculitis with meningeal involvement. Meropenem was discontinued after 13 days due to lack of improvement. With possible bone destruction and an immunocompromised patient, there was consensus of fungal infection being a likely cause and liposomal amphotericin B was initiated.

The next few days, the patient experienced back pain and her hearing impairment worsened. CRP increased to 375 mg/L. Vital signs were still stable. Mucorales PCR and *U. urealyticum* PCR in CSF came back negative (online supplemental table S1). Due to a clinical suspicion of fungal or mycobacterial aetiology, a new lumbar puncture was necessary to ensure sufficient volumes for adequate diagnostics, but the patient was reluctant. Eventually, a lumbar puncture was performed in sedation on day 19. The pleocytosis had declined to 1285 × 10^6/L (77% PMN); protein levels were still elevated and glucose was low (online supplemental

table S1). A new MRI showed thickening and marked contrast enhancing of the leptomeninges around the brain, medulla and nerve roots of the cauda equina. The CSF was now analysed in another in-house 16S rRNA PCR assay using different PCR primers than those previously used (online supplemental table S1). Sequencing of this PCR product identified the presence of *Ureaplasma* DNA, but due to the concurrent presence of the same level contaminant bacterial DNA from reagents used to prepare the sample, the result was deemed inconclusive.

A firm diagnosis was still not established, CRP kept rising and her condition deteriorated. Considering treatment options, the focus was now on rare infective agents so far not adequately covered, such as intracellular bacteria and non-tuberculous mycobacteria. On day 19, doxycycline, linezolid and moxifloxacin were initiated (figure 1). The following day, CRP declined from 376 to 277 mg/L. The patient was, however, less cooperative and refused any oral intake including tablets and nasogastric tube insertion. She was therefore transferred to the intensive care unit (ICU). Doxycycline was only available as tablets, and sedation was necessary for her to accept the nasogastric tube. Light sedation was used to be able to monitor her cerebral symptoms.

After 24 hours in the ICU, she was clinically stable with CRP further declining, but developed a high fever for the first time. High-dose steroid therapy was discussed with the rheumatology consult, as a flare of GPA still was a possible differential diagnosis. A meningeal biopsy was regarded necessary to establish the diagnosis. A craniotomy was performed on day 21, revealing thickening of the dura and pus in the subarachnoid space. Intubation was only possible with a small 5.0 oral tube due to her known subglottic tracheal stenosis and for safety reasons the patient was kept sedated on a ventilator overnight and planned for a tracheostomy and cessation of sedation the next day. A cerebral CT later the same night showed normal postoperative status. The following morning, that is, about 5 weeks after onset of her illness and 22 days after her first admission to the hospital, the patient presented with hyperacute hypertension, tachycardia and dilatation of pupils. Acute treatment with hyperventilation and infusion of hypertonic saline solution was performed, followed by an emergency cerebral CT scan showing diffuse oedema in the cerebrum, transtentorial herniation and reduced contrast filling of the intracranial arteries. The patient died not long after.

Around the time of death, the microbiology laboratory reported preliminary results from 16S rRNA sequencing of a PCR product from the meningeal biopsies, consistent with the finding of *U. parvum* DNA (online supplemental table S1). Autopsy revealed pus in all parts of the meninges. There were no signs of granulomatous inflammation indicative of GPA activity. Samples from spinal fluid, meningeal pus, meninges and adjacent brain tissue examined using the same 16S rRNA PCR primers, confirmed the presence of *U. parvum* DNA. Remaining eluates from previous CSF samples which previously reported negative for 16S rDNA analyses were re-evaluated using these primer pairs. *U. parvum* DNA was identified also in these samples. Moreover, the microbiology laboratory rapidly established an in-house *U. parvum* PCR,[43] which was positive in all available eluates from central nervous system (CNS) specimens, as well as in the eluates from ear and nasal discharge sampled days earlier (online supplemental table S1). There were no other positive analyses for an infectious agent (bacterial, fungal or viral). Evaluation of the PCR primers used in the initial 16S rDNA analyses showed significant target mismatch at the 3'end, which likely led to the initial false negative PCR results.

OUTCOME

Final diagnosis: the cause of death was brain herniation, as result of extensive meningitis caused by *U. parvum*.

DISCUSSION

Identifying *Ureaplasma* spp. as the causative agent of infection can be challenging, leading to prolonged illness, delayed diagnosis and increased mortality, as described in previous case reports. The unfortunate fatal outcome in this case report clearly illustrates the increased risk and serious nature of infections in the immunocompromised patient, who is prone to infections with both common and opportunistic pathogens.[44 45] Here, a definitive diagnosis and hence targeted treatment was delayed due to multiple factors. It was uncertain whether the likely cause was infectious or manifestations of the underlying disease. The inability to identify a causative infectious agent, despite extensive analyses, contributed to uncertainty in the assessment. Neither colleagues at the department of infectious diseases nor those at the department of rheumatology wanted to initiate immunosuppressive treatment against a possible GPA flare until we were more certain that the current illness was not caused by infection.

Significant CSF pleocytosis and particularly low glucose in combination with high lactate is indicative of an infectious cause. However, her clinical condition was remarkably stable during the first weeks. This is unusual for the most prevalent causes of acute infectious meningitis. Due to lack of improvement on broad antibacterial coverage with beta-lactam meropenem, we performed analyses for rare and opportunistic microbes. We particularly suspected a fungal cause for which empirical treatment was given for some time in order to assess possible clinical improvement. Unfortunately, this was not the case, as no fungal pathogen was detected and improvement failed to appear.

Adequate molecular diagnostics is critical when antimicrobials have been administered, cultures are negative and/or intracellular or fastidious microbes that do not grow on routine media are suspected. Here, unfortunately, a PCR primer-target mismatch likely led to false-negative results of the broad-range 16S rRNA PCR analyses of the initial CSF samples. Multiple pathogen-specific PCR analyses were applied in the extensive search for a causative pathogen, including *U. urealyticum* PCR, but unfortunately no *U. parvum* PCR was available prior to this incident. Although theoretically universal, the sensitivity of the 16S rRNA PCR assay is related to primer selection.[46 47] Metagenomic next-generation sequencing (mNGS) is an alternative unbiased diagnostic tool to identify suspected but unidentified pathogens. Although not yet available in our country, this method has become available at some clinical laboratories within recent years. Six cases report identifying invasive *Ureaplasma* infection using mNGS, five of them in patients with meningitis.[9 10 14 33 48 49] Hopefully, this method will become more widely available in the future.

Ureaplasma as a cause of infection in the central nervous system is considered extremely rare in adults. Only a few cases on adult CNS infections with *Ureaplasma* exist as of today.[10–14 27] Three of them report concomitant hypogammaglobulinaemia, similar to our patient.[12 14 27] Two other cases describe prior brain surgery[10 11] and one case a complicated kidney transplantation and organ rejection before onset of *Ureaplasma* meningitis.[13] We speculate that *Ureaplasma* as causative pathogen of infections in the CNS may not be as uncommon as generally believed. Here, the identification of *U. parvum* DNA from the ear and nasal discharge samples, combined with the patient's history of chronic otitis, suggest that this as a likely origin of infection and

route of entry to the CNS. Patients with hypogammaglobulinaemia appear more susceptible to colonisation with *Ureaplasma* and *Mycoplasma* of mucous membranes.[50]

Ureaplasma are intracellular bacteria that lack cell wall and are therefore naturally resistant to cell wall active beta-lactam antibiotics, which was given as empirical treatment in this case. Macrolides, tetracyclines, chloramphenicol and quinolones are preferred antibiotics in *Ureaplasma* infections. However, empirical data on treatment of *Ureaplasma* meningitis are sparse. Due to impaired CNS penetration, macrolides alone is not the preferred treatment option. There is also concern for increasing antibiotic resistance.[51] It has therefore been suggested that patients with severe infection caused by *Ureaplasma* are treated with agents from two different antibiotic classes to increase the likelihood of therapeutic success.[21]

Even in the presence of a known, susceptible organism and administration of appropriate antibiotics, the overall mortality in bacterial meningitis is high; in developed countries 10%–30%.[52] Together with septic shock, cerebral oedema with herniation and cerebral infarction are the main causes of death in bacterial meningitis.[53] In this case, a cerebral CT scan performed the night before herniation was inconspicuous. This may be explained by a very abrupt deterioration with increase in intracranial pressure (ICP), or by the fact that CT findings correlate poorly with invasive ICP measurements in this setting.[54 55] For patients with bacterial meningitis and severely impaired consciousness on admission, early neurointensive care with ICP monitoring and CSF drainage reduced mortality.[56 57] Raised ICP is observed in bacterial meningitis, even with low clinical suspicion, and has been associated with poor outcome. Therefore, some authors advocate that all patients with bacterial meningitis and severe impairment of consciousness should receive monitoring of ICP. However, evidence is sparse, and current guidelines advise not to use ICP-targeted treatment protocols for routine care of meningitis patients until this has been evaluated in randomised controlled trials.[58 59]

Learning points

- It is important to consider rare pathogens like intracellular bacteria such as *Ureaplasma parvum* when there is treatment failure with cell-wall targeting antibiotics, particularly in the immunosuppressed patient.
- Repeated sampling and alternative diagnostic assays may be necessary when standard microbiological testing is negative.
- Broad-range 16S rRNA PCR is useful in the identification of rare, unusual or difficult-to-culture bacteria, but has limitations. It is well known that the sensitivity is lower compared with agent-specific PCRs, prone to bias from bacterial DNA contamination, and that no PCR primers are absolutely universal. A negative broad-range PCR result should not be used to exclude infection when clinical suspicion prevails.
- Intracranial pressure monitoring in severe bacterial meningitis is not recommended by routine but should be considered in unconscious patients as cerebral oedema can arise rapidly.

Contributors All authors were responsible for drafting of the text, investigation results and critical revision for important intellectual content. All authors were responsible for drafting and revision of majority of the contents of the manuscript. BE: creating figure of time line. MSH: generating overview of microbiological analyses as shown in Table 1. All authors gave final approval of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

Provenance and peer review Not commissioned; externally peer reviewed.

Author note The PCR primer sequences used to diagnose the causative agent are stated in the supplementary table

ORCID iDs
Birgitta Ehrnström http://orcid.org/0000-0003-4233-5725
Jo Bønding Andreasen http://orcid.org/0000-0002-6615-4438

REFERENCES

1 McCormack WM, Almeida PC, Bailey PE, *et al*. Sexual activity and vaginal Colonization with genital Mycoplasmas. *JAMA* 1972;221:1375–7.
2 Domingues D, Tavira LT, Duarte A, *et al*. Ureaplasma Urealyticum Biovar determination in women attending a family planning clinic in Guine-Bissau, using polymerase chain reaction of the multiple-banded antigen gene. *J Clin Lab Anal* 2002;16:71–5.
3 Clegg A, Passey M, Yoannes M, *et al*. High rates of genital Mycoplasma infection in the Highlands of Papua New Guinea determined both by culture and by a commercial detection kit. *J Clin Microbiol* 1997;35:197–200.
4 Kim Y, Kim J, Lee KA. Prevalence of sexually transmitted infections among healthy Korean women: implications of Multiplex PCR pathogen detection on antibiotic therapy. *J Infect Chemother* 2014;20:74–6.
5 Zhang N, Wang R, Li X, *et al*. Are Ureaplasma Spp. a cause of Nongonococcal Urethritis? A systematic review and meta-analysis. *PLoS ONE* 2014;9:e113771.
6 Sprong KE, Mabenge M, Wright CA, *et al*. Ureaplasma species and Preterm birth: Current perspectives. *Crit Rev Microbiol* 2020;46:169–81.
7 Sweeney EL, Kallapur SG, Gisslen T, *et al*. Placental infection with Ureaplasma species is associated with histologic Chorioamnionitis and adverse outcomes in moderately Preterm and late-Preterm infants. *J Infect Dis* 2016;213:1340–7.
8 Wang Q, Wang K, Zhang Y, *et al*. Neonatal Ureaplasma Parvum meningitis: a case report and literature review. *Transl Pediatr* 2020;9:174–9.
9 Zhan C, Chen L, Hu L. Neonatal Ureaplasma Parvum meningitis complicated with Subdural Hematoma: a case report and literature review. *BMC Infect Dis* 2021;21:268.
10 Xing N, Zhao Z, Li Q, *et al*. Ureaplasma Parvum meningitis following atypical Choroid plexus papilloma resection in an adult patient: a case report and literature review. *BMC Infect Dis* 2021;21:1276.
11 Pailhoriès H, Chenouard R, Eveillard M, *et al*. A case of Ureaplasma Parvum meningitis in an adult after Transphenoidal ablation of Craniopharyngioma. *Int J Infect Dis* 2019;u84:5–7.
12 Madlener M, Breuninger M, Meißner A, *et al*. Brain abscess with Ureaplasma Parvum in a patient with granulomatosis with polyangiitis. *Infection* 2023;51:779–82.
13 Geissdörfer W, Sandner G, John S, *et al*. Ureaplasma Urealyticum meningitis in an adult patient. *J Clin Microbiol* 2008;46:1141–3.
14 Zhang T, Li H, Hou S, *et al*. Case report of Ureaplasma Urealyticum meningitis in a patient with Thymoma and Hypogammaglobulinaemia. *BMC Infect Dis* 2021;21:1142.
15 Heilmann C, Jensen L, Jensen JS, *et al*. Treatment of resistant Mycoplasma infection in immunocompromised patients with a new Pleuromutilin antibiotic. *J Infect* 2001;43:234–8.
16 Lapusan DL, Duffy L, Hamilos DL. Disseminated septic arthritis in a patient with common variable Hypogammaglobulinemia. *Ann Allergy Asthma Immunol* 2001;86:368–72.
17 Frangogiannis NG, Cate TR. Endocarditis and Ureaplasma Urealyticum Osteomyelitis in a Hypogammaglobulinemic patient. A case report and review of the literature. *J Infect* 1998;37:181–4.
18 Asmar BI, Andresen J, Brown WJ. Ureaplasma Urealyticum arthritis and bacteremia in Agammaglobulinemia. *Pediatr Infect Dis J* 1998;17:73–6.
19 Puéchal X, Hilliquin P, Renoux M, *et al*. Ureaplasma Urealyticum destructive septic Polyarthritis revealing a common variable immunodeficiency. *Arthritis Rheum* 1995;38:1524–6.
20 Cordtz J, Jensen JS. Disseminated Ureaplasma Urealyticum infection in a hypo-Gammaglobulinaemic renal transplant patient. *Scand J Infect Dis* 2006;38:1114–7.

21 Jhaveri VV, Lasalvia MT. Invasive Ureaplasma infection in patients receiving Rituximab and other humoral Immunodeficiencies-A case report and review of the literature. *Open Forum Infect Dis* 2019;6:ofz399.
22 El Zein S, Garvey T, Amin S, *et al*. Native joint Polyarticular septic arthritis secondary to disseminated Ureaplasma Urealyticum infection in a patient on Rituximab therapy with Hypogammaglobulinemia: A case report. *IDCases* 2023;32:e01744.
23 Schwartz DJ, Elward A, Storch GA, *et al*. Ureaplasma Urealyticum Pyelonephritis presenting with progressive Dysuria, renal failure, and neurologic symptoms in an immunocompromised patient. *Transpl Infect Dis* 2019;21:e13032.
24 Schwartz S, Aldrich A, Kessler E, *et al*. Disseminated Ureaplasma Polyarthritis in a renal transplant recipient. *Pediatr Transplant* 2023;27:e14538.
25 Arber C, Buser A, Heim D, *et al*. Septic Polyarthritis with Ureaplasma Urealyticum in a patient with prolonged Agammaglobulinemia and B-cell Aplasia after allogeneic HSCT and Rituximab pretreatment. *Bone Marrow Transplant* 2007;40:597–8.
26 Goulenok TM, Bialek S, Gaudart S, *et al*. Ureaplasma Urealyticum destructive septic arthritis in a patient with systemic lupus erythematosus after Rituximab therapy. *Joint Bone Spine* 2011;78:323–4.
27 Deetjen P, Maurer C, Rank A, *et al*. Brain abscess caused by Ureaplasma Urealyticum in an adult patient. *J Clin Microbiol* 2014;52:695–8.
28 George MD, Cardenas AM, Birnbaum BK, *et al*. Ureaplasma septic arthritis in an immunosuppressed patient with juvenile idiopathic arthritis. *J Clin Rheumatol* 2015;21:221–4.
29 Harold R, Simon GL, Akselrod H, *et al*. Ureaplasma septic polyarthritis in a young woman with neuromyelitis optica receiving rituximab. *BMJ Case Rep* 2021;14:e237916.
30 Verhagen I, Oudenhoven H, van Welzen B, *et al*. Ureaplasma Parvum bacterial arthritis of the elbow in a patient with rheumatoid arthritis treated with Rituximab. *Rheumatology (Oxford)* 2021;60:e17–8.
31 Gremark A, Axelsson O. Urogenital Ureaplasma Urealyticum can cause invasive infection in immunosuppressed patients. *Lakartidningen* 2022;119:22038.
32 Kvalvik SA, Skarstein I, Veddeng A, *et al*. An immunocompromised woman in her twenties with abdominal pain and vaginal discharge. *Tidsskr Nor Laegeforen* 2020;140:16.
33 Garzaro M, Zhao L-P, De Castro N, *et al*. Metagenomic next-generation sequencing restores the diagnosis of a rare infectious complication of B cell depletion. *Eur J Clin Microbiol Infect Dis* 2022;41:1269–73.
34 Gassiep I, Gore L, Dale JL, *et al*. Ureaplasma *Urealyticum Necrotizing* soft tissue infection. *J Infect Chemother* 2017;23:830–2.
35 Roerdink RL, Douw CM, Leenders ACAP, *et al*. Bilateral Periprosthetic joint infection with Ureaplasma Urealyticum in an immunocompromised patient. *Infection* 2016;44:807–10.
36 MacKenzie CR, Nischik N, Kram R, *et al*. Fatal outcome of a disseminated dual infection with drug-resistant Mycoplasma Hominis and Ureaplasma Parvum originating from a septic arthritis in an immunocompromised patient. *Int J Infect Dis* 2010;14 Suppl 3:e307–9.
37 Lemoine L, Le Brun C, Maillot F, *et al*. Dual Ureaplasma Parvum arthritis: a case report of U. Parvum septic arthritis following contralateral reactive arthritis in an immunosuppressed patient. *BMC Infect Dis* 2021;21:1117.
38 Yazdani M, Thupili CR. Cystitis, Pyelonephritis and Perinephric abscess due to Ureaplasma Urealyticum. *J Urol* 2012;188:2373–4.
39 Alhamadh MS, Alhowaish TS, Mathkour A, *et al*. Infection risk, mortality, and Hypogammaglobulinemia prevalence and associated factors in adults treated with Rituximab: A tertiary care center experience. *Clin Pract* 2023;13:1286–302.
40 Roberts DM, Jones RB, Smith RM, *et al*. Rituximab-associated Hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun* 2015;57:60–5.
41 Patel A, Harris KA, Fitzgerald F. What is broad-range 16S rDNA PCR *Arch Dis Child Educ Pract Ed* 2017;102:261–4.
42 Aggarwal D, Kanitkar T, Narouz M, *et al*. Clinical utility and cost-effectiveness of bacterial 16S rRNA and targeted PCR based diagnostic testing in a UK Microbiology laboratory network. *Sci Rep* 2020;10:7965.
43 Vancutsem E, Soetens O, Breugelmans M, *et al*. Modified real-time PCR for detecting, differentiating, and Quantifying Ureaplasma Urealyticum and Ureaplasma Parvum. *J Mol Diagn* 2011;13:206–12.
44 van Veen KEB, Brouwer MC, van der Ende A, *et al*. Bacterial meningitis in patients using immunosuppressive medication: a population-based prospective nationwide study. *J Neuroimmune Pharmacol* 2017;12:213–8.
45 Glimåker M, Naucler P, Sjölin J. Etiology, clinical presentation, outcome and the effect of initial management in immunocompromised patients with community acquired bacterial meningitis. *J Infect* 2020;80:291–7.
46 Church DL, Cerutti L, Gürtler A, *et al*. Performance and application of 16S rRNA gene cycle sequencing for routine identification of bacteria in the clinical Microbiology laboratory. *Clin Microbiol Rev* 2020;33:e00053-19.
47 Morel A-S, Dubourg G, Prudent E, *et al*. Complementarity between targeted real-time specific PCR and conventional broad-range 16S rDNA PCR in the syndrome-driven diagnosis of infectious diseases. *Eur J Clin Microbiol Infect Dis* 2015;34:561–70.
48 Qin L, Li Y-H, Cao X-J, *et al*. Clinical Metagenomic sequencing for rapid diagnosis of neonatal meningitis caused by Ureaplasma Parvum: A case report. *Medicine* 2022;101:e28662.
49 Duan J, Zhang C, Wang J, *et al*. Diagnosis of Ureaplasma Parvum meningitis by mNGS in an extremely low birth weight infant with multi-system lesions. *Indian J Med Microbiol* 2022;40:455–8.
50 Furr PM, Taylor-Robinson D, Webster AD. Mycoplasmas and Ureaplasmas in patients with Hypogammaglobulinaemia and their role in arthritis: Microbiological observations over twenty years. *Ann Rheum Dis* 1994;53:183–7.
51 Beeton ML, Spiller OB. Antibiotic resistance among Ureaplasma Spp. isolates: cause for concern *J Antimicrob Chemother* 2017;72:330–7.
52 McGill F, Heyderman RS, Panagiotou S, *et al*. Acute bacterial meningitis in adults. *Lancet* 2016;388:3036–47.
53 Larsen L, Poulsen FR, Nielsen TH, *et al*. Use of intracranial pressure monitoring in bacterial meningitis: a 10-year follow up on outcome and intracranial pressure versus head CT scans. *Infect Dis (Lond)* 2017;49:356–64.
54 Gladstone RA, McNally A, Pöntinen AK, *et al*. Emergence and dissemination of antimicrobial resistance in Escherichia coli causing bloodstream infections in Norway in 2002-17: a nationwide, longitudinal, microbial population Genomic study. *Lancet Microbe* 2021;2:e331–41.
55 Winkler F, Kastenbauer S, Yousry TA, *et al*. Discrepancies between brain CT imaging and severely raised intracranial pressure proven by Ventriculostomy in adults with Pneumococcal meningitis. *J Neurol* 2002;249:1292–7.
56 Lindvall P, Ahlm C, Ericsson M, *et al*. Reducing intracranial pressure may increase survival among patients with bacterial meningitis. *Clin Infect Dis* 2004;38:384–90.
57 Glimåker M, Johansson B, Halldorsdottir H, *et al*. Neuro-intensive treatment targeting intracranial hypertension improves outcome in severe bacterial meningitis: an intervention-control study. *PLoS One* 2014;9:e91976.
58 Cook AM, Morgan Jones G, Hawryluk GWJ, *et al*. Guidelines for the acute treatment of cerebral edema in Neurocritical care patients. *Neurocrit Care* 2020;32:647–66.
59 van de Beek D, Cabellos C, Dzupova O, *et al*. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clinical Microbiology and Infection* 2016;22:S37–62.