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CASE SERIES

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# The Utility of Plasma Microbial Cell Free DNA Testing in the Diagnosis of *Ureaplasma spp* Infections: A Case Series

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Volume 65 - Issue 12 - December 2025

*Ureaplasma* spp are normal colonizers of the urogenital tract in adults. They are implicated in a variety of infections in patients who are immunocompromised. *Ureaplasma* spp are difficult to diagnose because cultures require selective media, which results in delayed recognition and effective therapy. In addition, this diagnosis is rarely considered early in a patient's evaluation. Patients with immunosuppression have an increased risk for serious infections, including septic arthritis and disseminated disease.

Here, we present two cases of disseminated *Ureaplasma* spp infections in patients with iatrogenic hypogammaglobulinemia due to rituximab therapy. After diagnostic delays, both patients were ultimately identified via microbial cell–free DNA (mcfDNA) testing of plasma, which prompted appropriate treatment and clinical improvement.

Our cases illustrate the challenges in diagnosing *Ureaplasma* spp infections and demonstrate that plasma mcfDNA can facilitate prompt diagnosis in patients with immunosuppression when suspicion of infection is high and routine cultures are negative. Based on our case series, we encourage clinicians to consider plasma mcfDNA as an early adjunct to standard testing in the work-up of (seronegative) septic arthritis and/or disseminated infections in patients with immunosuppression.

**Introduction.** Septic arthritis and other life-threatening infections warrant rapid diagnosis and treatment to avoid serious complications and death. Mortality from septic arthritis is high at 11.5% and patients with rheumatologic conditions are at an even higher risk due to underlying joint damage and immunosuppressive treatments.[1,2]

In patients with immunosuppression, septic arthritis can be caused by an array of organisms including, but not limited to, mycobacteria, fungal pathogens, uncommon gram-negative bacteria, *Listeria*, *Mycoplasma*, and *Ureaplasma* species. *Ureaplasma* spp have been implicated in a variety of urogenital, surgical site

and *Ureaplasma* species. *Ureaplasma* spp have been implicated in a variety of urogenital, surgical site, and neonatal infections, even in patients who are immunocompromised.[3,4] There is a well-established association between humoral deficiency and *Ureaplasma* spp, recognized in the literature since the 1970s.[4-6] With the growing use of rituximab, a monoclonal antibody medication used to treat certain autoimmune diseases and types of cancer[7], patients receiving this treatment are at high risk of developing *Ureaplasma* spp infections. In a case series of 24 invasive *Ureaplasma* spp infections, 83% (20/24) were cases of septic arthritis, 79% (19/24) were cases involving patients who were immunocompromised (seven with common variable immunodeficiency; seven were on rituximab).[4]. *Ureaplasma* spp are not detected by routine culture media and require a specialized culture or 16S rRNA polymerase chain reaction (PCR) assay for diagnosis.[3] Plasma microbial cell free DNA (mcfDNA) has the potential to assist in diagnosing rare, atypical infections relatively quickly, helping prevent serious complications or mortality. Here, we present two cases of *Ureaplasma* spp septic arthritis in patients with iatrogenic hypogammaglobulinemia from rituximab who were ultimately diagnosed using plasma mcfDNA.

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**Case 1.**

**History:** A 26-year-old woman with systemic lupus erythematosus and class V lupus nephritis treated with hydroxychloroquine and rituximab (last dose 7 months prior), presented to the emergency department with acute left knee pain. She was afebrile, tachycardic, and normotensive. Her physical examination revealed an erythematous, painful, swollen, left knee with severely restricted range of motion.

**Diagnostic testing:** Her initial laboratory tests revealed neutrophilic leukocytosis of 21,000 c/mm^3 (4500 - 11000 c/mm^3), an erythrocyte sedimentation rate (ESR) of 64 mm/hr (0-20mm/hr), and a C-reactive protein (CRP) of 32 mg/L (0-10 mg/L). Synovial fluid analysis revealed an elevated total nucleated cell count (TNC) of 21,000 c/mm^3. Routine synovial and blood cultures (aerobic and anerobic) were sent but were ultimately negative for growth. Based on the patient's presentation, physical examination, and laboratory tests, we had the highest suspicion for septic arthritis; lower on differential was flare of inflammatory arthritis related to lupus.

**Differential diagnoses:** The potential diagnoses included a broad array of infections including common causes of septic arthritis such as staphylococcal and streptococcal species, as well as gonococcal disease. Other possibilities included rarer bacteria, reactive arthritis syndromes, and a flare of the patient's underlying rheumatologic disease.

**Treatment and outcome:** Given the concern for septic arthritis, orthopedic surgery was consulted and ultimately performed an arthroscopy. After the arthroscopy, empiric cefazolin was started (Cefazolin 2g q8hr for 4-6 weeks) and she was discharged home. Thirteen days after discharge, the patient returned to the emergency department due to persistent left knee pain and an inability to ambulate despite adherence to intravenous (IV) antibiotics. She underwent two additional joint aspirations with findings concerning for septic arthritis, but fluid cultures remained negative.

One day later, a repeat arthroscopy with washout was performed, which revealed chronic inflammatory changes with extensive adhesions. Her synovial gram stain revealed numerous white blood cells but no

bacteria. She was admitted and continued cefazolin (2g q8hr for 4-6 weeks) with infectious disease consultation. Multiple blood cultures and synovial fluid cultures remained negative.

The patient developed left wrist pain and swelling (Day 29); thus, an alternative diagnosis of an acute lupus flare was considered. Rheumatology was consulted and the patient was prescribed prednisone and hydroxychloroquine. Prednisone 30mg daily and hydroxychloroquine 200 mg daily. Initial rheumatologic workup was significant for an immunoglobulin G (IgG) level of 520 mg/dl (normal range, 650 –1600). Plasma mcfDNA was ordered on day 38.

On Day 40, the plasma mcfDNA testing results showed elevated levels of *Ureaplasma urealyticum*. Therefore, we initiated treatment with doxycycline while simultaneously tapering off steroids. Doxycycline 100mg q12h for at least 30 days, again final duration pending clinical improvement after discharge. Differential agar media culture, which was a send out test, resulted positive for *Ureaplasma* sp on Day 50. Adjuvant therapy with IV immunoglobulin (IVIG) was initiated on day 50 due to persistent hypogammaglobulinemia (IgG level 450 mg/dl) and lack of clinical improvement along with addition of moxifloxacin. (Moxifloxacin 400mg daily.)

Over the course of the next few days, her symptoms and pain significantly improved. She was discharged on Day 55 with oral doxycycline and moxifloxacin with the same dosages and durations. Upon outpatient follow-up 12 weeks after discharge, her symptoms had resolved except persistent pain and swelling in the left knee. Joint aspiration of the left knee revealed a small amount of fluid and *Ureaplasma* spp PCR was negative from synovial fluid. An MRI of the left knee revealed post-infectious degenerative changes. She completed the combination regime of oral moxifloxacin and doxycycline for 4 months without any adverse events.

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**Case 2.**

**History:** A 30-year-old woman with a history of B-cell acute lymphoblastic leukemia on maintenance therapy with vincristine-prednisone-dasatinib-rituximab, presented with acute left shoulder pain. Her physical examination revealed left shoulder tenderness and swelling with restricted range of motion.

**Diagnostic testing:** The patient's initial laboratory tests revealed a normal WBC count, an ESR of 26 mm/hr (0-20mm/hr), and a CRP of 9.1 mg/L (0-10 mg/L). Her synovial fluid analysis revealed an elevated total nucleated cell count of 18,700 c/mm^3. Routine synovial and blood cultures (aerobic and anerobic) were sent, and the patient received a one-time dose of vancomycin and piperacillin-tazobactam; her cultures were ultimately negative for growth.Vancomycin 1250mg x 1 and I am unsure of the piperacillin-tazobactam dose. Septic arthritis was highest on the differential, then a flare of inflammatory arthritis secondary to possible autoimmune disease, or reactive arthritis of unknown trigger.

**Differential diagnosis:** The differential diagnoses considered in this case was similar to Case 1, broadly considering infections versus autoimmune/reactive versus flare of her underlying rheumatologic condition.

**Treatment and outcome:** She was discharged with 5-days of cephalexin 1000mg every 8 hr but was subsequently re-admitted for ongoing diffuse joint pain and fever. Vancomycin and cefepime were initiated

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Vancomycin 1250mg x 1, cefepime 2g x 1 then 1g q8hr. She underwent an arthroscopy and washout of her left shoulder, as well as arthrocentesis of her right knee (days 8 and 18, respectively). Synovial fluid studies were notable for an elevated TNC count of 12,150 c/mm^3. Cultures continued to be negative, and she was presumed to have a reactive arthritis flare and treated with a prednisone taper Prednisone 60mg daily that was tapered off over 5 weeks. Her IgG level was low at 126 mg/dL. In addition, she was found to have a new exudative pleural effusion. Extensive infectious and rheumatologic workup were negative, including anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), cyclic citrullinated peptide (CCP), rheumatoid factor (RF), Anti-streptolysin O (ASO), and anti-DNase antibodies.

Forty-two days from the initial presentation, she returned with worsening symptoms of malaise, shortness of breath, and multiple joint pains, despite her steroid course. She also endorsed new watery diarrhea. She was admitted to the hospital and was started on IV methylprednisolone 40 mg daily. However, her symptoms continued to worsen, and she developed septic shock. She was transferred to the intensive care unit on Day 44. She required pressors for blood pressure support, and broad-spectrum antibiotic therapy was initiated (vancomycin, cefepime, and metronidazole). On the third day of this admission (Day 45), doxycycline 100 mg twice daily was added empirically with rapid clinical improvement. Plasma mcfDNA was ordered and sent on Day 48, and 2 days later returned positive for *Ureaplasma parvum* (Day 50). She was tapered off steroids, and treatment was targeted for *U. parvum* with azithromycin and doxycycline. Doxycycline 100mg q12h x 28 days, azithromycin 500mg/d x 7 days She was also given a dose of IVIG for hypogammaglobulinemia. She continued to improve and was discharged in stable condition (Day 56 total) and completed a 28-day course of doxycycline and azithromycin.

**Discussion.** Septic arthritis is a rheumatologic emergency, with an average mortality of 7%-15%, and upwards of 30% in elderly patients.[8] Despite clinical improvement, patients may face long-term sequelae secondary to joint destruction, including a six-fold increase in the annual risk of arthroplasty.[9] Prompt diagnosis is imperative for joint preservation. Delays only compound these poor outcomes while increasing total costs.[10]

Many infections, including septic arthritis, can be difficult to diagnose in patients who are immunocompromised. These patients may not exhibit classic signs and symptoms of septic arthritis due to a blunted immune response and they often have an insidious, rather than acute, onset of symptoms.[11-13] Furthermore, the causative organism(s) of septic arthritis in this patient population can be atypical, rare, and/or undetectable by standard culture methods as demonstrated in this case series. Our cases illustrate this challenge, featuring significant delays in diagnosis (which caused ongoing morbidity), excess hospital length of stay, and overuse of antibiotics.

Treatment duration for disseminated infections can vary depending on the clinical scenario and specific antibiotic used. A combination of azithromycin and doxycycline is recommended for 6 to 12 weeks; however, the duration should be tailored to the patient's clinical response and susceptibility testing results whenever available. Prognosis varies and depends on early diagnosis and degree of immunosuppression. It was not until much later in the workup that a fastidious pathogen was considered, and plasma mcfDNA was able to facilitate a rapid diagnosis at that time.

Plasma mcfDNA assists in the diagnosis of fastidious pathogens requiring specialized growth media (e.g., *Ureaplasma* spp), pathogens that cannot be cultured (e.g., *Bartonella*), and other uncommon or novel pathogens. Plasma mcfDNA can have a rapid turnaround time of 2-3 days. The Karius test is a commercially available plasma mcfDNA test that is Clinical Laboratory Improvement Amendments approved. It utilizes a small sample of a patient's plasma and can report more than 1000 species of bacteria, fungi, viruses, and parasites (that are present at a number greater than a defined threshold)[14-15]. Being able to quickly test for many pathogens is advantageous in patients who are immunocompromised when infection is suspected, and the differential is broad. Our cases demonstrate this notion as well, in which plasma mcfDNA was able to establish a diagnosis of disseminated *Ureaplasma* septic arthritis within a few days.

A prior review of *Ureaplasma* spp infections demonstrated significant burden of disease in patients who are immunocompromised and difficulty in timely diagnosis.[16] Our current case series highlight the utility of this test in overcoming those challenges. Furthermore, rituximab and similar B-cell depleting therapies are widely used and use is increasing exponentially,[17] thus we expect that the burden of *Ureaplasma* spp infections will only increase in the future. It is important that physicians consider this diagnosis and are aware of newer, rapid diagnostic options.

While plasma mcfDNA is promising, it is not without limitations. Concerns remain regarding standardization of mcfDNA methodology.[18] In addition, it can be difficult to differentiate infection from colonization,[18] although interpretation can be easier when results indicate a pathogen not known to be a colonizer in humans (e.g., *Mycobacterium tuberculosis* or *Ureaplasma* spp in this case). Despite these limitations, the use of plasma mcfDNA is becoming more widespread.[14-15, 18-21]

**Conclusion:** Plasma mcfDNA is a promising, non-invasive diagnostic tool that can hasten time to diagnosis, improving patient outcomes and potentially decreasing care costs. It should be considered early as an adjunct to standard testing in scenarios involving patients who are immunocompromised with (seronegative) septic arthritis and those with complex, multi-system febrile or inflammatory syndromes for which an infection is suspected. This is especially true in rheumatologic patients who are currently receiving B-cell-depleting drug therapies such as rituximab, where *Ureaplasma* spp infection is an important consideration.

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**CITATION:**
Austin WJ, Ruiz-Castaneda SM, Kotamarti R, Thyagarajan R, Mondy K, Patel V. The utility of plasma microbial cell–free DNA testing in the diagnosis of *Ureaplasma* spp infections: a case series. *Consultant*. Published online: DOI: 10.25270/con.2025.12.000003

Received March 8, 2025. Accepted July 10, 2025

**DISCLOSURES:**
None.

**ACKNOWLEDGMENTS:**
None.

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