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Ceftriaxone-Induced Hemolysis in a Child With Lyme Arthritis: A Case for Antimicrobial Stewardship

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abstract

Guidelines for the treatment of Lyme arthritis were published by the Infectious Diseases Society of America in 2006 and recommended oral doxycycline for initial therapy. We report here the case of a young girl treated with intravenous ceftriaxone who subsequently developed drug-induced autoimmune hemolytic anemia and renal failure. Her severe sequelae highlight the importance of antimicrobial stewardship. We review here the goals of antimicrobial stewardship and several strategies for achieving them. In addition, we briefly discuss the rare adverse drug event experienced by our patient. *Pediatrics* 2011; 128:e000

Antimicrobial stewardship is an increasingly important topic in this era of emerging bacterial resistance coupled with an empty pipeline for antibiotic development.[1] In addition to minimizing resistance, the goals of an antimicrobial stewardship program, as outlined by the Infectious Diseases Society of America, include enhancing clinical outcomes and improving patient quality and safety.[2] The case of this 11-year-old girl with ceftriaxone-induced renal failure during treatment for Lyme arthritis highlights how 2 strategies of antimicrobial stewardship—adherence to clinical guidelines and the use of oral medications when appropriate[2]—can have a clear effect on patient care and health care outcomes.

CASE REPORT

An 11-year-old girl presented to an orthopedic physician for a 3-week complaint of left knee swelling and morning stiffness. She had been afebrile and had no other complaints. Her past medical history and family history were unremarkable. Her exposure history was significant for tick bites acquired in New York 6 months before the onset of arthritis. She did not have an interim rash or neurologic symptoms. Physical examination was remarkable only for the knee effusion, with mild warmth and erythema of the joint.

The effusion was tapped, which revealed 10 500 white blood cells per μL (78% segmented neutrophils, 22% lymphocytes) and 600 red blood cells per μL. Bacterial culture of the fluid was negative. Blood studies revealed a normal complete blood count and comprehensive metabolic panel but an elevated erythrocyte sedimentation rate (106 mm/hour) and C-reactive protein level (5.6 mg/dL). Her blood tested negative for antinuclear antibody and rheumatoid factor. Results of a whole-

cell enzyme-linked immunosorbent assay for Lyme disease were positive, and results of subsequent immunoblotting were also positive for both immunoglobulin M (IgM) and IgG antibodies (3/3 and 10/10 diagnostically significant IgM and IgG bands present, respectively). Given her tick exposure in an area endemic for Lyme disease and positive *Borrelia burgdorferi* antibody studies, she was diagnosed with Lyme arthritis and started on ceftriaxone via a peripherally inserted central catheter (PICC) for a planned 28 days of treatment.

She followed up 1 week after starting therapy and complained of fever to 102°F with shaking chills and worsening knee pain immediately after her ceftriaxone infusions. She was afebrile and well-appearing in the clinic. Differential diagnosis for her new fever included infection of the PICC or a drug reaction. Laboratory evaluation from that day revealed a mild, normocytic anemia (hemoglobin: 10.3 g/dL; hematocrit: 32%) with no schistocytes. Results of a comprehensive metabolic panel including serum urea nitrogen, creatinine, and liver enzyme tests, were again normal. The erythrocyte sedimentation rate and C-reactive protein level were unchanged, and a blood culture from the PICC remained negative.

Five days later she began having new symptoms including emesis, abdominal pain, and anorexia with mild diarrhea. These symptoms were felt to be consistent with viral gastroenteritis, and no changes were made to her therapy. However, these symptoms persisted, and 2 days later she presented to the emergency department, where her examination was remarkable for mild dehydration and periumbilical tenderness. The knee effusion was still present but had decreased in size, and there was improved range of motion. Laboratory data at this visit, 13

days after the initiation of ceftriaxone, were striking: hemoglobin, 6.9 g/dL; hematocrit, 20%; erythrocytes, normocytic with no schistocytes; blood urea nitrogen, 50 mg/dL; and creatinine, 4.7 mg/dL. She had proteinuria on urinalysis. These results prompted admission for further care, and her ceftriaxone was immediately discontinued.

Additional evaluation revealed positive polyspecific direct antiglobulin test results; subsequent testing revealed that her erythrocytes were IgG-negative and complement component 3–positive. Prothrombin time, partial thromboplastin time, and fibrinogen were within normal limits; her lactate dehydrogenase level was elevated (1006 U/L), as was her D-dimer level (20.7 μg/mL); her haptoglobin level was low at 7 mg/dL. Renal ultrasound revealed enlarged, echogenic kidneys with poor corticomedullary differentiation. Renal biopsy revealed pigment-induced acute tubular necrosis with hemoglobin-type casts consistent with intravascular hemolysis. The glomeruli were normal, and results of immunofluorescence staining were unremarkable. These findings strongly suggested that the etiology of the rapidly decreasing hemoglobin level and renal failure was ceftriaxone-induced immune hemolytic anemia.

The patient's creatinine level continued to rise to a value of 7.2 mg/dL; the estimated creatinine clearance rate was 9.3 mL/minute. On day 2 of admission, hemodialysis was initiated, and she was given a pulse of intravenous methylprednisolone before starting a steroid taper. She required a packed red blood cell transfusion after becoming tachycardic with a hemoglobin level of 5.9 g/dL. Two weeks after admission, both her renal function and anemia had improved such that dialysis was discontinued. Results of a repeat renal ultrasound were normal,

and her urine showed no residual proteinuria or microalbuminuria. She was subsequently treated with 28 days of doxycycline and had complete resolution of her knee arthritis.

DISCUSSION

Clinical practice guidelines for the assessment, treatment, and prevention of Lyme disease were published in 2006 by the Infectious Diseases Society of America[3] and endorsed by the American Academy of Pediatrics. For the initial treatment of Lyme arthritis, the guidelines recommend 28 days of oral doxycycline (in children ≥8 years of age), amoxicillin, or cefuroxime axetil.[3] Recent pediatric literature supports this treatment with outcomes-based data: Tory et al[4] reviewed the medical records of 99 children with Lyme arthritis who were seen at tertiary care children's hospitals from 1997 to 2007. Of the 93 children treated in accordance with the Infectious Diseases Society of America and American Academy of Pediatrics guidelines, 95% achieved cure or remission; the other 5% were lost to follow-up. There were no instances of joint deformity or chronic arthritis. These data illustrate the efficacy of using practice guidelines to achieve optimal clinical outcomes while simultaneously using narrow-spectrum antibiotics, which accomplishes at least 2 goals of antimicrobial stewardship. Furthermore, guidelines can aid in standardizing care for a given illness, particularly when that disease is not one frequently encountered by a given clinician.

In addition to the use of clinical practice guidelines, a second strategy used by antimicrobial stewardship programs is to use oral therapies when appropriate.[2] In addition to decreasing health care costs,[2] this particular strategy targets another goal of antimicrobial stewardship: patient safety. Although the use of antibiotics carries inherent risks no matter the route of administration, the use of long-term, indwelling intravenous catheters, such as the PICC used for our patient, carries additional hazards. A recent study of 221 patients with 279 PICCs at a tertiary children's hospital in Israel found an overall complication rate of 37% necessitating removal: 13.6% were removed for infectious complications, 13.6% were removed for mechanical problems, and 9.3% were accidentally dislodged.[5] Older studies found complication rates from 4% to 29%.[6,7] Another uncommon but serious risk is that of fracture and embolization of the catheter; in a study of 1650 PICCs by Chow et al[8], 11 children required an invasive procedure to retrieve an embolized line fragment. For infections such as Lyme arthritis for which an oral alternative is both available and preferred, medication administration via an intravenous route places patients at unnecessary risk of harm.

Another important aspect of patient safety is physician awareness of the rare but serious adverse effects of commonly prescribed medications. Although ceftriaxone is a frequently used antibiotic in both inpatient and outpatient settings for its convenient dosing schedule and broad coverage of common infections, prescribers should be aware of multiple potential adverse events, including elevation of liver enzyme levels in 3% of patients, diarrhea in 2.7%, leukopenia in 2.1%, and hypersensitivity reactions in 1.7%.[9] Other rare (<0.1%) but serious complications include agranulocytosis, allergic pneumonitis, anaphylaxis, biliary lithiasis, colitis (including *Clostridium difficile* colitis), seizures, serum sickness, and Stevens-Johnson syndrome.[9] In a 2009 retrospective review of adverse drug events in patients who received prolonged outpatient parenteral therapy for osteomyelitis, ceftriaxone was the antibiotic most frequently discontinued as a result of adverse drug events.[10]

Ceftriaxone-induced autoimmune hemolytic anemia has been reported 27 times (including our case) since 1991 (PubMed online search; limits: English; terms: ceftriaxone and hemolysis, ceftriaxone and renal failure).[11–34] Of these 27 patients, 63% were younger than 18 years. Among the pediatric group there was a 47% mortality rate, and 1 additional patient had severe neurologic sequelae. At least 8 children experienced acute renal failure; 5 of the 8 had a fatal outcome. Almost one-third of the 17 pediatric patients had underlying sickle cell disease, and 4 had HIV. It is unclear whether the underlying disease processes contributed to the development of anticeftriaxone antibodies and hemolysis, if repeated exposure to the drug was important, or both.[14]

CONCLUSIONS

The significant sequelae experienced by the patient in this case epitomize how strategies of antimicrobial stewardship—following practice guidelines and choosing oral medication options when available—can maximize clinical outcomes and patient safety. The choice to deviate from consensus guidelines should be taken with great care and be based on the unique circumstances of the individual patient with full awareness of potential adverse effects.

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