

Successful Treatment of Human Granulocytic Ehrlichiosis in Children Using Rifampin

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ABSTRACT. Human granulocytic ehrlichiosis (HGE) is an emerging tick-borne infectious disease caused by *Anaplasma phagocytophilum*. Clinical features include a flu-like illness that usually resolves within 1 week. More serious infection may occur that requires hospital admission or culminates in death. Doxycycline is the treatment of choice for HGE but may cause permanent staining of teeth in children younger than 8 years of age. We report successful treatment of HGE with rifampin in 2 children, 4 and 6 years old. A course of rifampin for 5 to 7 days should be considered in children younger than 8 years of age who experience non-life-threatening *A phagocytophilum* infection. *Pediatrics* 2003;112:e252–e253. URL: <http://www.pediatrics.org/cgi/content/full/112/3/e252>; human granulocytic ehrlichiosis, HGE, *A phagocytophilum*, rifampin.

ABBREVIATIONS. HGE, human granulocytic ehrlichiosis; WBC, white blood cell count.

Human granulocytic ehrlichiosis (HGE), a tick-borne zoonoses that was first reported in 1994, is an emerging public health problem in the northeastern and northern Midwestern United States.¹ The name of the causative pathogen was recently changed from “the agent of human granulocytic ehrlichiosis” to *Anaplasma phagocytophilum*.² While its epidemiologic and public health significance remain to be fully defined, HGE has been responsible for hundreds of cases and several fatalities.^{3–10} Clinical information on HGE in children is limited to individual case reports.^{4,8} Treatment in children is complicated because doxycycline, the antibiotic of choice, may cause permanent staining of the teeth in children younger than 8 years of age.^{11,12} We report 2 children who experienced *A phagocytophilum* infection and were successfully treated with rifampin.

CASE REPORTS

Case 1

A 6-year-old female kindergarten student from northwestern Wisconsin presented on June 17, 1998, with a 1-day history of fever, mild sore throat, intermittent headache, generalized myalgia, malaise, and shaking chills. She had noticed neck pain after

the removal of a small brown tick attached behind her left ear 7 days earlier. The physical examination was unremarkable other than a temperature of 39.8°C. The hemogram showed a white blood cell count (WBC) of $10.9 \times 10^9/L$ with 61% segmented neutrophils, 24% band neutrophils, 10% lymphocytes, and 5% monocytes, and a platelet count of $238 \times 10^9/L$. Microscopic examination of 800 leukocytes on a Wright-stained peripheral blood smear failed to reveal diagnostic inclusions (morulae) in neutrophils. The patient was thought to have a viral syndrome, and she was asked to return for follow-up examination in 48 hours. Her fever exceeded 39°C and her other symptoms persisted.

At a follow-up visit 2 days later on June 19, 1998, the total WBC was $2.5 \times 10^9/L$ and the platelet count was $153 \times 10^9/L$. Hepatic transaminase concentrations in serum were normal and repeated blood smear evaluation failed to detect morulae. HGE was suspected, and she was given oral rifampin (10 mg/kg orally twice daily). Her fever defervesced 24 hours later and she was back to her normal physical activities within 72 hours of the initiation of therapy. Rifampin was stopped after 7 days. The diagnosis of HGE was confirmed when she experienced *A phagocytophilum* seroconversion. Her sera failed to react to *A phagocytophilum* antigen on immunofluorescent antibody testing during acute illness (June 19) but was reactive at dilutions of ≥ 2560 , 1280, and 320, respectively 1, 6, and 12 months later. The patient felt well at the 6-week check-up.

Case 2

A previously healthy 4-year-old female from a wooded area of Connecticut presented to her pediatrician on June 3, 2002, with a 9-day history of fever as high as 40.6°C, shaking chills, sore throat, myalgias, and fatigue. The child had experienced 3 bites by “poppy seed-sized” ticks (thought by her parents to be “deer ticks”) in late spring, the most recent being 3 weeks before admission. There was no history of infectious disease exposures or recent travel. Laboratory studies showed a WBC of $5.5 \times 10^9/L$ (36% granulocytes, 54% lymphocytes, and 9% monocytes with a few atypical lymphocytes), hemoglobin of 12.0 g/dL, platelet count of $93 \times 10^9/L$, and an erythrocyte sedimentation rate of 39 mm/h. Serologic tests for Lyme borreliosis and Epstein Barr virus infection were negative. She was diagnosed to have a viral illness.

Her symptoms continued to worsen, and she was reevaluated 3 days later. Repeat laboratory studies showed a WBC of $7.3 \times 10^9/L$ (41% granulocytes, 13% bands, and 46% lymphocytes), platelet count of $104 \times 10^9/L$, erythrocyte sedimentation rate of 81 mm/h, aspartate aminotransferase of 48 U/L, alanine aminotransferase of 26 U/L, and bilirubin of 0.6 mg/dL. She was admitted to Connecticut Children’s Medical Center the following day for persistent fever and the onset of abdominal pain, loose stools, and bilious vomiting. Her temperature was 41°C; pulse, 176 beats per minute; respiratory rate, 72 breaths per minute; blood pressure, 100/54; and oxygen saturation was 97% in room air. Other pertinent findings on physical examination included mildly injected conjunctiva and small (2-mm) bilateral hemorrhages in the superior-nasal area, an erythematous, blanching, maculopapular rash on her neck and back, and mild tenderness to palpation in the left upper quadrant of her abdomen. Hepatic transaminases; rheumatoid factor; antinuclear antibody; cultures of blood, urine, and stool; enzyme-linked immunosorbent assay and Western blot antibodies for *Borrelia burgdorferi*; and a chest radiograph were all normal or negative. A blood smear showed morulae in granulocytes, consistent with HGE. *A phagocytophilum* DNA was amplified in a blood sample using polymerase chain reaction. Her sera

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reacted to *A phagocytophilum* recombinant p44-based antigen using enzyme-linked immunosorbent assay at a dilution of >1:2560 for immunoglobulin G and 1:128 for immunoglobulin M.

The child was treated with rifampin (10 mg/kg orally twice daily) and became afebrile within 6 hours of the initial dose. Her appetite improved, myalgias diminished, and she was markedly more alert, active, and playful the day after rifampin therapy. She had no further vomiting or diarrhea. She remained afebrile and was discharged from the hospital 2 days after her first dose of rifampin. One week after discharge she continued to improve and the rifampin was discontinued. One month after discharge she was feeling well.

DISCUSSION

Doxycycline is the preferred antibiotic for treatment of HGE.^{13,14} Tetracycline is a recommended alternative, but both antibiotics may cause staining of permanent teeth and phototoxic hypersensitivity reactions in children younger than 8 years of age.^{11,12} The staining of teeth by the use of tetracyclines is dose-related and uncommon after less than a 1 week course, while doxycycline is even less likely to result in teeth staining than tetracycline. Pediatricians are reluctant to prescribe tetracycline or doxycycline for young children, however. The American Academy of Pediatrics recommends doxycycline for treatment of HGE in children.¹³ Although it certainly should be used for any child experiencing life-threatening HGE, some physicians have questioned its use in young children who experience mild episodes of this disease. The CAFÉ Society, a consensus group of clinicians and laboratory medicine experts, recently recommended that all individuals with laboratory-confirmed *A phagocytophilum* infection receive antibiotic therapy because it is difficult to predict whether patients will experience a mild or severe clinical course.¹⁴

Few therapies are available for treatment of HGE other than doxycycline or tetracycline. Chloramphenicol is inactive against *A phagocytophilum* in vitro and has questionable clinical activity against *A phagocytophilum* in vivo.^{15,16} Chloramphenicol has been associated with potentially fatal adverse reactions, and a child who was treated with chloramphenicol for human monocytic ehrlichiosis died as the result of treatment failure.⁸ Rifampin may be a more effective antibiotic with fewer associated adverse effects. Unlike chloramphenicol, it has excellent activity against *A phagocytophilum* in vitro and is associated with fewer serious adverse reactions.^{15,17,18} Rifampin has successfully been used to treat 2 women who experienced HGE during the third trimester of pregnancy. Our 2 children with well-documented *A phagocytophilum* infection were successfully treated with rifampin.

Based on these considerations, we recommend the following therapeutic strategy in children experiencing HGE. Children older than 8 years of age or any child with life-threatening illness, including those who are admitted to an intensive care unit, should be given doxycycline according to recommended guidelines.^{13,15} The dose for children 8 years and older is 100 mg twice daily for 1 week and for children younger than 8 years is 3 to 4 mg/kg every 12 hours for 1 week. Rifampin therapy (20 mg/kg/d, given in divided doses every 12 hours for 5–7 days) should be

considered for all other children younger than 8 years of age who experience *A phagocytophilum* infection. Currently, there is no diagnostic test that can identify patients who will develop severe illness.^{15,19} Although it is likely that early rifampin treatment for young children experiencing HGE infection will prevent disease progression and will clear infection, prospective therapeutic trials are needed.

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