Journal of Pediatric Sciences

Ceftriaxone-Induced Hemolysis in Pediatric Patients with Sickle Cell Disease

Stacy Kautza, Tsz-Yin So

Journal of Pediatric Sciences 2011;3(3):e83

How to cite this article:

Kautza S, So TY. Ceftriaxone-Induced Hemolysis in Pediatric Patients with Sickle Cell Disease. Journal of Pediatric Sciences. 2011;3(3):e83

REVIEW ARTICLE

Ceftriaxone-Induced Hemolysis in Pediatric Patients with Sickle Cell Disease

Stacy Kautza, Tsz-Yin So

Abstract:
Objective: To provide a review on the case reports of ceftriaxone-induced hemolytic anemia in pediatric patients with sickle cell disease, present a proposed mechanism of the reaction, and provide an alternative antimicrobial regimen for these patients. **Data sources:** Literature retrieval was accessed through PUBMED (1985-present) using the terms pediatric, sickle cell disease, ceftriaxone, hemolytic anemia, and hemolysis. In addition, reference citations identified from these publications were reviewed. **Study selection and data extraction:** All articles in English identified from the data sources were evaluated. All case reports and studies were included in the review. **Data synthesis:** Ceftriaxone, a third-generation cephalosporin that is frequently used for the empiric treatment of suspected infections in pediatric patients with sickle cell disease, has been linked to cases of hemolytic anemia. Ceftriaxone has many favorable attributes to promote its use: broad-spectrum antimicrobial activity, long half-life, and no requirement for dose adjustment in patients with renal dysfunction. Hemolytic anemia is a very serious condition and can be fatal. Children with sickle cell disease have a reduced number of red blood cells, and therefore, hemolytic anemia can potentially be detrimental to these children. Five case reports of ceftriaxone-induced hemolytic anemia are presented, in which the typical onset was three to seven days into therapy and all patients had received ceftriaxone courses during prior hospitalizations. There have been several proposed mechanisms of drug-induced hemolytic anemia, and ceftriaxone appears to induce hemolysis through an immune reaction involving immunoglobulin M and complement found on the surfaces of red blood cells. The hemolysis can be managed by immediately stopping the offending agent, giving packed red blood cell transfusions, and there is possibly a role for intravenous corticosteroids, plasmapheresis, and intravenous immunoglobulin. Cefotaxime is a safe and effective alternative antibiotic in this patient population. **Conclusions:** Although rare, ceftriaxone appears to induce hemolytic anemia in pediatric patients with sickle cell disease. Cefotaxime provides a safe and effective alternative in this population.

Keywords: ceftriaxone, pediatric, sickle cell disease, hemolytic anemia, hemolysis
Received: *09/03/2011;* ***Accepted:*** *02/04/2011*

Introduction

Children with sickle cell disease (SCD) can often be hospitalized and may require multiple courses of antibiotics. These children are thought to have an increased risk of infection due to their impaired splenic function and defective opsonization [1]. The most implicated organisms are the encapsulated bacteria that express polysaccharide antigens, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*. Patients infected with such organisms have been noted to have mortality rates as high as 20% and 15%, respectively [1,2]. Of note, the patients in this cohort were on penicillin prophylaxis and had received the pneumococcal polysaccharide vaccination. Other organisms that are common in pediatric SCD are *Salmonella*, *Klebsiella* species, and *Escherichia coli* [3]. A cephalosporin is usually started when a SCD patient

Stacy Kautza, Tsz-Yin So

Department of Pharmacy, Moses H. Cone Hospital, 1200 N. Elm Street, Greensboro, NC 27401, USA

Corresponding author:
Tsz-Yin So, PharmD
Pediatric Clinical Pharmacist

Department of Pharmacy, Moses H. Cone Hospital, 1200 N. Elm Street, Greensboro, NC 27401-1020, USA
Tel : 336/832-8611
Fax: 336/832-7198
E-mail: Jeremy.So@mosescone.com

comes in with a febrile episode [4]. Ceftriaxone has been a preferential empiric antibiotic choice for treatment in these patients when admitted to the hospital since its spectrum of activity includes all of these organisms. Ceftriaxone or cefotaxime are considered to be the ideal antibiotics to cover most of the bacterial pathogens likely to be associated with septic episodes in pediatric patients with SCD [5]. Pediatric patients presenting with acute chest syndrome are also treated empirically with ceftriaxone, as shown in a study by Srair and colleagues [6]. Patients who are febrile and are deemed to be at low risk of sepsis, can safely and effectively be given ceftriaxone daily and intramuscularly in the outpatient setting, alternatively to being admitted to the hospital. This practice has also been demonstrated to decrease costs [7,8]. Even though ceftriaxone has all these benefits over other antibiotics, it is not without problems, one being the possibility of causing hemolytic anemia. There have been increasing case reports of ceftriaxone-induced hemolytic anemia, and many of these reports are in children with SCD.

Hemolytic anemia is characterized by the reduction in erythroycte survival [9]. This can be measured by metabolic products produced by hemolysis: increased indirect bilirubin, increased lactate dehydrogenase, and reduced haptoglobin. Reticulocytosis is also commonly seen, which is the body's way of compensating to help maintain sufficient amount of red blood cells (RBCs) to carry and deliver oxygen. These lab abnormalities are also characteristic signs that are regularly seen in sickle cell patients; therefore, unless there are dramatic changes in these values, it is difficult to distinguish between the natural course of SCD and drug-induced hemolytic anemia. In severe hemolytic anemia, the onset can be acute, and symptoms include pallor, jaundice, and hemoglobinuria [9].

Drug-induced hemolytic anemia is a very rare occurrence, reported to be around only one in one million of the population [10]. Comparatively, drug-induced thrombocytopenia and neutropenia are more prevalent (10 to 18 and 2 to 15 cases per million, respectively,) [10]. Hemolytic anemia is seen more with autoimmune disease with incidence of one in 80,000 people [9]. Since only severe cases of hemolytic anemia are reported, drug-induced hemolytic anemia may be more prevalent than noted due to underreporting. In the 1970s the majority of the causative agents of drug-induced hemolytic anemia were methyldopa and penicillin (67% and 23%, respectively). Since the late 1980s, the second- and third-generation cephalosporins, cefotetan and ceftriaxone (75% and 13%, respectively) are the most implicated ones [11-13]. Quillen and colleagues studied 64 patient samples to evaluate the prevalence of ceftriaxone-induced RBC antibodies [14]. These samples were from pediatric patients with SCD or human immunodeficiency virus infection (HIV) (45 HIV, 19 SCD). The anti-ceftriaxone antibody was present in 12.5% (8 of 64) of the samples. Two of the eight cases had hemolysis clinically; both of these patients were in the HIV group. Patients with SCD had been exposed to ceftriaxone more, but had a lower prevalence of the anti-ceftriaxone antibody (5.3% versus 15.6%). This article will provide a summary of the case reports of pediatric SCD patients with ceftriaxone-induced hemolytic anemia, the proposed mechanism of the hemolytic reaction, and a potential alternative antibiotic regimen for these patients.

Data Sources

Literature retrieval was accessed through PUBMED (1985 – January 2011) using the terms pediatric, sickle cell disease, ceftriaxone, hemolytic anemia, and hemolysis. In addition, reference citations identified from these publications were reviewed. All articles in English identified from the data sources were evaluated. All case reports and studies were included in this review.

Evidence

No clinical trials have been completed in children or adults examining ceftriaxone-induced hemolytic anemia. According to Garrety there have been 29 cases (including 10 fatalities) of ceftriaxone induced immune hemolytic anemia from 1971-2008 [10]. The evidence presented here reviews cases of ceftriaxone-induced hemolytic anemia in children with SCD.

Case 1

A 24-month African American male with SCD presented to the emergency department with fever [15]. Baseline labs and blood cultures were obtained, which revealed stable baseline labs for the patient, and per protocol he received ceftriaxone (75 mg/kg/day). Twenty minutes after administration he had a cardiopulmonary arrest and had repeat lab

Table 1. Case 1 Laboratory Results at Baseline and After Hemolysis Reaction[15]

	Baseline	Post Reaction
Hemoglobin (gm/dL)	7	0.9
Hematocrit (%)	20	1.5
Leukocyte count (x 10^9 cells/L)	23	6.7
Platelets (x10^9 cell/L)	399	50

testing that revealed severe anemia (Table 1).

The patient experienced shock and passed 36 hours later. He had received a total of 14 doses of ceftriaxone on several occasions prior to the hemolytic anemia reaction. After review of his medical chart it was noted that he had experienced five separate transient episodes of hemoglobinuria immediately after prior ceftriaxone infusions. Serologic studies were performed after the patient's hemolytic anemia episode. The patient was found to have a strong positive direct antiglobulin test that showed agglutination to immunoglobulin G (IgG) and complement. When the patient's enzyme-treated RBCs were added to plasma, complement, and ceftriaxone, agglutination and hemolytic reactions were noted. When dithiothreitol was added at 37 degrees Celsius, the agglutination was reversed indicating that immunoglobulin M (IgM) antibodies were present. This case supports the IgM mechanism of causing hemolytic anemia (Table 2).

Case 2

A 6-year old Bedouin male with SCD was hospitalized for a vaso-occlusive crisis and developed a fever in which ceftriaxone (75 mg/kg/day) was used empirically [16]. Thirty minutes after his fourth infusion of ceftriaxone, he complained of severe abdominal and back pain. He then developed tachycardia and hypotension. The patient had received ceftriaxone on six prior occasions. The patient was given two units of packed RBCs and hydrocortisone, and he returned to baseline clinically. Labs indicated severe anemia (Table 3).

Table 2. Case 1 Serologies After Hemolysis Reaction[15]

Test (post hemolytic anemia episode)	Results
Direct antiglobulin test + patient's cells	Agglutination 3+
IgG	Agglutination ±
C3	Agglutination ±
Serum complement + patient's serum	
C3 (mg/dl)	69 (range 73-180)
C4 (mg/dl)	9.9 (range 15-45)
Patient's ceftriaxone-coated RBCs + patient's serum	Nonreactive
Patient's untreated RBCs + plasma, complement, and ceftriaxone	Agglutination 3.5+
Patient's enzyme-treated RBCs + plasma + fresh complement + ceftriaxone	Agglutination 2.5+ Hemolysis 3+
Patient's enzyme-treated RBCs + plasma + fresh complement + ceftriaxone + dithiothreitol at 37°C	Negative (indication of IgM antibodies present)

Note: Agglutination and hemolysis are scored on scale from 0 to 4+

The patient had a negative Coombs' test (direct antiglobulin test) on admission and tested positive after the hemolysis reaction. The patient's labs revealed a positive antiglobulin test with anti-complement activity; anti-IgG was not observed. The antibodies were found to be of the IgM class by using the dithiothreitol test. Therefore, this is another case to support the proposed IgM mechanism (Table 4).

Case 3

A 10-year old African American male with SCD was admitted to a hospital for pneumonia and was treated empirically with ceftriaxone [17,18]. On the third day of hospitalization, two hours after the administration of ceftriaxone, the patient had a sudden onset of generalized seizures and loss of consciousness.

Labs indicated severe anemia (Table 5). The patient

Table 3: Case 2 Laboratory Results at Baseline and After Hemolysis Reaction[16]

	Baseline	Post Reaction
Hemoglobin (gm/dL)	9.7	2.8
Hematocrit (%)	25	Unavailable
Platelets ($x10^9$ cell/L)	267	146
Reticulocytes (%)	1.1	9
Prothrombin time (sec)	11.2	19.3
Thromboplastin time (sec)	32.2	Uncoagulable
Total bilirubin (mg/ml)	1.3	27
Direct coombs' test	Negative	Positive

had received ceftriaxone two years prior to this admission. After discontinuation of ceftriaxone, the patient's anemia improved, and he made a full recovery. Serologic studies were performed (Table 6) and confirmed that the antibody in the serum was predominantly IgM by the negative dithiothreitol test.

Case 4

A 6-year old African American female with SCD was hospitalized for vaso-oclusive crisis [19]. On day two of hospitalization, she developed a fever and was empirically started on ceftriaxone (50 mg/kg/day). Hemoglobin was stable at baseline and trended slowly down over five days at which time she received a packed RBCs infusion. Twelve hours after her infusion she became unresponsive, transferred to the intensive care unit, and was thought to have had an acute transfusion reaction. Ceftriaxone was not given during this time and patient was transferred back to the general floor. Ceftriaxone was restarted and twenty minutes after the ceftriaxone infusion was started, she was found unresponsive and a code was called. Labs revealed severe anemia (Table 7). The patient was treated with corticosteroids, plasmapharesis, and intravenous immunoglobulin. She had received ceftriaxone on multiple occasions prior to this admission. Serologic studies were completed four weeks after the event and revealed that the patient had made antibodies to ceftriaxone but was negative for anti-IgM, which is unlike the majority of the cases presented earlier (Table 8).

Table 4: Case 2 Serologies After Hemolysis Reaction[16]

Test (post hemolytic anemia episode)	Results
Direct antiglobulin test	Strongly positive
Anti-IgG	Negative
Anti-C3	Strongly positive
Patient's serum + ceftriaxone + fresh complement + ficin-treated RBC (patient's) at 37°C	Strongly positive agglutination and antiglobulin test
Patient's serum + ceftriaxone + fresh complement + ficin-treated RBC (patient's) at 37°C + dithiothreitol	Negative

Table 5: Case 3 Laboratory Results at Baseline and After Hemolysis Reaction[17,18]

	Baseline	Post Reaction
Hemoglobin (gm/dL)	7.3	<2
Hematocrit (%)	23	10

Table 6: Case 3 Serologies After Hemolysis Reaction[17,18]

Test (post hemolytic anemia episode)	Results
Direct antiglobulin test	Positive (3+)
Polyspecific antiglobulin reagent	Positive
Anti-C3d	Positive (1+)
Patient's serum + ceftriaxone at 37°C	Positive (4+)
Patient's serum + ceftriaxone at 37°C + dithiothreitol	Negative

Table 7: Case 4 Laboratory Results at Baseline and After Hemolysis Reaction[19]

	Baseline	Post Reaction
Hemoglobin (gm/dL)	8.6	0.4

Table 8: Case 4 Serologies After Hemolysis Reaction[19]

Test (4 weeks post hemolytic anemia episode)	Results
Direct antiglobulin test	
Anti-IgG	Weak reactivity
Anti-C3d	Weak reactivity
Anti-IgM	Negative
Anti-IgA	Negative
Patient's serum + ceftriaxone + 37°C	Strong agglutination
Antiglobulin test	Weakly reactive
Patient's serum + ceftriaxone + 37°C + enzyme-treated RBCs	Moderately hemolyzed
Antiglobulin test	Strongly reactive

Case 5

A 5-year old Saudi male with SCD was admitted to a hospital with sepsis and vaso-occlusive crisis [20]. Immediately after his first dose of ceftriaxone he developed an anaphylactic reaction consisting of skin rash, fever, chills, hypotension, and shock. It was reported that there was a rapid fall in hemoglobin and platelet counts, but the values were not reported. The patient experienced multi-organ failure and seizures, and he was eventually discharged in stable condition. He had never received ceftriaxone prior to this admission. No serologic studies were completed; therefore the underlying mechanism of this case was not evaluated.

Proposed Mechanisms of Ceftriaxone-Induced Hemolytic Anemia

Drug-induced hemolytic anemia takes place when antibodies are directed against RBCs. Cephalosporins are known to interact with the RBC membrane without causing hemolysis by modifying it and causing non-immunologic protein adsorption [9,21]. This can exhibit as a positive direct antiglobulin test because the proteins bound to the RBC are of the IgG or complement nature. This can potentially lead to hemolytic anemia via interaction of macrophages with these proteins. First generation cephalosporins are thought to cause hemolysis by IgG adsorbing to the RBC membrane and activating complements which leads to hemolysis [9,10]. Ceftriaxone appears to have a slightly different mechanism through an immune-complex reaction in which IgM antibodies are directed against ceftriaxone and cause erythrocyte destruction through complement activation [9]. In an analysis of 21 patients by Garratty, ceftriaxone was the second most implicated drug behind cefotetan in causing drug-induced immune hemolytic anemia [10]. All of these patients had received ceftriaxone previously and hemolysis was noted to begin ≤1 hour after receiving ceftriaxone. Fatal hemolytic anemia occurred in 38% of the cases and the direct antiglobulin test was usually positive (all had RBC-bound complement and most had IgG as well). Ceftriaxone antibodies were also usually detected. All patients, except for one, presented in this case series had received ceftriaxone on a prior occasion, with the majority having multiple exposures [15-20]. The reaction also took place several days (3-7 days) into the therapy predominantly in all of the cases. The majority of the cases presented support the IgM antibody mechanism as evidenced by the serologic studies. Since not all the cases reported the presence of IgM, there could be other mechanisms by which ceftriaxone induces hemolytic anemia. All of the results presented in the case reports are only related to IgM or IgG antibodies, therefore, allergic/anaphylactic reactions do not appear to be the cause.

Treatment Options

Treatment for drug-induced hemolytic anemia involves discontinuing the medication that may be the causative agent immediately [9,10]. If the hemolysis is severe, immediate transfusion of RBCs is indicated. Corticosteroids can also be used to

induce remission of antibody production, but this therapy has limited effect. Also, case reports that demonstrated the efficacy of corticosteroids were confounded by simultaneous discontinuation of the offending drug [22]. The majority of the case reports presented managed the patient with supportive care with packed RBCs and a couple used corticosteroids. In one case it was reported that intravenous hydrocortisone was used, and the other case only specified that high-dose corticosteroid was administered [16,19]. Although there is not any primary literature supporting the use of corticosteroids for drug-induced hemolytic anemia, there is evidence of using corticosteroids in warm-reactive autoimmune-hemolytic anemia. This type of anemia is when IgG auto-antibodies coat autologous erythrocytes and induce erythrocyte destruction. Complement can also be involved, which is also a proposed mechanism of drug-induced hemolytic anemia, and this is the reason that corticosteroids may be helpful in ceftriaxone-induced hemolytic anemia [23]. Although our case reports support IgM and complement mechanism, IgG was found to be present in some of the patients. Treatment with corticosteroids for severe warm-reactive autoimmune-hemolytic anemia include intravenous methylprednisolone at 1-2 milligrams per kilograms every 6 hours for the first 24 to 72 hours and then transition to a total dose of 1-2 milligrams per kilogram per day of prednisone for two to four weeks. The dose is then tapered over two to three months, and this regimen resulted in a response rate of nearly 80 percent [24]. Plasmapheresis and intravenous immunoglobulin dosed at 1 gram per kilogram were also used successfully in one case.[19] Intravenous immunoglobulin is a potent inhibitor of the reticuloendothelial system and therefore is thought to rid the body of the ceftriaxone-induced antibodies on RBCs [23].

A study conducted by Arndt and Garratty looked at antibodies associated with hemolytic anemia and found that cefotaxime showed a weak cross-reactivity with ceftriaxone's antibodies by immune complex testing [25]. Therefore, cefotaxime can be a potential alternative antibiotic to ceftriaxone in pediatric patients with SCD admitted for infection. A review of literature indicates that cefotaxime has not been associated with the induction of hemolytic anemia. Cefotaxime is renally dose-adjusted, therefore, renal function should be monitored in these patients. Usual dosages of cefotaxime is 100-200 milligrams per kilogram per day intravenously divided every six to eight hours in children with normal renal function from one month to 12 years of age and less than 50 kilograms; and 1-2 grams intravenously every 6-8 hours for children >12 years old or anyone more than 50 kilograms [26]. Cefotetan should not be considered as an alternative agent, as it has also been implicated as having an increased risk of causing hemolytic anemia when compared to ceftriaxone [25].

Conclusion

Ceftriaxone-induced hemolytic anemia in pediatric patients is a very rare condition. No clinical trials have been performed to evaluate what the true prevalence is, or to really delve into the mechanism underlying the reaction. The majority of the cases are in pediatrics with an immunologic condition, SCD being the most prevalent. This case series demonstrate that there is an association between administration ceftriaxone and hemolytic anemia. The cases demonstrate that this phenomenon predominantly occurs after multiple doses of ceftriaxone. The potential mechanism in which ceftriaxone induces hemolytic anemia is through an immune-complex reaction with IgM mediated antibodies that induce erythrocyte destruction. Based on the increasing case reports, ceftriaxone should be cautiously used in pediatric patients with SCD, even if the patient has been safely treated with ceftriaxone on a prior occasion. Further studies are needed to look into other potential mechanistic cause of this adverse drug effect.

REFERENCES

1. Adamkiewicz TV, Sarnaik S, Buchanan GR, et al. Invasive pneumococcal infection in children with sickle cell disease in the era of penicillin prophylaxis, antibiotic resistance, and 23-valent pneumococcal polysaccharide vaccination. *J Pediatr* 2003;143:438-444.
2. Gill FM, Sleeper LA, Weiner SJ, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative study of sickle cell disase. *Blood* 1995;86:776-783.
3. Battersby AJ, Knox-Macaulay HHM, Carrol ED. Susceptibility to invasive bacterial infections in children with sickle cell disease. *Pediatr Blood Cancer* 2010;55(3):401-6.

4. Wethers DL. Sickle cell disease in childhood: Part II. Diagnosis and treatment of major complications and recent advances in treatment. *Am Fam Physician* 2000;62(6):1309-14.
5. Wong WY. Prevention and management of infection in children with sickle cell anemia. *Paediatr Drugs* 2001;3(11):793-801.
6. Srair HA, Owa JA, Aman HA, Madan MA. Acute chest syndrome in children with sickle cell disease. *Indian J Pediatr* 1995;62(2):201-5.
7. Wilimas JA, Flynn PM, Harris S, et al. A randomized study of outpatient treatment with ceftriaxone for selected febrile children with sickle cell disease. *N Engl J Med* 1993:329(7):472-6.
8. Williams LL, Wilimas JA, Harris SC, Day SW, Dancy RM, Wang WC. Outpatient therapy with ceftriaxone and oral cefixime for selected febrile children with sickle cell disease. *J Pediatr Hematol Oncol* 1996;18(3):257-61.
9. Habibi B, Homberg JC, Schaison G, Salmon C. Autoimmune hemolytic anemia in children. A review of 80 cases. *Am J Med* 1974;56(1):61-9.
10. Garratty G. Drug-induced immune hemolytic anemia. *Hematology Am Soc Hematol Educ Program* 2009:73-9.
11. Petz LD, Garratty G. *Acquired Immune Hemolytic Anemias* New York, NY:Churchill Livingstone;1980:37-50.
12. Garratty G. Immune cytopenia associated with antibiotics *Transfus Med Rev* 1993;7:255-267.
13. Arndt PA, Leger RM, Garratty G. Serology of antibodies to second- and third-generation cephalosporins associated with immune hemolytic anemia and/or positive direct antiglobulin tests. *Transfusion* 1999;39:1239-1246.
14. Quillen K, Lane C, Hu E, Pelton S, Bateman S. Prevalence of ceftriaxone-induced red blood cell antibodies in pediatric patients with sickle cell disease and human immunodeficiency virus infection. *Pediatr Infect Dis J* 2008;27(4):357-8.
15. Bernini JC, Mustafa MM, Sutor LJ, Buchanan GR. Fatal hemolysis induced by ceftriaxone in a child with sickle cell anemia. *J Pediatr* 1995;126(5 Pt 1):813-5.
16. Viner Y, Hashkes PJ, Yakubova R, Sega-Kupershmit D, Luder A. Severe hemolysis induced by ceftriaxone in a child with sickle-cell anemia. *Pediatr Infect Dis J* 2000;19(1):83-5.
17. Kakaiya R, Cseri J, Smith S, Simone S, Rubinas TC, Hoffstadter A. A case of acute hemolysis after ceftriaxone. *Arch Pathol Lab Med* 2004;128(8):905-7.
18. Corso M, Ravindranath TM. Albuterol-induced myocardial ischemia in sickle cell anemia after hemolysis from ceftriaxone administration. *Pediatr Emerg Care* 2005;21(2):99-101.
19. Schuettpelz LG, Behrens D, Goldsmith MI, Druley TE. Severe ceftriaxone-induced hemolysis complicated by diffuse cerebral ischemia in a child with sickle cell disease. *J Pediatr Hematol Oncol* 2009;31:870-872.
20. Al-Hawsawi ZM, Turkistani WA, Al-Aidaros MA, Al-Harbi DL. Ceftriaxone induced acute multi-organ failure syndrome in a Saudi boy with sickle cell disease. *Saudi Med J* 2010;31(7):826-828.
21. Petz LD, Garratty G. *Immune Hemolytic Anemias*. 2nd ed. Philadelphia: Churchill Livingstone; 2004:261-317.
22. Salama A. Drug-induced immune hemolytic anemia. *Expert Opin Drug Saf* 2009;8:73-79.
23. Vaglio S, Arista MC, Perrone MP, et al. Autoimmune hemolytic anemia in childhood: serologic features in 100 cases. *Transfusion* 2007;47(1):50-4.
24. Collins PW, Newland AC. Treatment modalities of autoimmune blood disorders. *Semin Hematol* 1992;29(1):64-74.
25. Arndt PA, Garratty G. Cross-Reactivity of cefotetan and ceftriaxone antibodies, associated with hemolytic anemia, with other cephalosporins and penicillin. *Am J Clin Pathol* 2002;118:256-262.
26. Lexi-Comp ONLINE Web site. http://crlonline.com/crlsql/servlet/crlonline. Accessed Jan 24, 2011.