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LEARNING OBJECTIVES

Upon completion of this exercise, the participant should be able to

- recognize immune-mediated hemolysis.
- develop a differential diagnosis for immune-mediated hemolysis.
- diagnose drug-induced immune hemolytic anemia.
- diagnose drug-induced immune thrombocytopenia.
- recommend appropriate management for both conditions.

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HISTORY

A 73-year-old woman underwent surgical repair of a ventral hernia. After an uneventful postoperative course, she was discharged on postoperative day 4. Around day 9, she developed progressive weakness, lightheadedness, and dark urine, and had 1 episode of emesis of clear fluid. She presented to the authors’ institution on day 14. Review of all other systems was unremarkable. Her medical history was significant for colon cancer 7 years earlier treated with surgical resection and chemotherapy, hypertension, hyperlipidemia, hypothyroidism, and gastroesophageal reflux disease. Her outpatient medications included carvedilol, nifedipine, captopril, losartan-hydrochlorothiazide, ezetimibe-simvastatin, thyroxine, esomeprazole, ranitidine, aspirin, and tramadol.

Her vital signs were: blood pressure, 128/93 mmHg; pulse rate, 81/min; respirations, 18/min; and temperature, 98.4°F (36.9°C). Oxygen saturation on room air was 100%. Her abdominal wound was healing with no evidence of bleeding or infection. No skin rashes, petechiae, ecchymoses, or mucosal hemorrhages were present. The fecal occult blood test result was negative. The rest of her physical examination results were unremarkable.

Relevant admission laboratory results are shown in Laboratory Data. The patient had severe anemia with evidence of hemolysis, including reticulocytosis, unconjugated hyperbilirubinemia, a low haptoglobin level, an elevated level of lactate dehydrogenase, and hemoglobinemia. The peripheral smear showed abundant microspherocytes and no schistocytes. Her blood type was group A Rh+. The antibody screen result was negative. The direct antiglobulin test (DAT) result was positive for IgG and negative for C3. An acid elution was performed, and the eluate was nonreactive with reagent red blood cells (RBCs). She was admitted for RBC transfusions and evaluation of her hemolytic anemia.

LABORATORY DATA.

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, ×10^3/µL (×10^9/L)</td>
<td>5.50 (5.50)</td>
<td>3.28-9.29 (3.28-9.29)</td>
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<tr>
<td>Red blood cell count, ×10^6/µL (×10^12/L)</td>
<td>1.96 (1.96)</td>
<td>3.76-4.93 (3.76-4.93)</td>
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<tr>
<td>Hemoglobin, g/dL (g/L)</td>
<td>6.2 (62)</td>
<td>11.5-14.6 (115-146)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>18.7</td>
<td>34.0-42.1</td>
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<tr>
<td>Platelet count, ×10^3/µL (×10^9/L)</td>
<td>207 (207)</td>
<td>143-398 (143-398)</td>
</tr>
<tr>
<td>Mean corpuscular volume, fl</td>
<td>95.4</td>
<td>79.0-95</td>
</tr>
<tr>
<td>Absolute reticulocyte count, ×10^6/µL (×10^9/L)</td>
<td>0.1942 (194.2)</td>
<td>0.0273-0.1072 (27.3-107.2)</td>
</tr>
<tr>
<td>Haptoglobin, mg/dL (µmol/L)</td>
<td>&lt;8 (&lt;0.8)</td>
<td>30-190 (3.0-19.0)</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/L</td>
<td>1575</td>
<td>91-223</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL (µmol/L)</td>
<td>4.0 (68.4)</td>
<td>0.2-1.1 (3.4-18.8)</td>
</tr>
<tr>
<td>Conjugated bilirubin, mg/dL (µmol/L)</td>
<td>0.6 (10.3)</td>
<td>0.0-0.2 (0-3.4)</td>
</tr>
<tr>
<td>Plasma free hemoglobin, mg/dL (g/L)</td>
<td>20.0 (200)</td>
<td>0.5-5.0 (5-50)</td>
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<tr>
<td>Ferritin, ng/mL (µmol/L)</td>
<td>740 (1663)</td>
<td>8-150 (18-337)</td>
</tr>
<tr>
<td>Iron, µg/L (µmol/L)</td>
<td>198 (35.4)</td>
<td>23-182 (4.1-32.6)</td>
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<tr>
<td>Iron binding capacity, µg/dL (µmol/L)</td>
<td>308 (55.1)</td>
<td>240-520 (43.0-93.1)</td>
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<tr>
<td>Prothrombin time, s</td>
<td>10.6</td>
<td>9.1-11.1</td>
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<tr>
<td>International normalized ratio</td>
<td>1.1</td>
<td>0.8-1.3</td>
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<tr>
<td>Partial thromboplastin time, s</td>
<td>23.6</td>
<td>24.6-30.9</td>
</tr>
</tbody>
</table>
DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA AND THROMBOCYTOPENIA

Recognition of Immune-Mediated Hemolysis
In immune-mediated hemolysis, RBCs are coated in vivo with antibodies; leading to either extravascular or complement-associated intravascular destruction. The presence of IgG antibodies or complement proteins on the surface of RBCs results in a positive DAT reaction, making the DAT the most useful tool to distinguish immune-mediated hemolysis from nonimmune hemolysis. There are 2 important caveats, however. A weakly positive reaction can be seen in up to 7% to 8% of hospitalized patients and may be a nonspecific finding, particularly if no evidence of hemolysis is present.¹ The DAT result may be negative in cases of immune-mediated hemolysis if all the IgG- or complement-coated RBCs have been destroyed and in the rare cases of autoimmune hemolytic anemia (AIHA) mediated by IgA or IgM antibodies. Tests to confirm IgA- or IgM-mediated AIHA are usually available only at specialized laboratories. Otherwise, a negative result on the DAT strongly favors nonimmune hemolysis, and clinical history and laboratory tests are used to identify the specific cause.

Differential Diagnosis and Laboratory Testing of Immune-Mediated Hemolysis
A diagnostic algorithm for immune-mediated hemolysis is shown in the Figure. When the DAT result is positive for IgG in a patient with hemolytic anemia, an elution test should be performed to elute off the antibody and determine its specificity with a panel of reagent RBCs of known phenotype.

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**Figure.** Diagnostic algorithm for immune-mediated hemolysis. AIHA indicates autoimmune hemolytic anemia; DAT, direct antiglobulin test; DIIHA, drug-induced immune hemolytic anemia.

*Obtain drug history, confirm diagnosis with drug-dependent antibody tests if appropriate.

¹Obtain history of recent transfusion.
with a panel of reagent RBCs of known phenotype. The differential diagnosis includes warm AIHA, acute and delayed hemolytic transfusion reactions, and drug-induced immune hemolytic anemia (DIIHA). In warm AIHA, the eluted antibodies are directed against RBC antigens found on most RBCs, including the patient’s own. Therefore, the antibodies are panreactive to a panel of reagent RBCs and the patient’s own RBCs. In acute and delayed hemolytic transfusion reactions, the eluted antibodies show reactivity to only the reagent RBCs bearing the specific antigen(s). They are nonreactive to the patient’s own RBCs and RBCs lacking these specific antigens. If the eluate is nonreactive, DIIHA should be considered, particularly if the reaction is strongly positive.

A positive DAT result for C3 indicates that RBCs are coated with complement proteins. The main diagnostic considerations are cold agglutinin disease (CAD), DIIHA, and the very rare disease of paroxysmal cold hemoglobinuria. In CAD, autoantibodies (typically IgM) and complement mediate intravascular and extravascular hemolysis after exposure to cold temperatures. Cold autoantibodies are readily detected by a cold agglutinin titer. A positive test result, however, is not diagnostic of CAD, because many patients have cold autoantibodies reactive at less than 30°C. Thermal amplitude testing is required to identify cold antibodies likely to be clinically significant, ie, ones reactive at 30°C or above. In paroxysmal cold hemoglobinuria, biphasic autoantibodies (typically IgG) directed against the P antigen present on most RBCs fix complement at colder temperatures in peripheral circulation and cause intravascular hemolysis as the temperature increases in core circulation. A positive Donath-Landsteiner test result confirms the diagnosis by demonstrating in vitro hemolysis when the patient sample is maintained first at 4°C and then raised to 37°C, but lack of hemolysis when the patient sample is maintained continuously at 4°C or 37°C. DIIHA can show C3 binding alone or have combined IgG and C3 binding. These cases are often associated with significant intravascular hemolysis. Warm AIHA is also included in the differential diagnosis, as 10% of cases show reactivity for both IgG and C3.

**Drug-Induced Immune Hemolytic Anemia**

**Background and Pathophysiology**

DIIHA is a rare disease that can cause mild to severe hemolysis, which can be fatal in a minority of cases. The incidence is estimated at 1 in 1 million people; however, the actual incidence is probably higher. In the 1960s, DIIHA was most commonly associated with methyldopa and high-dose penicillin. The list of causative agents has since grown to include more than 125 drugs. From a practical standpoint, most cases of DIIHA are caused by second- and third-generation cephalosporins. Cefotetan alone is implicated in more than 70% of the cases, and ceftriaxone is responsible for about another 10%. β-lactamase inhibitors and piperacillin are the next most identified drugs, though they constitute a much smaller percentage.

DIIHA occurs through both drug-dependent and drug-independent mechanisms. The earliest drug-dependent model showed that certain drugs like penicillin and cefotetan bind covalently to RBC membrane proteins. If the patient makes an IgG antibody to the drug, the antibody can bind to the drug-coated RBC and facilitate extravascular hemolysis. The DAT result is usually strongly positive for IgG and
negative for C3. The eluate is nonreactive because the reagent RBCs lack the drug required for the antibody to bind. Other drugs, such as ceftriaxone and piperacillin, bind noncovalently to RBCs, leading to an immune response and production of a drug antibody (typically IgM). These antibodies can activate complement, leading to intravascular hemolysis. Hemoglobinuria, renal failure, and death are more common in this group. The DAT result is usually weakly positive for only C3. There are 2 methods for detecting drug-dependent antibodies, depending on the drug in question. Testing for cefotetan drug-dependent antibodies involves adding the patient’s serum or eluate to RBCs coated with cefotetan. A positive reaction (agglutination or indirect antiglobulin test) is diagnostic. Ceftriaxone drug-dependent antibodies are detected by mixing ceftriaxone with the patient’s serum or plasma (which contains the drug antibodies and complement) with RBCs and observing a positive reaction (agglutination, hemolysis, or indirect antiglobulin test). As noted, immune-mediated hemolytic anemia including DIIHA may produce a negative DAT reaction if all the IgG- or complement-coated RBCs have been destroyed. Thus, the diagnosis of DIIHA should not be excluded solely on the basis of a negative reaction.

Though uncommon, drugs can induce formation of true autoantibodies, which bind directly to RBCs in a drug-independent fashion. This type of DIIHA is clinically and serologically indistinguishable from warm AIHA, and no laboratory tests can prove that the autoantibodies were drug induced. Methyldopa, procainamide, and fludarabine are capable of inducing RBC autoantibodies. A compatible clinical history demonstrating the temporal relationship of drug therapy and hemolysis is crucial in establishing the diagnosis.

The most recently proposed model suggests that some drugs may modify the RBC membrane, allowing proteins, including IgG and C3, to be nonimmunologically absorbed into the membrane. This shortens RBC survival even in the absence of drug antibodies. This phenomenon has been described with cefotetan, β-lactamase inhibitors, and platinum family drugs.

**Diagnosis and Management**

The diagnosis of DIIHA requires a high index of suspicion based on compatible clinical and medication history. As a general rule, a period of at least 6 days from the initial drug exposure is required for hemolysis to develop. Exceptions can occur when a previously sensitized patient is reexposed to the same drug, resulting in immediate hemolysis, and in children, who can hemolyze within 1 hour following the initial administration of ceftriaxone. Though available only at specialized laboratories, drug-dependent antibody tests are diagnostic, except in cases of DIIHA caused by autoantibodies induced by drugs. In such cases, clinical information and medication history are important in differentiating this entity from warm AIHA not induced by drugs.

The initial and most important step in managing DIIHA is discontinuation of the offending drug. The hemolysis usually resolves within a few days. Following acute intravascular hemolysis, transfusions are often needed in the initial period. To avoid reexposure, patients must be counseled and their drug allergy lists updated. In cases of cefotetan and ceftriaxone DIIHA, it may be advisable to avoid all cephalosporins owing to a risk of cross-reactivity. Steroids are often given, but their benefit has not
Drug-Induced Immune Thrombocytopenia (DIIT)

Background and Pathophysiology

In addition to hemolytic anemia, drugs can cause thrombocytopenia through similar immune-mediated processes. Heparin-induced thrombocytopenia is the most common and well described of these entities and is caused by antibodies with specificity to complexes of platelet factor 4 and heparin. This results in moderate thrombocytopenia 5 to 14 days after treatment. Bleeding is uncommon, but thrombosis occurs in more than one half of patients. DIIT due to other drugs is rare and is associated with more severe thrombocytopenia and increased risk of bleeding. The incidence of DIIT is estimated at 10 persons per million per year, though this is likely an underestimate. The data of George and colleagues, who reviewed cases of DIIT reported through 2008, is available online: http://www.ouhsc.edu/platelets. According to their criteria (explained in detail at the website), 51 drugs are definite and 17 others are probable causes of DIIT. Based on their analysis, DIIT is most commonly associated with quinine and sulfonamide antibiotics. Quinidine, nonsteroidal anti-inflammatory drugs, rifampin, vancomycin, anticonvulsants, gold salts, antineoplastics (fludarabine, oxaliplatin), and platelet inhibitors (tirofiban, epifibatide, and abciximab) are also implicated.

Several pathophysiologic mechanisms have been proposed. An early model suggested that drugs bind covalently to platelet membrane proteins and act as haptens to induce formation of drug-dependent antibodies in a process analogous to DIIHA caused by high-dose penicillin. This may account for the rare cases of thrombocytopenia caused by penicillin, piperacillin, and cephalosporins, but does not explain DIIT caused by other drugs. For more than 20 years, the major hypothesis was the “immune complex” mechanism, which proposed that some drugs can react directly with antibodies to produce immune complexes that target platelets for destruction. However, these complexes have never been demonstrated experimentally, and this hypothesis has since fallen out of favor. A newer model suggests that drug-dependent antibodies are probably derived from naturally occurring autoantibodies with weak affinity for platelet membrane glycoproteins. The presence of certain drugs improves the binding of the antibody to the platelet membrane glycoprotein (GP; typically GPIIb-IIIa or GPIb-V-IX). Examples of such drugs include quinine, sulfonamide antibiotics, nonsteroidal anti-inflammatory drugs, and anticonvulsants.

Some drugs induce formation of true autoantibodies that can bind directly to platelets in a drug-independent manner. One to 2% of patients treated with gold salts develop platelet autoantibodies. Autoantibodies can also arise in response to L-dopa, procainamide, penicillamine, interferon α and β, and occasionally sulfonamide antibiotics. This form of DIIT is clinically indistinguishable from idiopathic thrombocytopenic purpura and is diagnosed on clinical grounds. Several novel DIIT mechanisms have been described and are worth noting. Fibans are a class of platelet inhibitor drugs that includes tirofiban and epifibatide. They work by binding to the recognition site on GPIIb-IIIa, preventing its interaction
with fibrinogen. Fiban binding causes structural changes to the GPIIb-IIIa called neoepitopes. Preexisting antibodies can bind to these neoepitopes, leading to thrombocytopenia. Abciximab is a monoclonal chimeric human-mouse antibody specific for GPIIIa. Acute thrombocytopenia occurs within a few hours in 1% to 2% of patients receiving abciximab for the first time and in 10% to 12% of those treated for the second time.12,13 This appears to be caused by preexisting antibodies specific for murine components in abciximab. In the absence of preexisting antibodies, patients can present with delayed thrombocytopenia after they start producing murine antibodies, several days after exposure to abciximab.

Diagnosis and Management
DIIT often presents as sudden thrombocytopenia 5 to 7 days after the first administration or 2 to 3 days after a subsequent administration of the causative drug.14 The exception is abciximab, which can cause acute thrombocytopenia after the first dose. Most patients with DIIT have moderate to severe thrombocytopenia with platelet counts of less than 50,000/µL (<50 ×10³/µL).15 Petechial hemorrhages and ecchymoses may be the only clinical manifestation. Not uncommonly, patients have platelet counts of less than 10,000/µL (<10 ×10³/µL), which can result in purpura as well as bleeding from the gastrointestinal tract, urinary tract, and mucosal surfaces, ie, “wet bleeding.” Death can occur and is usually due to intracranial or intrapulmonary hemorrhage.12,13 Identifying DIIT is often difficult because the differential diagnosis for thrombocytopenia is vast. Factors that favor DIIT include unexplained acute thrombocytopenia following any drug administration, severe thrombocytopenia (a platelet count of <20,000/µL [<20 ×10³/µL]), and resolution of the thrombocytopenia upon discontinuation of the drug. Drug-dependent antibody tests confirm the diagnosis, but they are usually performed only at specialized laboratories. Platelet immunofluorescence can detect platelet-bound immunoglobulin.16 Enzyme-linked immunosorbent assay and Western blot can determine the presence and specificity of drug-dependent antibodies.14 Flow cytometry is highly sensitive for the detection of drug-dependent antibodies induced by the most commonly implicated drugs, such as quinine and sulfonamides.14-16

When the offending drug is identified, it must be discontinued and noted in the patient’s drug allergy list. The symptoms often improve within 1 to 2 days, and platelet counts return to normal in 1 week.12 Corticosteroids, intravenous Ig, and plasma exchange have been used, but their efficacy is not proven.13 Platelet transfusions are often given to patients with wet purpura due to the risk of intracranial and intrapulmonary hemorrhage; however, its effectiveness has not been formally studied.13

Case Summary and Discussion
The patient presented with hemolytic anemia, and the positive DAT result for IgG was consistent with an immune-mediated process. In view of her recent surgery, a delayed hemolytic transfusion reaction was high on the differential diagnosis list. However, this possibility was eliminated when it was discovered that no blood products had been transfused. The nonreactive eluate was a useful finding because it further argued against a hemolytic transfusion reaction due to RBC alloantibodies as well as warm AIHA. DIIHA was considered, and suspicion of DIIHA grew
on discovery that cefotetan and cefazolin were administered prophylactically for surgery. To evaluate for possible DIIHA, the patient’s serum and eluate were sent to the American Red Cross Reference Laboratory (Pomona, CA) with the following results: The patient’s undiluted serum caused complete hemolysis of cefotetan-coated RBCs; a 1:100 dilution of serum strongly agglutinated cefotetan-coated RBCs; the eluate also reacted with cefotetan-coated RBCs; all test results of non–drug-coated RBCs were negative; and parallel test results for cefazolin drug-dependent antibodies were negative. The findings confirmed the diagnosis of DIIHA due to cefotetan. Furthermore, the in vitro lysis of cefotetan-coated RBCs supported the suspicion that intravascular hemolysis had occurred in vivo. Cefotetan DIIHA typically presents with IgG-mediated extravascular hemolysis, which the patient clearly had, based on the positive IgG, unconjugated hyperbilirubinemia, and the microspherocytes on the peripheral smear. Occasionally, cefotetan DIIHA involves complement-mediated intravascular hemolysis producing a DAT positive for C3.3 The evidence of intravascular hemolysis in the patient included hemoglobinemia, nearly absent haptoglobin, and a very high lactate dehydrogenase level. Although C3 was not detected in the patient’s DAT, the authors suspect that this was due to total hemolysis of the complement-coated RBCs in vivo.

Despite the patient’s severe anemia, she recovered after transfusion of several units of RBCs and was discharged in stable condition. After the diagnosis of cefotetan DIIHA was confirmed, she was advised to avoid cefotetan, and her drug allergy list was updated.

REFERENCES


CME DOCUMENTATION QUESTIONS

1. Which of the following sets of laboratory data is most consistent with immune-mediated hemolysis?
   A) Hemoglobin (Hg), 8.2 g/dL (11.5-14.6); total bilirubin, 4.5 mg/dL (0.2-1.1 mg/dL); conjugated bilirubin, 3.9 mg/dL (0.0-0.2 mg/dL); lactate dehydrogenase (LDH), 305 U/L (91-223 U/L); haptoglobin, 35 mg/dL (30-190 mg/dL); absolute reticulocyte count, 0.0513 ×10^6/µL (0.0273-0.1072 ×10^6/µL); direct antiglobulin test (DAT), 1+ (weak) IgG
   B) Hg, 6.6 g/dL; total bilirubin, 3.1 mg/dL; conjugated bilirubin, 0.3 mg/dL; LDH, 1703 U/L; haptoglobin, <8 mg/dL; absolute reticulocyte count, 0.2101 ×10^6/µL, DAT, negative
   C) Hg, 8.5 g/dL; total bilirubin, 2.8 mg/dL; conjugated bilirubin, 0.1 mg/dL; LDH, 514 U/L; haptoglobin, <8 mg/dL; absolute reticulocyte count, 0.1605 ×10^6/µL; DAT, 3+ IgG
   D) Hg, 10.1 g/dL; total bilirubin, 0.9 mg/dL; conjugated bilirubin, 0.2 mg/dL; LDH, 187 U/L; haptoglobin, 145 mg/dL; absolute reticulocyte count, 0.0013 ×10^6/µL; DAT, negative

2. A 54-year-old man with an unremarkable medical history has hematemesis from a bleeding gastric ulcer. He requires 2 units of RBCs before undergoing surgery. Ceftriaxone is administered prophylactically. One week later, he presents with hemolytic anemia; his DAT result is 1+ for C3. The antibody screen is negative. Which of the following is the most likely diagnosis, and how would it be confirmed?
   A) Drug-induced immune hemolytic anemia (DIHIA) due to ceftriaxone; nonreactive eluate
   B) DIHIA due to ceftriaxone; positive drug-dependent antibody test result
   C) Delayed hemolytic transfusion reaction; elution of an alloantibody
   D) Delayed hemolytic transfusion reaction; positive Donath-Landsteiner test result
   E) Warm autoimmune hemolytic anemia (AIHA), elution of a panreactive autoantibody

3. A patient has DIHIA due to cefotetan, and the drug is discontinued. You advise the patient that
   A) other cephalosporins can be used safely.
   B) penicillins should be avoided.
   C) steroids will shorten the duration of symptoms.
   D) the hemolysis should subside within a few days.
   E) he will probably need several RBC transfusions during the next 3 to 4 weeks.
4. A 42-year-old woman presents with thrombocytopenia (platelet count 24,000/µL) 1 week after starting quinine for nocturnal muscle cramps. Drug-induced immune thrombocytopenia (DIIT) is suspected. Which of the following is true?

A) Detection of drug-induced antibodies (by flow cytometry) is often diagnostic.
B) DIIT is unlikely because platelet counts are rarely less than 50,000/µL.
C) DIIT is unlikely because the interval between drug administration and thrombocytopenia is too short.
D) The diagnosis of DIIT due to quinine is clinical because it cannot be distinguished from idiopathic thrombocytopenic purpura by laboratory tests.

5. A 25-year-old woman presents with purpura and epistaxis 8 days after starting trimethoprim-sulfamethoxazole for cystitis. A complete blood cell count demonstrates a platelet count of 45,000/µL. After the diagnosis of DIIT is confirmed, you advise the patient that

A) Upon cessation of the drug, at least 3 weeks are required for the platelet count to return to normal.
B) Platelet transfusions will reduce her mortality.
C) Plasma exchange hastens recovery.
D) Corticosteroids have no proven benefit.

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