PERSPECTIVE

'LESS IS MORE

# Balanced Coagulopathy in Cirrhosis—Clinical Implications
## A Teachable Moment

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### Story From the Front Lines

A 61-year-old woman with compensated hepatitis C cirrhosis was seen at the emergency department for a painful umbilical hernia. The hernia was reduced without incident, although given her painful presentation and the risk of an incarcerated hernia developing, surgical correction was recommended. Her baseline serum creatinine level was 1.1 mg/dL (to convert to micromoles per liter, multiply by 88.4), with a Model for End-Stage Liver Disease score of 15, but given her cirrhosis and the concern for bleeding risk, she was admitted to the hospital the day prior to surgery for medical optimization. The morning of her surgery, routine laboratory tests revealed an international normalized ratio (INR) for prothrombin time of 1.8, which was not significantly different from values over the past year. She was ordered 1 unit of fresh frozen plasma (FFP) to bring her INR down to 1.5 or less prior to the operation. Within 30 minutes of starting FFP infusion, the patient developed a diffuse urticarial cutaneous eruption. Transfusion was stopped, diphenhydramine and methylprednisolone were administered, and the patient had complete resolution of her symptoms. However, because of this reaction, hernia repair was cancelled and she was discharged the next day with instructions to follow up with a hematologist for consultation regarding coagulopathy management.

### Teachable Moment

Determining the bleeding and thrombosis risk in a patient with cirrhosis remains challenging, and the use of INR to assess bleeding risk in patients with cirrhosis has not been validated.[1] Furthermore, the degree of coagulopathy as determined by the INR is not predictive of bleeding complications in patients with compensated cirrhosis, defined as the absence of major complications such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatopulmonary syndrome.[2] Patients with cirrhosis have derangements of both procoagulant and anticoagulant factors that appear to achieve a relative balance that is not adequately reflected by measurement with conventional tests of coagulation such as partial thromboplastin time (PTT) and INR. In addition, the conventional wisdom that patients with cirrhosis are "autoanticoagulated" has been largely refuted by Dabbagh et al[3] and others who have demonstrated increased rates of DVT associated with hospitalization in patients with cirrhosis despite their elevated INRs compared with healthy individuals.

Despite published data demonstrating the lack of correlation between INR and bleeding risk in cirrhosis, FFP is still routinely used in patients with cirrhosis for prophylaxis in the absence of any trials demonstrating its benefit.[4] Furthermore, while guidelines exist regarding optimal dose of FFP for INR correction in the general population, it is not clear how this applies to patients with INR elevation due to cirrhosis. One study demonstrated that conventional doses of FFP only reduced prothrombin time to within 3 seconds of normal in 10% to 12% of patients with cirrhosis.[5] Given this lack of INR correction with conventional doses, patients with cirrhosis often receive numerous units of FFP, which may be complicated by significant volume expansion with increased portal pressures that may result in portal hypertensive bleeding complications, which may then be mistakenly attributed to deranged hemostasis.[2] In fact, there is increasing evidence that the majority of clinically significant bleeding episodes in patients with cirrhosis are the consequence of increased portal venous pressure and not due to deranged hemostasis as once believed.[2] Higher volume of administered blood products is also associated with increased risk of transfusion reactions, as illustrated in our case, ranging from febrile and allergic reactions to hemolytic reactions and acute lung injury.[2]

Finally, in addition to patient safety concerns, it should also be noted that prophylactic correction of coagulopathy based on laboratory measures of hemostasis is associated with substantial clinical costs. Patients with cirrhosis routinely account for approximately a third of FFP use in hospitals, and given the finite nature of the resource, the volume being administered, the lack of demonstrated efficacy, and the potential for adverse outcomes, the financial burden is substantial.[4]

The long-taught assumption that patients with cirrhosis have increased risk for bleeding due to liver-related coagulopathy is not supported by clinical and laboratory data. Rather, patients with compensated cirrhosis appear to have developed a hemostatic balance that is not appreciated with conventional tests of hemostasis. Based on these data, the routine administration of FFP in patients with cirrhosis solely for primary prophylaxis prior to invasive procedures is not recommended and exposes patients to unnecessary harm. Cases such as ours should serve as drivers for the development of assays that can identify patients with cirrhosis who are at increased risk for bleeding.

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PERSPECTIVE

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# More Than Skin Deep—The Costs of Antibiotic Overuse
## A Teachable Moment

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### Story From the Front Lines

A 55-year-old man with a history of hyperlipidemia visited his primary care physician for evaluation of persistent sinus congestion in the late fall season. He reported cough and rhinorrhea with mucous but no purulent secretions for the prior 7 days. He was initially recommended supportive treatment and over-the-counter decongestants. He was also prescribed a 5-day course of azithromycin, which he had never taken before, with instructions to initiate the antibiotic and return for follow-up if he had symptomatic worsening.

He began azithromycin treatment 2 days later. On the third night of taking azithromycin, he noted a new oral pain sensation and swelling of his gums, which evolved into painful mouth sores, irritation of his upper lip, odynophagia, redness of his eyes, and mild dysuria by the next morning. Despite hydrating with oral fluids intake and stopping azithromycin use on the fourth day of treatment, he continued to worsen, developing fevers and a new cutaneous eruption on the penis. He presented to the emergency department with edematous eyelids, conjunctival injection, and numerous painful erosions on the tongue, soft palate, buccal mucosa, and lips, which demonstrated hemorrhagic crusting (**Figure**). After excluding infectious causes of his eruption, he was diagnosed as having Stevens-Johnson syndrome. Azithromycin treatment had already been discontinued, and he was treated with close observation, aggressive emollients, fluid hydration, and conservative management in the hospital for 3 days.

### Teachable Moment

Antibiotic overuse is associated with several repercussions at the individual, population, and system levels. Antibiotics are frequently associated with untoward adverse effects and reactions in patients on either initial or repeated exposure; they are common causes of severe cutaneous eruptions including Stevens-Johnson syndrome, as in this case. The development of resistant organisms and rise of secondary infections such as *Clostridium difficile*–associated diarrhea resulting from antibiotic overuse pose serious public health challenges. Finally, the financial costs of antibiotic overuse and the associated complications contribute to increasing health care system expenditures.

This clinical vignette highlights a potential danger of the overuse of empirical antibiotics in the management of acute upper respiratory tract infection, which are generally of viral rather than bacterial etiology. Recent systematic reviews have demonstrated no benefit for antibiotics in the management of the common cold, acute purulent rhinitis, or acute bronchitis.[1,2] Several international organizations and physician specialty associations, including the Centers for Disease Control and Prevention, the UK National Institute for Health and Clinical Excellence, the American Academy

Figure. The Patient's Lips Demonstrated Multiple Erosions and Hemorrhagic Crusting Consistent With Stevens-Johnson Syndrome