Balancing the myths of corticosteroid therapy

Widespread skin-thickening with hyperpigmented plaques

Phenytoin-induced gingival overgrowth

Mucinous ascites in a 59-year-old man

Nasal herpes simplex virus infection

Clues to Addison disease in a 66-year-old woman

Diversifying medical humanities: The case for Jay-Z

Steroids in the acutely ill: Evolving recommendations and practice

Preventing atherosclerotic cardiovascular disease: A case-based approach

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Balancing the myths of corticosteroid therapy

No class of drug has more mythical attributes, interfaces with different medical specialties, or clinical street lore than corticosteroids. As posited in the 1978 satirical novel *The House of God,* no one acutely ill should die in the hospital without consideration to receive some “roids.” The striking benefits of corticosteroid treatment for many inflammatory conditions are well accepted. Demonstration of their efficacy in treating rheumatoid arthritis resulted in a Nobel prize in physiology and medicine being awarded in 1950 to Hench, Kendall, and Reichstein.

Steroids have been a linchpin treatment of inflammatory disease since then. There has been recognition for their lifesaving potential, and also for toxicities associated with their use. When I discuss treatment options with my patients, I emphasize that the newer nonsteroid immunosuppressive drugs have potential toxicities that are indeed scary and may occur, but that corticosteroids, due to their hormonal activity, have adverse effects that will occur with ongoing use. Strategies to limit these adverse effects include alternate-day therapy (this works for a few diseases), local application to limit systemic effects (inhaled, intralesional, and intra-articular), and “pulse dosing” utilizing a super-high dose for a few days. The last has achieved, appropriately or not, an iconic place in established as well as “Hail Mary” treatment paradigms for a host of inflammatory conditions.

Pulse dosing, several days of as much as a gram of intravenous methylprednisolone, was introduced around 1970 to treat the early rejection of transplanted kidneys. Mechanistic rationales included potential lytic effects of high doses on lymphocyte subsets, effects on the time course of lymphocyte migration, and provision of a time-limited intense treatment course to minimize adverse effects of long-term corticosteroid therapy. With our increasing but still incomplete understanding of how these drugs work, it seems possible that ultra-high doses of corticosteroids may have direct membrane-active effects in addition to their inhibitory effects on nuclear transcription mediated by nuclear factor kappa B and other steroid-responsive nuclear factors. But a substantial clinical benefit of pulse dosing has yet to be documented in a rigorous way for most conditions for which it is utilized. There remains the fear of “What if we didn’t give enough?”—while at the same time, clinical investigators are evaluating the necessity of traditional high doses given for induction therapy in the treatment of inflammatory diseases including severe ANCA-associated vasculitis.

Clearly the best way to limit the adverse effects of corticosteroid therapy is to limit their use. There has been an aggressive movement within rheumatology and nephrology to limit the use of corticosteroids in the management of several immunologic conditions, including renal transplantation, lupus nephritis, ANCA-associated vasculitis, and giant cell arteritis. This strategy is bolstered by recent publications indicating toxicity of even low-dose corticosteroid use over time, as well as the apparent lack of additional therapeutic benefit provided by higher vs lower doses of corticosteroids for systemic vasculitis. The availability of a structured approach to track glucocorticoid toxicity in clinical trials (and in practice) should provide an ongoing impetus to further this movement.

All clinicians share concern for increased risk of infections in patients treated with corticosteroids—from the annoying yet manageable oral candidiasis to potentially life-threatening pulmonary and systemic fungal infections, and the delayed recognition of deep-seated infections. In
addition, the administration of corticosteroids increases the peripheral neutrophil count and can suppress fever, thus complicating diagnostic and management decisions. So it has seemed almost paradoxical to be purposefully and effectively treating certain infections with corticosteroids (in addition to providing appropriate anti-infective agents). And yet there is reasonable evidence from clinical trials to support corticosteroid cotherapy in the management of selected patients with severe bacterial or pneumocystis pneumonia, bacterial meningitis, tuberculous pericarditis, bacterial native joint infections, and COVID-19, with significant pulmonary involvement.

A decades-long debate continues over the use of corticosteroids in sepsis. Forty years ago, a series of papers presented dramatic data showing the lifesaving effect of corticosteroids (with gentamycin) when provided very early following the administration of a lethal dose of *Escherichia coli* to baboons.\(^5\) Since then, animal studies and clinical trials have attempted to determine the efficacy or detriment of corticosteroid use in patients with sepsis, sepsis syndromes, and associated parenchymal injury like adult respiratory distress syndrome.

In this issue of the *Journal*, Pastores\(^6\) very nicely reviews the data and discusses his approach to the use of steroids in sepsis and the acutely ill. It seems for the moment that the “fat man” and colleagues from *The House of God* were correct: “roids” for the acutely ill may indeed be warranted, for the short term, with questions still to be answered regarding appropriate dosing and precise patient selection.

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2022

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USING DATA TO IMPROVE QUALITY OF CARE
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- Summarize the most recently published data from research and clinical trials and discuss their clinical implications for primary care medicine.
- Integrate a model for shared decision-making for older adults with multiple chronic comorbidities.
- Critically review the evidence on pre-exposure prophylaxis for HIV and AIDS.
- Discuss the impact of a patient’s race on the management of kidney disease.
- Review the clinical implications of recently published research on topical areas of interest to primary care practitioners, including diabetes, weight management, adult attention deficit disorders, treatment-resistant depression, heart failure, delayed gastric emptying, and dysautonomia conditions.

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A 37-year-old white male presented with skin-thickening and hyperpigmentation, the onset of which correlated with an increasingly sedentary lifestyle. He noted a subjective decrease in muscle density and a 40-pound weight gain in the decade following active military duty. His height was 6’1” (185.4 cm) and body mass index 32.3 kg/m².

At presentation, the patient had extensive velvety hyperpigmented plaques on the forehead, corners of the lips, neck, axillae, trunk (including areolae), extremities, and groin, amounting to approximately 10% to 15% of the body surface area (Figure 1).

Clinical features and skin-shave biopsy (showing epidermal papillomatosis) at initial presentation supported the diagnosis of acanthosis nigricans. The distribution and body surface area involvement prompted an initial laboratory workup, with a complete blood cell count, lipid panel, renal panel, and endocrine panel, all of which were normal. Multiple management strategies were attempted, including metformin, isotretinoin, topical therapies (steroids and calcineurin inhibitors), and weight loss. The patient initially experienced mild improvement in visual appearance and pruritus from weight loss and tacrolimus ointment. Though he felt systemically well, his acanthosis nigricans progressively worsened over the next 2 to 3 years (Figure 2). This prompted a cancer screening workup (Table 1), but to date no major abnormalities have been identified except gradual elevation over 2 years of the total cholesterol level of 202 mg/dL.

PATHOPHYSIOLOGY AND CLINICAL VARIANTS

Acanthosis nigricans classically presents in skin folds (eg, neck, axillae) with symmetrically distributed hyperpigmented plaques with a velvety or verrucous texture. It is more common in Native Americans and African Americans. The precise pathophysiology of acanthosis nigricans is unknown but attributed to insulin-mediated stimulation of keratinocytes and fibroblasts via insulin-like growth factor receptors and epidermal growth factor receptors.
Common causes of acanthosis nigricans include obesity, medications, and endocrine abnormalities, with rarer cases due to paraneoplastic phenomenon or a familial trait via germline fibroblast growth factor receptor 3 mutations. Obesity-associated acanthosis nigricans can present together with insulin resistance, high body mass index, diabetes, metabolic syndrome, or polycystic ovarian syndrome. Medications associated with acanthosis nigricans include niacin, oral corticosteroids, oral contraceptives, methyltestosterone. The paraneoplastic form is most often seen with gastric adenocarcinoma, though other causes have also been identified.

Acanthosis nigricans with abrupt features such as severe and rapid onset, atypical sites (eg, palms or mucosa), widespread distribution at any age, or new onset in patients over age 40 should prompt evaluation for malignancy. A thorough history and physical examination followed by judicious use of laboratory and other investigations should help determine the underlying cause of acanthosis nigricans.

**DIFFERENTIAL DIAGNOSIS OF SKIN-THICKENING AND HYPERPIGMENTATION**

Other notable conditions can present with skin-thickening or hyperpigmentation:
- Confluent and reticulated papillomatosis is more diffuse with a net-like appearance
- Terra firma-forme dermatosis easily wipes off with rubbing alcohol
- Hemochromatosis, Addison disease, and erythema dyschromicum perstans (ashy dermatosis) all present with flat hyperpigmentation only, without skin-thickening
- Pemphigus vegetans is a rare form of pemphigus with warty (verrucous) ulcerated plaques.

**MANAGEMENT**

Acanthosis nigricans is first treated by addressing underlying causes with diet and exercise and oral metformin in obesity-associated acanthosis nigricans, surgery or chemotherapy for paraneoplastic...
acanthosis nigricans, and removal of the offending agent in drug-induced acanthosis nigricans. 2–6 Skin treatments can help with the cosmetic appearance of plaques. Topical keratolytics (retinoids, salicylic acid, ammonium lactate, chemical peels) may help soften the appearance of acanthosis nigricans but carry a risk of skin irritation. Systemic isotretinoin may be considered in consultation with a dermatologist.

**TAKE-HOME POINTS**

While patients with milder acanthosis nigricans will not necessarily require a workup for malignancy, close clinical monitoring is recommended as the condition can be the first sign of diabetes or malignancy.6 Because approximately 17% of malignant acanthosis nigricans appears prior to tumor diagnosis, progression to severe acanthosis nigricans in this patient was the rationale for a more extensive clinical investigation.5–7

**DISCLOSURES**

Dr. Das has disclosed ownership interest (stock, stock ownership in a publicly owned company) in Bristol-Myers Squibb and Crisper Therapeutics, and work as advisor for Skin Analytics. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

**REFERENCES**


**TABLE 1**

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<td>• Colonoscopy, endoscopy</td>
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<tr>
<td>• Renal and gallbladder ultrasonography</td>
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<tr>
<td>• Consider computed tomography of abdomen and pelvis</td>
</tr>
<tr>
<td>• Consider referral to gastroenterology</td>
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</tbody>
</table>

<sup>a</sup> Screening for intra-abdominal adenocarcinoma in most cases, but also gastric, ovarian, endometrial, uterine/cervical, breast, liver, lung, pancreas, colorectal.

<sup>b</sup> Based on US Preventive Services Task Force guidelines for patients at average risk. See reference 1.

<sup>c</sup> Not performed in our male patient.
A 27-YEAR-OLD MAN PRESENTED TO OUR NEUROSURGERY CLINIC WITH A 3-MONTH HISTORY OF LOWER-EXTREMITY weakness and slurred speech.

After a traffic accident 1 year earlier, he had undergone right decompressive hemicraniectomy to evacuate an acute subdural hematoma, and after an episode of posttraumatic seizure associated with the hemicraniectomy, he was prescribed phenytoin for seizure prophylaxis and has been taking it ever since.

The patient had no past history of significant neurologic abnormalities. On examination, a Medical Research Council grade of 4/5 was noted bilaterally in his lower limbs. Nerve conduction studies showed increased latency and decreased conduction velocity in major nerves of the lower limbs. No other abnormalities were noted relative to gait, reflexes, or autonomic function, and he had no nystagmus or confusion.

Intraoral examination revealed generalized puffy, lobulated, swollen gums in the upper and lower jaws. The gingival swelling covered more than one-third of the tooth crown in the upper row and more than two-thirds in the lower row (Figure 1). The gingival lesions did not bleed on probing but were tender and suppurative at some places. In addition to gingival overgrowth, there was hypertrichosis over the upper and lower extremities.

Given the patient’s history of phenytoin use and the known association of phenytoin with gingival overgrowth, his serum concentration of phenytoin was measured and was found to be greater than 40 μg/mL (reference range 10–20). Phenytoin-induced peripheral neuropathy and gingival overgrowth were diagnosed, and his antiseizure medication was changed to carbamazepine. After 2 months, the gingival growth had regressed significantly (Figure 2).
Further, there was improved strength in the patient’s lower extremities, and the hair growth over his arms and legs had lessened. We referred him to our periodontal department for further management.

## GINGIVAL ENLARGEMENT

Inflammatory gingival enlargement is a risk in several clinical settings. It can occur after long-standing gingivitis secondary to local irritants such as dental plaque and calculus, as a complication of fractured teeth or ill-fitting dentures, and as a consequence of mouth-breathing. Hereditary conditions such as gingival fibromatosis, Zimmermann-Laband syndrome, Rutherford syndrome, Ramon syndrome, and some lysosomal storage diseases can also cause gingival enlargement. Systemic conditions associated with generalized gingival enlargement include leukemia, granulomatosis with polyangiitis, sarcoidosis, and tuberculosis.

Drug-induced gingival overgrowth also causes diffuse gingival enlargement. In most cases, the diagnosis can be made on the basis of the history, physical examination, laboratory investigation, and histopathologic testing, as well as associated systemic features present in many of these conditions.

### A drug side effect

Drug-induced gingival overgrowth is a notable side effect of anticonvulsant drugs (phenytoin, vigabatrin, ethosuximide, topiramate, lamotrigine, valproate, phenobarbital), immunosuppressants (cyclosporine, tacrolimus, sirolimus), and calcium channel blockers (nifedipine, felodipine, verapamil, diltiazem). Phenytoin is the most common culprit, and gingival enlargement is reported in up to 50% of patients who take the drug. It has a direct action on high-activity gingival fibroblasts, and the related severity of gingival enlargement is dose-dependent.

Drug-induced gingival overgrowth usually presents as enlargement of gingival tissue that encroaches on the tooth crowns. Secondary inflammation of these lesions leads to gum bleeding and discomfort with chewing or toothbrushing. It is diagnosed clinically when a patient has gingival enlargement, is taking a medication from one of the causative classes, and has no intraoral or general physical examination features that suggest an inflammatory, hereditary, or systemic condition.

Discontinuing the offending drug coupled with meticulous oral hygiene may lead to resolution, but surgical intervention to the gingiva is usually required. Seizure prophylaxis is not indicated in all cases of posttraumatic seizure. However, because our patient had a history of late posttraumatic seizure, we changed his medication from phenytoin to carbamazepine, a safer alternative, rather than stop his anti-seizure treatment.

**Phenytoin treatment: Educate and monitor**

Phenytoin is commonly used for prophylaxis and treatment of epilepsy. Clinicians who prescribe it are advised to educate their patients regarding the adverse effects of phenytoin-like drugs and to monitor patients at consistent intervals. Dental referral is advisable for patients who are taking phenytoin and develop gingival hypertrophy, not only for proper management of the condition but also to enhance motivation to maintain proper oral hygiene.

### DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Mucinous ascites: Pseudomyxoma peritonei

A 59-year-old man with a history of hypertension presented with 2 months of progressive abdominal distention associated with abdominal pain and fatigue. Point-of-care ultrasonography revealed large-volume ascites. The patient’s abdominal swelling limited his activities of daily living and oral intake, resulting in hospital admission for new-onset ascites.

At admission, the patient’s temperature was 36.7°C (98.1°F), heart rate 82 beats per minute, respiratory rate 18 breaths per minute, and blood pressure 111/63 mm Hg. Results of pulmonary and cardiovascular examinations were normal, including the jugular venous pressure. Abdominal distention and bulging flanks were noted. However, there were no spider telangiectasias, palmar erythema, or distended abdominal veins. During abdominal paracentesis, the hospitalist procedure team noted that the ascitic fluid had a markedly viscous, jelly-like consistency (Figure 1).

THE EVALUATION

Laboratory testing revealed the following:
- Serum creatinine 0.86 mg/dL (reference range 0.50–1.39)
- Albumin 3.8 g/dL (3.2–5.6)
- Total bilirubin 0.8 mg/dL (< 1.2)
- Direct bilirubin 0.3 mg/dL (< 0.4)
- Alkaline phosphatase 69 U/L (35–137)
- Aspartate aminotransferase 24 U/L (< 40)
- Alanine aminotransferase 26 U/L (7–45)
- International normalized ratio 1.09 (0.83–1.19)
- Carcinoembryonic antigen 0.9 ng/mL (< 2.5)
- Cancer antigen 19–9 46.8 U/mL (< 35 U/mL).

Ascitic fluid analysis showed the following:
- White blood cells 2,016/μL (reference range < 300), with 43% neutrophils, 29% lymphocytes, 26% macrophages, 2% monocytes
- Red blood cells 3,000/μL (0)
- Culture: no bacterial growth
- Chemistries including protein, albumin, triglycerides and amylase could not be completed due to fluid viscosity
- Fluid cytology: positive for mucin and atypical malignant cells.

The fluid’s viscous appearance prompted consideration of pseudomyxoma peritonei (PMP) over more common causes of ascites due to the presence of portal hypertension. With a negative fluid culture, spontaneous bacterial peritonitis was unlikely in the absence of cirrhosis or portal hypertension despite the ascitic fluid neutrophil count being greater than 250 μL.

Magnetic resonance imaging of the abdomen revealed thickening (ie, “caking”) of the greater omen-
MUCINOUS ASCITES

Figure 2: Positron emission tomography/computed tomography performed after therapeutic paracentesis. There is significant hypermetabolic activity along the margin of the greater omentum (arrow) consistent with peritoneal carcinomatosis.

tum, with new dilation of the pancreatic duct and a possible mass within the tail of the pancreas. Computed tomography (CT) revealed a normal appendix without another source for a primary tumor. Positron emission tomography/CT showed increased uptake along the greater omentum, suggestive of peritoneal carcinomatosis (Figure 2). Peritoneal biopsy revealed an immunohistochemical profile suggestive of a well-differentiated pancreaticobiliary adenocarcinoma. Colonoscopy and upper gastrointestinal endoscopy did not reveal another primary tumor. The combination of findings indicated either a ruptured intraductal papillary mucinous neoplasm (IPMN) complicated by invasive carcinoma or a pancreatic adenocarcinoma as the primary tumor.

■ PSEUDOMYXOMA PERITONEI

Pseudomyxoma peritonei is a rare clinicopathologic syndrome with an incidence of 0.2 per 100,000 people per year.1 It is characterized by mucinous ascites associated with peritoneal and omental implants.1-3 Mucin-producing neoplastic cells rupture and seed the peritoneum.3 This results in a distinct gelatinous quality of the ascitic fluid. Patients with PMP typically present between ages 40 and 55, and the syndrome is often diagnosed as an incidental finding on imaging or during laparotomy.2 At later stages, PMP presents as new-onset ascites and abdominal distention.1,2

Low-grade or high-grade appendiceal mucinous neoplasms are the main cause of PMP.1 The primary differential diagnostic consideration is between an appendiceal mucinous neoplasm and peritoneal carcinomatosis in which invasive implants of mucinous adenocarcinoma result in mucinous ascites.3 Clinical outcomes for patients with peritoneal carcinomatosis are poor compared with those for patients with appendiceal mucinous neoplasms causing PMP.5 When confronted with PMP that is not of appendiceal origin, it is essential to determine the origin of the tumor, as neoplasms of the ovary, gallbladder, colon, urachus, and pancreas are associated with PMP.1 The relationship between IPMN and PMP is hypothesized based on case reports.4

■ TREATMENT AND FOLLOW-UP

The cornerstone of treatment for PMP is surgical debulking and hyperthermic intraperitoneal chemotherapy.2,3 Patients with unresectable disease and severe symptoms due to ascites may require serial paracenteses. Those with ascitic fluid viscosity that prohibits bedside drainage with traditional catheters may require referral to interventional radiology or possibly surgery for palliative laparoscopic evacuation of the ascites.5

Due to the rarity of PMP that is not of appendiceal origin, our patient’s treatment required a multidisciplinary approach to assess surgical risk and indications for systemic chemotherapy based on the tumor’s primary site of origin. The pathology suggested pancreatic adenocarcinoma, which prompted initial treatment with leucovorin, fluorouracil, irinotecan, and oxaliplatin (ie, the FOLFIRINOX regimen). Unfortunately, the patient experienced significant adverse effects and progressive functional decline. He declined additional surgical management, opting for palliative and comfort-based treatments, and died 8 months after the initial diagnosis.

New-onset ascites is a common patient presentation. Although PMP is rare, the unique, viscous quality of the ascitic fluid is easily recognizable. The presence of mucinous ascites on bedside paracentesis should prompt evaluation for an etiology of PMP including ascitic fluid cytology testing and cross-sectional abdominal imaging.

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.
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Nasal herpes simplex virus infection

A 37-year-old man with epilepsy presented to the emergency department with a 1-week history of skin changes of the nose that began after being scratched on the nose. A few days after the scratch, he hit the tip of his nose on steel bundles during a seizure. He then developed a headache, and his nose began to swell and develop a black appearance at the tip. He had sought attention at another hospital, where he was prescribed doxycycline due to concern for a skin and soft-tissue infection.

At our emergency department, physical examination revealed hemorrhagic crusting, ulceration, and black eschar with peripheral erythema of the tip of the nose and extending upward to the dorsal surface (Figure 1), prompting concern for extensive nasal skin necrosis. Therefore, intravenous vancomycin, clindamycin, and piperacillin-tazobactam were started empirically.

■ EXTENSIVE EVALUATION

Laboratory testing demonstrated only an elevated C-reactive protein, and blood cultures and lumbar puncture were negative. Head, facial, and sinus computed tomography revealed soft-tissue edema without bony erosion. Nasal endoscopy showed healthy nasal mucosa.

Shave biopsy demonstrated ulceration with spongiosis, serous crust, and a lymphohistiocytic infiltrate. Tissue culture was negative for fungi and acid-fast bacilli but positive for group B Streptococcus. Polymerase chain reaction testing was negative for herpes simplex virus type 1 (HSV-1) and varicella-zoster virus but positive for HSV-2. Therefore, the patient was continued on vancomycin (total of 7 days) and started on acyclovir (for 2 days) during hospitalization, and was discharged with a 10-day course of oral valacyclovir 1 g twice daily and amoxicillin-clavulanate. The patient’s nose continued to improve on this therapeutic regimen as an outpatient.

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Figure 1. Herpes simplex virus infection of the nose with extensive ulceration with hemorrhagic crust, dark eschar, and peripheral erythema. Shave biopsy of the lateral border of the ulcerated plaque (arrow) revealed ulceration with spongiosis, serous crust, and a lymphohistiocytic infiltrate.

■ THE DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this patient’s presentation included infections such as HSV-1, HSV-2, Chikungunya virus, invasive fungal infections, rhinoscleroma, Hansen disease (formerly leprosy), and Mycobacterium tuberculosis; inflammatory conditions such as granulomatosis with polyangiitis; and neoplasms such as natural killer or T-cell lymphomas.

In this patient, hemorrhagic ulceration, immuno-
NASAL HSV

competence, limited comorbidities, and no known exposure to uncommon infectious agents served as clues for a diagnosis of HSV infection. HSV infection commonly presents as vesicles or ulcers, which may represent deroofed vesicles. Additionally, ulcers may have an overlying yellow crust due to serous exudate from the disrupted vesicles or from secondary impetiginization. Skin lesions caused by invasive fungal infection can be the result of a localized or disseminated process and are often characterized by central necrosis. These infections commonly affect patients with underlying immunosuppression (eg, human immunodeficiency virus infection, hematologic malignancy, glucocorticoid use) or diabetes mellitus. Lupus vulgaris, a cutaneous form of mycobacterial infection, usually presents on the head or neck in adults in a variety of ways including plaque, ulcerative, vegetative, papulonodular, and tumorlike forms, but lesions tend to be chronic and progressive in nature.

NASAL HERPES SIMPLEX VIRUS INFECTION

HSV infection may present as gingivostomatitis, eczema herpeticum, erythema multiforme, herpetic whitlow, genital ulcerations, keratitis, chorioretinitis, encephalitis, Bell palsy, esophagitis, and hepatitis. It can be responsible for primary, latent, and recurrent infections as it is dormant in the dorsal root ganglion of sensory neurons. Potential triggers for reactivation include physical stress, psychological stress, and immunosuppression.

HSV is most commonly found in the oral mucosa but has also been detected in tears and nasal mucosa of immunocompetent adults. Cutaneous or mucosal HSV can be assessed with polymerase chain reaction testing or culture of swabs of the base of the ulcerative lesions. As in this patient, vesiculation and ulceration of the dorsal surface of the nose without intranasal involvement due to HSV infection has been reported in an immunocompetent individual with a remote history of trauma to the nose. Intranasal HSV infection with and without evidence of necrosis has been reported in immunocompromised individuals, and this presentation is frequently mistaken for invasive fungal rhinosinusitis. Management with systemic antiviral therapy is effective, and surgical debridement is required only in severe cases.

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Cardiovascular Update for the Primary Care Provider

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A 66-year-old woman presented to our department with generalized fatigue and loss of appetite. A review of her medical record showed that at age 52 she had undergone kidney transplant for end-stage kidney disease, receiving treatment of tacrolimus and mycophenolate after induction therapy with methylprednisolone 1,000 mg/day tapered over 3 months. After that, without steroids or antihypertensive drugs, her blood pressure had remained within the normal range. Mild hyperkalemia had been noted, and her fasting blood glucose was in the normal range.

On admission, her heart rate was 74 beats per minute and her blood pressure was 117/80 mm Hg. Physical examination revealed hyperpigmentation of her tongue and soft palate (Figure 1), as well as the buccal mucosa, lower lip, fingers, and nail beds. The eyelids, neck, nipples, elbows, back, knees, and soles had very mild or no pigmentation. When asked about the hyperpigmentation, the patient said that she had first noticed it more than 20 years ago but that it had not interfered with her daily life, and she had never sought medical attention for it.

**INITIAL WORKUP**

Laboratory testing at admission showed the following:

- Potassium 5.7 mmol/L (reference range 3.6–4.8)
- Adrenocorticotropic hormone (ACTH) of 372 pg/mL (7.2–63.3)

![Figure 1. Skin pigmentation in the patient's tongue (left) and on the soft palate (right).](image-url)
• Dehydroepiandrosterone sulfate 15 μg/dL (12–133)
• Estimated glomerular filtration rate of 33.2 mL/min/1.73 m² (≥ 60)
• Morning cortisol 8.93 μg/dL (6.24–18.00)
• 24-hour urinary free cortisol less than 12.5 μg/day (11.2–80.3)
• Plasma renin activity and plasma aldosterone concentration were normal
• Anti-adrenal antibody testing and cytomegalovirus antigenemia test were negative
• Rapid ACTH stimulation test showed no significant increase in serum cortisol.

Computed tomography of the abdomen showed no adrenal hyperplasia, nodules, or malignant lesions. These findings and the results of laboratory testing supported the diagnosis of Addison disease. The patient received glucocorticoid-replacement therapy without mineralocorticoid, which relieved the hypornatremia, hyperkalemia, and general symptoms. One month after the start of replacement therapy, the hyperpigmentation had improved slightly.

■ CAUSES AND SYMPTOMS OF PRIMARY ADRENAL INSUFFICIENCY

Addison disease, or primary adrenal insufficiency, is an uncommon disease caused by destruction of the adrenal cortex, usually owing to an autoimmune process. Other causes include infections, malignant infiltration, metabolic dysfunction, and granulomatous disease, as well as genetic, neonatal, vascular, pharmacologic, neoplastic, and surgical factors.1

Common clinical manifestations are fatigue, weight loss, orthostatic hypotension, skin and mucosal hyperpigmentation, nausea, vomiting, abdominal pain, libido reduction, depression, and salt-craving, depending on any deficiencies of glucocorticoids, mineralocorticoids, or androgens.1,2

Most manifestations are nonspecific and slowly progressive, so the diagnosis of Addison disease is often difficult or delayed. However, hyperpigmentation, caused by excess binding of ACTH and alpha-melanocyte stimulating hormone to the melanocortin 1 receptor,3 is a characteristic feature and a diagnostic clue for Addison disease.2

Diffuse hyperpigmentation is also caused by medications (eg, chemotherapeutic agents, antimlarials, oral contraceptives, prostaglandin agonists, amiodarone, minocycline) and by endocrine and metabolic diseases (hyperthyroidism, diabetes mellitus, hemochromatosis).4 This patient was taking none of these agents, and there was no endocrine or metabolic disease present to produce hyperpigmentation other than Addison disease.

■ FEATURES OF HYPERPIGMENTATION OFFER DIAGNOSTIC CLUES

The characteristics of skin hyperpigmentation can offer clues to the cause. For example, aminoquinoline drugs can induce gray-blue pigmentation on pretilial surfaces, oral mucosa, sclera, and subungual areas. Minocycline induces 3 patterns: generalized brown discoloration, dark blue discoloration confined to acne scars or areas of skin inflammation, and gray-blue discoloration on the front of the lower extremities or in exposed areas. In Addison disease, hyperpigmentation is muddy and diffuse on buccal, conjunctival, and genital mucosa and on nail beds, palmar creases, and nipples.4

■ TAKE-HOME MESSAGE

When Addison disease is considered in the differential diagnosis, it is important to review the patient’s medical history, to examine the skin and mucous membranes for hyperpigmentation, to measure early-morning plasma ACTH and serum cortisol, and to perform the ACTH stimulation test. Glucocorticoid and mineralocorticoid replacement therapy is essential.

■ DISCLOSURES

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Diversifying medical humanities: The case for Jay-Z

The underpinnings of medicine are based in science, but its practice—like all human endeavors—is bound up in history, sociology, philosophy, and ethics. These have traditionally been considered concerns of the humanities, and medical education now formally embraces humanities training. However, there are criticisms of the current approach to narrative-based medical humanities training. Banner has argued that humanities and medicine have paid insufficient attention to race, choosing instead to be apolitical. Adams and Reisman have called for prioritizing the intersection of humanities with structural racism. The blind spots are made clear when some medical humanities advocates call for reform of humanities teaching in medical schools by finding “common ground” with the 1910 Flexner report on medical education reform. These calls conveniently gloss over the fact that the author, Abraham Flexner, argued for the closure of most Black medical schools: “A well-taught negro sanitarian will be immensely useful; an essentially untrained negro wearing an M.D. degree is dangerous.” A devastating real-world consequence of the Flexner report was that all but two extant Black medical schools soon closed, leading to approximately 35,000 fewer Black physicians in the United States. An inclusive medical humanities program could have prevented such embarrassing “advocacy” by humanities experts.

### RESHAPING THE CANON

If we are to truly diversify the medical humanities curriculum, as we must, how should the canon be reshaped? One way would be to continue relying on narratives from conventional spaces, but with an intentional emphasis on voices from communities of people of color. For a more truly inclusive approach, however, one does not have to look too far: hip-hop, an art form only a few decades old, has evolved to become a voice for the oppressed in many different societies and cultures worldwide.

One of the most well-known pioneers of hip-hop is Shawn Carter, known professionally as Jay-Z. He grew up in the Marcy housing projects in Brooklyn, NY, initially pursuing crime before being redeemed by the rewards of his art. Author Zadie Smith has described Jay-Z’s works as “showrooms of hip-hop, displaying the various possibilities of the form.” On a superficial level, Jay-Z’s lyrics celebrate his successes and transformation from poverty to enormous wealth. But the key to a deeper reading is to understand the form of hip-hop itself. Many object to the focus on materialism, but braggadocio is as integral to hip-hop’s form as romance is to sonnets. Indeed, as Smith says, “Asking why rappers always talk about their stuff is like asking why Milton is forever listing the attributes of heavenly armies.”

This surface-level story—“the hustler’s story”—serves as a stand-in for the struggles of life. As Jay-Z explains it, hustling is “the ultimate metaphor for […] the struggle to survive and resist […] to win and make sense of it all.” An alert reader who looks past this surface-level celebration of consumerism will be rewarded with truth-telling about the pathologies of poverty, crime, and American society and their interaction with health inequities. As Jay-Z himself states, “To tell the story of the kid with the gun without telling the story of why he has it is to tell a kind of lie.” Or more poetically, “Marcy raised me, and whether right or wrong/Streets gave me all I write in the song.”

A large body of literature describes the association between racism and racial health inequities. Both structural and interpersonal racism can impact the care of individual patients, including their
BELOW THE SURFACE: LAYERS OF MEANING

Certainly, hip-hop is not without critique: the glorification of violence, consumerism, misogyny, and toxic masculinity plague the genre. However, this critique is itself subject to criticism as being selectively applied to hip-hop and not to other artistic genres, and in many ways reflects systematically biased ways of approaching art. Misogyny is also rife in the works of Hemingway, Updike, and Mailer (who famously stabbed his wife), yet they remain canonical.

However, even if we take the criticism of misogyny in hip-hop at face value, it is crucial to understand that the words critics are objecting to have layers of meaning and context. Sometimes the lyrics are the words of a character who is misogynist. Sometimes they are provocations to identify disingenuous listeners. Sometimes they are used ironically. And sometimes they are truly misogynistic. An illustration of superficial reading by critics is one of Jay-Z’s best-known songs, “99 Problems,” which uses what may be thought of as a misogynistic word—but only if you don’t read the full verse. If you do, you will realize that at no point does the artist refer to a woman. It is, as Jay-Z says, “a deliberate provocation to simple-minded listeners.”

He elaborates: “The art of rap is deceptive. It seems so straightforward and personal and real that people read it completely literally, as raw testimony or autobiography … It’s all white noise to [critics] until they hear it completely literally, as raw testimony or autobiography.”

In any case, the hip-hop form is evolving toward a more self-critical phase. In “Minority Report,” an elegy for the predominantly Black lives lost in the flooding that followed Hurricane Katrina in New Orleans, Jay-Z initially identifies systemic racism as the cause of the neglect and “otherization” of the victims: “And the next five days, no help ensued/They called you a refugee because you seek refuge.” But then he recognizes his own culpability as a person of means who donated but did not truly volunteer to help: “Silly rappers, because we got a couple Porsches/MTV stopped by to film our fortresses/We forget the unfortunate/Sure I ponied up a mill, but I didn’t give my time/So in reality I didn’t give a dime, or a damn.” In “4:44,” he admits obliquely to straying in his marriage and confesses openly about the shame he feels that his daughter will grow up to discover his
faults as a husband and father: “My heart breaks for the day I have to explain my mistakes/And the mask goes away/And Santa Claus is fake.”24 Perhaps most heartrendingly, Jay-Z confronts his own past misdeeds in “Beach Chair,” worried that his then-unborn child will pay the price: “See I got demons in my past/so I got daughters on the way/If the prophecy’s correct/Then the child should have to pay/For the sins of a father So I barter my tomorrows against my yesterdays/In hopes that she’ll be okay.”25 This piece, written in the form of a will, finds the narrator hoping to ensure financial security for her, but also praying that she will have more serenity in his life than he did: “I will prepare/A blueprint for you to print/A map for you to get back/A guide for your eyes…/My last will written in the form of a will, finds the narrator hoping to ensure fi nancial security for her, but also praying that she will have more serenity in his life than he did: “I will prepare/A blueprint for you to print/A map for you to get back/A guide for your eyes…/My last will and testament I leave my heart/My share of Roc-A-Fella Records and a shiny new beach chair.”25

■ EMPATHY WITHOUT BOUNDARIES

The purpose of medical humanities is to provide physicians and healthcare providers in training or otherwise with alternative perspectives on life, and to engender empathy for the suffering and lived experiences of our patients. When we restrict humanities curricula to what feels comfortable, we are by defniition restricting ourselves to points of view we wish to appreciate and empathize with. When we only embrace literary experiences that align with certain social classes or race, we send the message that our empathy has boundaries that align with social class or race.

Physicians carry considerable power in the patient-physician relationship. Opening our minds to the viewpoints of others diffuses some of that power and grounds us in the communities we serve. This is needed. As the poetry and poets of hip-hop evolve outside the confines of academia, leveling the playing field for countless oppressed voices worldwide, it is past time for literature in medicine to evolve as well—to listen to and refect upon these voices that, in turn, refect all facets of our societies and represent the worldview of all of our patients.

■ DISCLOSURES

The author has disclosed consulting for Anthos, Bayer, BMS, Genzyme/Sanofi, and Pfizer.


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Steroids in the acutely ill: Evolving recommendations and practice

ABSTRACT

Critical illness-related corticosteroid insufficiency (CIRCI) is a state of systemic inflammation involving dysregulation of the hypothalamic-pituitary-adrenal axis, altered cortisol metabolism, and tissue resistance to corticosteroids. Many conditions may be associated with CIRCI, including sepsis, septic shock, acute respiratory distress syndrome, and severe community-acquired pneumonia. Recommendations and practice for diagnosing and treating this condition have evolved as information has emerged. Here, the author reviews the current thinking.

KEY POINTS

Guidelines suggest giving intravenous (IV) hydrocortisone 200 mg/day (50 mg IV every 6 hours or as a continuous infusion) to patients who have septic shock and ongoing need for vasopressor therapy to maintain adequate blood pressure, but not to those who have sepsis without septic shock.

Guidelines suggest giving IV methylprednisolone 1 mg/kg/day or dexamethasone 20 mg/day to those with acute respiratory distress syndrome, provided it is early (within 72 hours of onset) and severe (with a PaO₂/FiO₂ ratio < 200).

Dexamethasone 6 mg IV once daily for up to 10 days is recommended for hospitalized patients with COVID-19 who require supplemental oxygen, noninvasive respiratory support, or invasive mechanical ventilation.

Using and tapering steroids should always be guided by clinical response and side effects.

The term CIRCI, or critical illness-related corticosteroid insufficiency, was coined in 2008 by an international multidisciplinary task force of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine when they released the guidelines for the diagnosis and treatment of CIRCI. The guidelines were updated in 2017 and are being updated for publication in 2023.

Recommendations have evolved as new information has been generated with regards to what causes CIRCI, how to diagnose it, who should receive corticosteroid treatment, and what regimens to use.

THREE MAIN MECHANISMS

In 2008, we described CIRCI as a syndrome of inadequate corticosteroid activity for the severity of the patient’s illness, that may occur with a decrease in adrenal steroid production (adrenal insufficiency) or from tissue resistance to glucocorticoids with or without adrenal insufficiency. To these mechanisms we now add alterations in cortisol metabolism.

During critical illness, production of adrenocorticotropic hormone (ACTH) is often low, while cortisol levels tend to be normal or, usually, high. The diurnal rhythm in cortisol levels (normally lower in the evening and higher in the morning) is also lost.

More than 90% of circulating cortisol is bound to corticosteroid-binding globulin, which tends to fall during critical illness. Only 5% to 10% of cortisol is free and biologically active.

Normal total cortisol levels are between 5 and 24 μg/dL.
Cortisol is a lipophilic hormone that enters cells passively and binds to specific glucocorticoid receptors in the cytoplasm, or to membrane sites. Cortisol is metabolized primarily in the liver by 5 alpha/beta-reductases and in the kidneys by the 11-beta-hydroxysteroid dehydrogenase (11-beta-HSD) type 2 enzyme. During severe stress states, the expression and activity of these enzyme systems is reduced, leading to decreased clearance of cortisol. Upon binding of glucocorticoid, the glucocorticoid receptor undergoes a conformational change, dissociates from the chaperone proteins, and enters the nucleus and mitochondria, where it binds to positive (transactivation) or negative (cis-repression) specific DNA regions termed glucocorticoid responsive elements to regulate transcription and translation of target genes in a cell- and gene-specific manner. Nuclear factor kappa B is the major transcription protein that glucocorticoids inhibit, and this inhibition is responsible for downregulating the actions of proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin 1, and interleukin 6. Glucocorticoids also act through a nongenomic pathway.

**CIRCI IS COMMON**

The incidence of CIRCI varies widely, depending on the population studied and the diagnostic criteria used: 20% to 60% of patients with septic shock in a medical intensive care unit, 21% to 75% of patients with human immunodeficiency virus infection who are critically ill, and 15% to 50% of patients with traumatic brain injury.\(^4,5\)

The common clinical features are hemodynamic instability despite adequate fluid resuscitation, and fever and inflammation without an obvious source of infection that does not respond to empiric antimicrobial therapy. Other, nonspecific signs and symptoms can include altered mental status, gastrointestinal symptoms, hypoglycemia, eosinophilia, hyponatremia, and hyperkalemia. Hyponatremia and hyperkalemia are less common than in patients with primary adrenal insufficiency, in whom they may be more prominent.

Many conditions can be associated with CIRCI: sepsis, septic shock, acute respiratory distress syndrome (ARDS), major trauma, severe bacterial pneumonia, bacterial meningitis, and nonseptic shock states, such as in patients with cardiopulmonary bypass, post cardiac arrest, cardiogenic shock, and burns.

**NO SINGLE TEST CAN RELIABLY DIAGNOSE CIRCI**

In 2008, the Corticosteroid Guideline Task Force recommended two ways of testing for CIRCI in the critically ill:

- The cosyntropin stimulation test (an increase in the total serum cortisol from baseline of less than 9 μg/dL 60 minutes after giving an intravenous (IV) 250-μg dose of cosyntropin, a synthetic formulation of natural ACTH)
- A random total plasma cortisol level (of less than 10 μg/dL).

However, in 2017, we concluded that no single test can reliably diagnose the syndrome, and we could not reach a consensus (> 80% agreement) on whether the ACTH stimulation test is superior to random cortisol for the routine diagnosis of CIRCI.

If the ACTH stimulation test is used, we recommend that the high dose of cosyntropin (250 μg IV) be used for testing rather than the low dose (1 μg), because the latter has mediocre sensitivity in critically ill patients. This was a weak recommendation based on low-quality evidence.

We advised against measuring plasma free cortisol. We found no randomized trial that compared serum total vs free cortisol levels to diagnose CIRCI. A prospective study of 112 critically ill adults with treatment-insensitive hypotension, published after the 2008 recommendations, found a good correlation between serum concentrations of free and total cortisol before and after 250 μg ACTH stimulation testing.\(^6\) Measurement of free cortisol is cumbersome to perform and may not be widely available in hospital laboratories, and so for practical purposes we felt that measurement of total cortisol would be preferable for most clinicians.

We also suggested against the use of salivary cortisol levels, as it would not be cost-effective, practical, or feasible given that it is tested by enzyme immunoassay, which may not be routinely available at most centers.

Most importantly, we emphasized that if corticosteroids are clinically indicated in acutely ill or critically ill patients, there is no need to do a cosyntropin stimulation test.

Patients already on steroids (ie, ≥ 5 mg of prednisone or 20 mg of hydrocortisone per day for at least 3 weeks) are at risk of hypothalamic-pituitary-adrenal axis suppression. Cosyntropin stimulation testing is recommended only for those who are more likely to develop either permanent, secondary adrenal insufficiency or CIRCI, to confirm or deny need for perma-
nent replacement therapy or to monitor their recovery during the final phases when tapering the corticosteroid. Dexamethasone does not interfere with the cortisol response or with the cortisol assay. However, if someone is taking hydrocortisone, it should be discontinued the evening before stimulation testing.

**DIFFERENT GLUCOCORTICOID PREPARATIONS**

The biologic rationale for glucocorticoid use in acutely ill patients relates to its potent anti-inflammatory effects and to its effects on cardiovascular tone, including enhanced vasoconstrictor response to exogenous catecholamines and inhibition of cyclo-oxygenase-2 and inducible nitric oxide synthase. Hydrocortisone tends to be preferred as replacement therapy, as it has a short duration of action which allows the hypothalamic-pituitary-adrenal axis to recover between doses. However, prednisone, dexamethasone, and methylprednisolone are the agents we generally use, particularly in those with severe inflammation including bacterial pneumonia and ARDS.

**SIDE EFFECTS**

Steroids are not benign drugs. They can be associated with several side effects, most notably hyperglycemia, but also hypernatremia, neuromuscular weakness, myopathy, superinfections, upper gastrointestinal bleeds, arrhythmias, and steroid-induced psychosis.

**STERIODS TO TREAT SEPTIC SHOCK**

Corticosteroids have been used in septic shock for nearly 6 decades, and practice has changed as information has emerged.

1976—Schumer\(^7\) performs the first randomized controlled trial, using very large doses of steroids, ie, dexamethasone 3 mg/ kg or methylprednisolone in doses of nearly 2 g daily, in 172 patients with clinical septic shock and finds a reduction in mortality.

1980s—Bone et al\(^8\) and Sprung et al\(^9\) find that high-dose methylprednisolone (30 mg/kg daily) does not increase survival, and it induces superinfections in many patients. For the next 15 years, steroids are avoided in patients with septic shock.

2002—Annane et al\(^10\) find that the combination of hydrocortisone 50 mg IV every 6 hours plus fludrocortisone 50 μg enterally daily is associated with a lower mortality rate, especially in those who do not respond to the cosyntropin stimulation test. However, patients who do respond derive no benefit. In the next few years, cosyntropin stimulation testing becomes popular, and nonresponders get hydrocortisone plus fludrocortisone.

2008—The Corticosteroid Therapy of Septic Shock (CORTICUS) trial\(^11\) finds no benefit to the use of hydrocortisone 50 mg IV every 6 hours in terms of survival, but shock reversal is faster. Response to the cosyntropin stimulation test does not seem to matter. Many clinicians begin to abandon the stimulation test in patients deemed to already have an indication for corticosteroids, ie, refractory septic shock.

2016—The Hydrocortisone for Prevention of Septic Shock (HYPRESS) trial\(^12\), with 380 patients, finds that hydrocortisone 200 mg/day IV for 5 days does not prevent progression from sepsis to septic shock, indicating steroids should not be used for patients with sepsis who are not in refractory shock.

2018—The Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock (ADRENAL) trial,\(^13\) in 3,800 patients, finds that hydrocortisone 200 mg by IV infusion for 7 days compared with placebo was not associated with survival benefit, but shock reversal is faster, duration of mechanical ventilation is shorter, and fewer blood transfusions are needed, with relatively few side effects, mainly hyperglycemia.

2018—The Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial,\(^14\) in 1,241 patients, uses the combination of hydrocortisone 200 mg IV in divided doses (50 mg IV every 6 hours) and fludrocortisone 50 μg enterally daily for 7 days. At 90 days, fewer patients in the steroid group had died, shock reversal was faster, and the steroid regimen was found to be safe; hyperglycemia was the most common adverse reaction. At 180 days, the survival benefit remained.

2019—A Cochrane meta-analysis\(^15\) finds that corticosteroid therapy "probably" reduces hospital mortality (by about 9%), and results in large reductions in length of stay in the intensive care unit (by about 1 day) and in the hospital (by about 1 and one-half days). Corticosteroid therapy was associated with increased risk of hyperglycemia, hypernatremia, and muscle weakness but no increased risk of superinfection and little or no difference in gastrointestinal bleeding, neuropsychiatric, stroke, or cardiac events.

2020—Enter artificial intelligence. Pirracchio et al\(^16\) enter data from about 2,500 patients from 4 septic shock clinical trials into an artificial intelligence program to attempt to more precisely determine who should receive corticosteroids, based on multiple
patient variables. This seems to be where the future lies. They found that strategies to treat all patients with corticosteroids or to treat no one were associated with a worse outcome. In contrast, an individual estimation-based treatment strategy always yielded a positive net benefit.

2017 guidelines
The 2017 guidelines were issued just before the results of the ADRENAL and APROCCHSS trials were published. Our suggestions at that time were as follows:

Consider the use of IV hydrocortisone less than 400 mg/day for at least 3 days in patients in septic shock who already got adequate fluid resuscitation and still need moderate to high-dose vasopressor therapy (conditional recommendation, low quality of evidence).

Do not use corticosteroids in adult patients with sepsis who are not in refractory shock (conditional recommendation, moderate quality of evidence).

Steroid use should always be guided by clinical response and tapered slowly to avoid the rebound phenomenon.

Surviving Sepsis Campaign guidelines 2021
Recommendations from the Surviving Sepsis campaign published in 2021 are similar, suggesting intravenous corticosteroids (eg, hydrocortisone 200 mg per day in divided doses or as continuous infusion) for adult patients in septic shock who continue to need vasopressor therapy (conditional recommendation, low quality of evidence).

Stopping steroids
If the patient no longer needs vasopressor therapy, is out of shock, and is maintaining adequate blood pressure for at least 12 to 24 hours, it is probably time to consider tapering or discontinuing steroids.

An exception is in patients who have an underlying endocrine disorder or indication for using corticosteroids: in those patients you have to taper the corticosteroids back to their usual dose. This has to be done carefully. One recommendation is to decrease by 10 to 20 mg over several days to weeks, depending on how much they required for maintenance therapy.

Steroid use should always be guided by clinical response and tapered slowly to avoid the rebound phenomenon.

STEROIDS IN ACUTE LUNG INJURY AND ARDS
The ARDS Network study showed that corticosteroids should not be used in patients in the late phase of ARDS, ie, after 2 weeks on a ventilator. But what about early?

Meduri et al performed a randomized, double-blind placebo-controlled trial in 91 patients with severe early ARDS (within 72 hours), 66% of whom had sepsis. They randomized these patients in a 2:1 ratio to methylprednisolone infusion 1 mg/kg/day vs placebo. They tapered the steroid slowly, keeping the same dose for 14 days, cutting it in half on day 15 to day 21, in half again from day 21 to 28, and then stopping. More importantly, they did surveillance with frequent bronchoscopies to rule out infection, and they avoided neuromuscular blockade so as not to accentuate neuromuscular weakness, a side effect of steroids.

The primary outcome was a reduction in the Lung Injury Score or successful extubation by day 7, both of which were achieved. There were also significant reductions in the duration of mechanical ventilation, length of stay in the intensive care unit, and mortality.

The 2017 guidelines gave a weak recommendation for the use of methylprednisolone 1 mg/kg/day in patients with ARDS, specifically patients receiving at least 50% FiO₂ on mechanical ventilation with positive end-expiratory pressure of 10 cm H₂O or more who have a PaO₂/FiO₂ ratio under 200. The tradeoff is hyperglycemia. We felt there was no increased risk of neuromuscular weakness, gastrointestinal bleeding, or nosocomial infection.

Villar et al performed a study in 277 patients who had moderate to severe ARDS, with PaO₂/FiO₂ ratios less than 200 despite lung-protective ventilation and other strategies to optimize them on mechanical ventilation; 77% of these patients had either pneumonia- or sepsis-associated ARDS. They randomized the patients to dexamethasone 20 mg/day for 5 days, and then 10 mg/day on days 6 to 10, and then stopped the steroid shortly after that in most patients. The study was conducted over 5 years. The trial was stopped by the Data and Safety Monitoring Board due to low enrollment rate after enrolling nearly 90% of the planned sample size. The investigators found significant benefits with dexamethasone in terms of ventilator-free days, all-cause mortality at day 60, and duration of mechanical ventilation.

STEROIDS IN SEVERE BACTERIAL PNEUMONIA
In 2017, we suggested using corticosteroids in hospitalized patients with severe community-acquired
pneumonia who required mechanical ventilation or vasopressor therapy (conditional recommendation, moderate quality of evidence).\textsuperscript{21}

This was largely based on a trial by Torres et al,\textsuperscript{22} published in 2015, in patients with severe community-acquired pneumonia and a high systemic inflammatory response, with C-reactive protein levels greater than 15 mg/L, requiring mechanical ventilation or vasopressor therapy. Corticosteroid therapy was associated with improvement in survival. Hyperglycemia was the most common adverse effect.

A Cochrane review\textsuperscript{23} in 2017 looked at 17 randomized controlled trials involving 2,264 patients and showed corticosteroids to significantly reduce mortality and morbidity rates in patients with severe community-acquired pneumonia, but not in those with nonsevere community-acquired pneumonia.

\section*{COVID-19}

The initial flulike symptoms of COVID-19 are usually associated with bioreplication, and by the time the patients come to the hospital with respiratory symptoms they usually are already at risk with a severe inflammatory response that can progress to ARDS and the need for invasive mechanical ventilation. These patients have elevations in proinflammatory markers and inflammatory cytokines such as C-reactive protein, IL-6, and IL-1.

In April 2020, we argued in favor of corticosteroid therapy in patients with severe COVID-19-associated ARDS based on available observational evidence at that time and the extremely high mortality associated with the disease, and in favor of not waiting for the results of the randomized controlled trials.\textsuperscript{24}

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial\textsuperscript{25} published its results a few months later. It was large, with 6,425 patients, of whom 2,104 received dexamethasone 6 mg IV daily for up to 10 days, and the rest usual care. Dexamethasone reduced mortality by one-third in those who required mechanical ventilation and by one-fifth in those receiving supplemental oxygen. However, there was no benefit in patients who were not receiving respiratory support, and there was even the suggestion of harm that could not be excluded.

A meta-analysis conducted by the World Health Organization Rapid Evidence Appraisal for COVID-19 Therapies Working Group\textsuperscript{26} showed that the mortality rate at 28 days was significantly lower in patients with COVID-19 pneumonia and ARDS who got corticosteroid therapy, compared with those who did not receive corticosteroids (32.7\% vs 41.5\%, respectively).

\section*{Is viral shedding a problem?}

In the influenza H1N1 and SARS epidemics, when steroids were given very early, they were associated with adverse outcomes. However, by the time patients with COVID-19 come to the hospital and need supplemental oxygen or mechanical ventilation, they are usually in a very proinflammatory phase, and at that point there is probably already less likelihood of delay in SARS-CoV-2 viral clearance.

Cano et al\textsuperscript{27} reviewed 73 studies involving 21,350 patients, which showed there was clearly a benefit of using corticosteroids in terms of mortality in very sick patients with COVID-19. They did not find any significant impact on viral shedding.

\section*{The mortality rate is significantly lower in severely ill patients with COVID-19 who receive dexamethasone}

\subsection*{Low vs high dose of dexamethasone in COVID-19}

Why not use a higher dose of dexamethasone? Dexamethasone 6 mg is equivalent to only about 30 mg of methylprednisolone. Would 12 mg be better than 6 mg?

Two randomized controlled trials\textsuperscript{28,29} did not show a statistically significant benefit in terms of survival at 28 days in patients who received 12 mg compared with those who received 6 mg. Therefore, 6 mg of dexamethasone is still most commonly given. In my own practice, I occasionally either double the dose if patients are on 6 mg and not clinically responding and remain very hypoxic, or switch to methylprednisolone 1 mg/kg/day, and see if they respond. You can double it up to 2 mg per kg depending on inflammatory markers if they have ARDS.

Comparing dexamethasone and methylprednisolone, I favor methylprednisolone because it resides longer in the lung and is more potent as an anti-inflammatory agent, but always start with 6 mg of dexamethasone and then move from there depending on how sick the patient is.

The National Institutes of Health guidelines\textsuperscript{30} recommend the following:

- Remdesivir, dexamethasone, or both for hospitalized patients who require supplemental oxygen
- Dexamethasone with or without remdesivir for patients who require oxygen through a high-flow nasal cannula or noninvasive ventilation (plus either baricitinib or IV tocilizumab for patients with
randomized controlled trials. They concluded the use of corticosteroids “probably” reduces mortality in patients with ARDS of any etiology, and patients who got a longer course of corticosteroids (more than 7 days) had higher rates of survival than those who got a shorter course.

■ DISCLOSURES

Dr. Pastores has disclosed serving as advisor or review panel participant for Abbvie Pharmaceuticals, as research investigator with bioMerieux, Eisai, and Revimmune, receiving royalty fees as textbook editor for McGraw-Hill.

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26. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of...


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Primary and secondary prevention of atherosclerotic cardiovascular disease: A case-based approach

ABSTRACT
Estimating the risk of atherosclerotic cardiovascular disease (ASCVD) is a daily challenge for clinicians and is crucial to tailoring preventive medical care and guiding shared decision-making. New imaging modalities and novel biomarkers allow for more accurate assessment of patient risk and minimize the risk of over- or undertreating patients. Major cardiovascular medicine societies have incorporated new diagnostic modalities in their guidelines to aid clinical decision-making for primary and secondary prevention of ASCVD. This review presents commonly encountered cases relevant to estimating and reducing ASCVD risk based on available guidelines and expert opinion.

KEY POINTS
- The coronary artery calcium score may be used in patients with borderline or intermediate risk of ASCVD to guide statin initiation.
- Lipoprotein(a) is an important and often overlooked risk factor for ASCVD.

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality worldwide. Statins have been the mainstay therapy in the primary prevention of ASCVD, while the role of aspirin in this patient population has been decreasing. However, the decision of starting either medication, particularly for primary prevention, can be challenging due to either the lack of benefit or the absence of robust data for certain age groups or patient subpopulations. With the availability of advanced imaging modalities and novel biomarkers, guidelines have amended the indications for primary and secondary prevention of ASCVD, incorporating new therapies to further reduce patient residual risk of ASCVD. In this case-based review, we present commonly encountered clinical cases that may pose clinical challenges for both internists and cardiologists in dealing with decisions on primary and secondary prevention of ASCVD.

CASE 1
A 58-year-old white male presented to the outpatient clinic for routine annual visit. On examination, his blood pressure was 146/88 mm Hg and his body mass index (BMI) was 29 kg/m². He confirmed being a current smoker. Lab results revealed hemoglobin A1c (HbA1c) of 8.9% (reference range 4%–5.6%), total cholesterol 147 mg/dL (reference range < 200 mg/dL), high-density lipoprotein cholesterol (HDL-C) 54 mg/dL (reference range > 40 mg/dL),
low-density lipoprotein cholesterol (LDL-C) 92 mg/dL (reference range < 100 mg/dL), and spot urine albumin-to-creatinine ratio > 300 mg/g (reference range < 30 mg/g). He regularly takes lisinopril and hydrochlorothiazide. Concerned about his mother’s death from myocardial infarction at the age of 48, the patient is looking for risk-reduction strategies of future cardiovascular events. Other than emphasizing a healthy lifestyle and controlling blood pressure and diabetes, how would you further manage this patient?

A. Initiate simvastatin 40 mg
B. Initiate rosuvastatin 10 mg and aspirin 81 mg
C. Initiate atorvastatin 80 mg
D. Initiate rosuvastatin 40 mg and aspirin 81 mg

Answer: D

■ CASE 2

A 50-year-old African American female presented to the preventive cardiology clinic for an annual check-up with a history of rheumatoid arthritis and preeclampsia during her first pregnancy and her mother having passed away at the age of 45 from myocardial infarction. On examination, her blood pressure was 155/85 mm Hg and her BMI was 25 kg/m². She exercises 4 times per week and does not use nicotine or alcohol. Her lipid profile revealed total cholesterol 200 mg/dL, HDL-C 33 mg/dL, and LDL-C 160 mg/dL. Moreover, HbA1c was 4.8% and high-sensitivity C-reactive protein (hs-CRP) was 4 mg/L (reference range < 3.0 mg/L). Other than controlling the patient’s hypertension, which of the following would be the best option to reduce risk of future ASCVD events?

A. Initiate atorvastatin 20 mg
B. Initiate atorvastatin 80 mg and aspirin 81 mg
C. Initiate atorvastatin 80 mg
D. Initiate atorvastatin 20 mg and aspirin 81 mg

Answer: C

■ RATIONALE

In case 1, the patient had a 10-year risk of ASCVD of 22.7% (high risk) that qualified him for high-intensity statin therapy (rosuvastatin 40 mg or atorvastatin 40–80 mg). In addition to his high ASCVD risk, the patient did not seem to be at elevated risk for bleeding. Therefore, it is reasonable to add low-dose aspirin after clinician-patient discussion about risks and benefits.

In case 2, the patient presented with a 10-year ASCVD risk of 8.4% (intermediate risk). However, the patient had a history of rheumatoid arthritis, preeclampsia, family history of premature heart disease, and elevated hs-CRP (> 2 mg/L). The pooled cohort equation may underestimate the 10-year ASCVD risk in patients with chronic inflammatory disorders such as those with human immunodeficiency virus (HIV) taking antiretroviral therapy, patients with rheumatoid arthritis or sarcoidosis. Therefore, it may be beneficial to consider other risk-enhancing factors in overall ASCVD risk assessment, especially because some factors may be targeted with specific therapies.

■ EVIDENCE

The role of statins in the prevention of ASCVD

The role of statins in primary prevention of ASCVD among adults has been validated in several studies and strongly supported by major cardiovascular medicine societies. The American Heart Association (AHA) and American College of Cardiology (ACC) recommend statin therapy for primary prevention for patients if LDL-C levels exceed 190 mg/dL, if they have diabetes, or if they are 40 to 75 years of age with increased risk of ASCVD (≥ 7.5%) after clinician-patient discussion of the potential benefits and harms. Figure 1 summarizes the current evidence algorithm for using aspirin and statins for primary prevention of ASCVD. The role of statins in the elderly (> 75 years of age) is less certain, and thus their use must be tailored to every patient after discussing the risks and benefits. The latest ACC/AHA Blood Cholesterol and Primary Prevention of ASCVD guidelines state that statin therapy is reasonable in elderly patients who are expected to derive net clinical benefit from treatment. A meta-analysis from the Cholesterol Treatment Trialists’ Collaboration group among 14,483 adults and a more recent retrospective cohort study among 326,981 older US veterans (mean age 81) without ASCVD who were followed for approximately 6.8 years showed that initiation of statin therapy was significantly associated with reductions in major cardiac events in this population, including cardiovascular mortality (hazard ration [HR] = 0.80, 95% confidence interval [CI] 0.78–0.81), and all-cause mortality (HR = 0.75, 95% CI 0.74–0.76). Importantly, potential side effects of statins are of
Figure 1. Decision-making flowchart to guide strategies for reducing the risk of atherosclerotic cardiovascular disease.

*Avoid aspirin use in patients with a high risk of bleeding.

ASA = acetylsalicylic acid; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol

Adapted from Grundy et al, reference 2.
concern in the elderly population mainly due to their more complicated health status and frailty. On the other hand, statins require about 4 to 5 years to show stroke-reducing benefits suggesting that patient life expectancy should also be considered in the overall decision-making process to direct statin therapy.2,3

The estimation of the individual’s 10-year ASCVD risk score using the pooled cohort equation remains the mainstay for primary prevention.2,3 The ASCVD calculator (https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/) is available for free online and offers a clinical decision tool. Furthermore, the latest ACC/AHA guidelines on the primary prevention of cardiovascular disease highlighted several risk-enhancing factors to guide treatment decisions2,3:

- Chronic inflammatory diseases (eg, rheumatoid arthritis, psoriasis, HIV)
- High-risk race or ethnicity (eg, South Asian ancestry)
- Persistently elevated triglycerides ≥ 175 mg/dL
- Metabolic syndrome
- Preeclampsia and premature menopause
- Chronic inflammatory diseases (eg, rheumatoid arthritis, psoriasis, HIV)
- High-risk race or ethnicity (eg, South Asian ancestry)
- Persistently elevated triglycerides ≥ 175 mg/dL

The following are measurable risk factors:

- hs-CRP ≥ 2.0 mg/L
- Lipoprotein(a) (Lp[a]) levels ≥ 50 mg/dL or 125 nmol/L
- Apolipoprotein B ≥ 130 mg/dL
- Ankle-brachial index < 0.9

In adults at intermediate risk (7.5% to 20%), moderate-intensity statins are indicated to decrease LDL-C levels by 30% or more. However, in those with high ASCVD risk (> 20%), high-intensity statins are recommended to reduce LDL-C levels more than 50%.2

Aspirin and primary prevention of ASCVD

The role of aspirin in secondary prevention is well established; however, its role in primary prevention has been debatable and recently studied in multiple large randomized clinical trials targeting different patient populations.14 As such, the latest guidelines on cardiovascular disease prevention from the European Society of Cardiology do not recommend the use of aspirin in primary prevention (low-to-moderate risk patients), while the American Diabetes Association recommends that aspirin therapy (75–162 mg/day) may be considered for primary prevention if the patient is at increased risk of cardiovascular disease.16,17

Three recent large-scale clinical trials18–20 provided concrete evidence on the role of aspirin in primary prevention. The ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) trial,19 a prospective, randomized, double-blinded trial, included 12,546 patients without diabetes at moderate risk of ASCVD. Aspirin 100 mg/day did not reduce the primary outcome of composite all-cause or cardiovascular mortality. Instead, it significantly increased gastrointestinal bleeding (HR 2.11, P = .0007). The ASCEND trial (A Study of Cardiovascular Events in Diabetes)19 investigated outcomes with aspirin 100 mg/day in 15,480 patients with diabetes without established cardiovascular disease and did not show a reduction in all-cause or cardiovascular deaths. Although, major bleeding events were increased significantly with an absolute risk increase of 0.9% (number needed to harm = 111), the number needed to treat (NNT = 91) to prevent an ASCVD event remained lower based on an absolute risk reduction of 1.1%. Further, in patients age 70 or older, the use of aspirin for primary prevention was associated with higher all-cause mortality in the ASPREE trial (Aspirin in Reducing Events in the Elderly),20 which enrolled 19,114 patients assigned to receive 100 mg of enteric-coated aspirin or placebo (HR = 1.14, 95% CI 1.01–1.29).20

In light of the accumulating evidence on the limited role of aspirin in primary prevention for ASCVD and potential harm associated with it in the trials highlighted above as well as prior multiple meta-analyses, the most recent ACC/AHA guidelines recommend low-dose aspirin (75–100 mg/day) for the primary prevention of ASCVD in select adults ages 40 to 70 who have elevated ASCVD risk but are not at increased bleeding risk (class of evidence IIb, level of evidence A).2,3 Factors associated with increased risk of bleeding include history of gastrointestinal bleeding, chronic predisposing conditions such as coagulopathy, chronic kidney disease, chronic inflammatory conditions with use of nonsteroidal anti-inflammatory medications, and use of anticoagulation.

Alternatively, the role of coronary artery calcium (CAC) scores to direct aspirin initiation for primary prevention of ASCVD has been illustrated in some observational studies.21,22 In one analysis from the Multiethnic Study of Atherosclerosis cohort,21 patients with CAC score of zero Agatston units are less likely to benefit from aspirin therapy even with family history of premature cardiovascular disease. In another analysis from the Multiethnic Study of Atherosclerosis trial,22 CAC scores were more likely to identify subgroups that would benefit from aspirin.
therapy in patients with high ASCVD risk scores compared with pooled cohort equations. According to this analysis, only patients with a CAC score ≥ 100 Agatston units would gain net clinical benefit from aspirin for primary prevention, while the use of aspirin in patients with a CAC score < 100 Agatston units would probably yield greater net harm. However, in the absence of robust data and the concomitant risk of radiation exposure, the use of CAC scores to direct aspirin therapy in intermediate risk patients is still under investigation.

■ CASE 3

A 44-year-old African American male with a history of well-controlled hypertension and HIV on antiretroviral therapy, presented to the clinic for an annual physical examination and to establish care. He had no history of family with premature heart diseases. On examination, his blood pressure was 125/79 mm Hg and BMI was 35 kg/m². The rest of the physical examination was non-revealing. Blood tests showed LDL-C 123 mg/dL, HDL-C 49 mg/dL, total cholesterol 223 mg/dL, triglycerides 255 mg/dL (reference range < 160 mg/dL), and serum creatinine 0.9 mg/dL (reference range 0.6 to 1.3 mg/dL). He is a former smoker (quit 20 years ago) with a sedentary lifestyle. Review of outside records revealed cardiac computed tomography done within the year with a CAC score of zero Agatston units (Figure 2). Which of the following would you recommend for this patient?

A. Initiate atorvastatin 20 mg
B. Initiate aspirin 81 mg
C. Initiate atorvastatin 20 mg and aspirin 81 mg
D. Measure serum Lp(a)
E. Encourage healthy lifestyle changes for weight loss and smoking cessation
F. D and E

Answer: F

■ RATIONALE

The patient in case 3 has a 10-year ASCVD risk score of 6.4% (borderline). In the absence of coronary calcification with a CAC score of zero Agatston units, it is reasonable to withhold statin therapy and reassess in 5 to 10 years (class of evidence IIa; level of evidence B). Further, measurement of Lp(a) is a reasonable once-in-a-lifetime test, is an affordable screening tool, can establish a reference value, and can qualify patients for risk-reducing therapies. Importantly, statins interact with several antiretroviral agents, particularly protease inhibitors, and can increase the risk of toxicity associated with statins, including myopathy and rhabdomyolysis.

■ EVIDENCE

The role of coronary artery calcium scoring in the primary prevention of ASCVD

The latest AHA/ACC cholesterol management guideline sheds light on the role of CAC testing to further stratify patients with borderline to intermediate ASCVD risk. While the pooled cohort equation remains the cornerstone to estimate ASCVD risk, it can overestimate or underestimate risk in some sub-
Atherosclerotic cardiovascular disease populations. Hence, it is reasonable to consider individual risk factors that may refine patient risk and subsequently individualize treatment strategy. However, if risk assessment is still uncertain after accounting for risk-enhancing factors in patients with borderline or intermediate risk or if the patient is still reluctant to start treatment, obtaining a CAC score is reasonable (class IIa). The following include scenarios where obtaining a CAC score and knowing the score is zero would support clinical decision-making:

- Patients reluctant to initiate statin who wish to understand their potential risk and benefit more precisely
- Patients who are not adherent to statin therapy due to side effects but are willing to reinitiate statins for risk reduction
- Older patients (men ages 55–80, women ages 60–80) with low burden of cardiovascular risk factors who question the benefit from statins
- Middle-aged adults (ages 40–55) with a 10-year risk of ASCVD 5% to < 7.5%, in the absence of high-risk conditions such as cigarette smoking, family history of premature ASCVD, or diabetes mellitus.

Thus, a zero CAC score may be used to defer statin initiation in adults ages 40 to 75 without diabetes and with an LDL-C 70 to 189 mg/dL if there are no additional risk factors such as smoking or significant family history of premature ASCVD, and if the patient can be reassessed in 5 to 10 years (class of evidence IIa; level of evidence B). It is important to note that the vast majority of data regarding CAC scores to guide primary prevention of ASCVD is derived from observational studies, and physicians should be aware of risks associated with exposing patients to radiation with unclear long-term side effects associated with such exposure. Of note, the radiation exposure (mean 1 mSv) required to obtain a CAC score is comparable to that of mammogram screening. Therefore, clinician-patient discussion is highly encouraged when considering CAC measurements for further risk stratification.

The role of lipoprotein(a) in cardiovascular disease prevention

The role of Lp(a) in the pathogenesis of ASCVD is well established. Promising results from recent early-stage clinical trials using targeted therapy for Lp(a) have shown substantial reductions from baseline levels. Yet, there are no clear thresholds to define high Lp(a) levels mainly due to heterogeneity in approaches to measure Lp(a) and prevalence among different patient populations. For example, Black individuals of African descent and South Asian populations have higher median Lp(a) levels than White or East Asian individuals. Moreover, around 70% to ≥ 90% heterogeneity of Lp(a) levels are genetically determined with an autosomal codominant inheritance pattern. Therefore, a single measurement could be sufficient to estimate patient ASCVD risk more accurately and allow for initiation of screening of family members due to the inheritance pattern and significant association with ASCVD burden. Hence, it is reasonable to measure Lp(a) in patients with poorly controlled LDL-C, including those already on high-intensity statins and ezetimibe along with patients with a strong family history of premature ASCVD. Yet it is important to note that some intraindividual temporal variability has been documented. Thus, obtaining the mean of two Lp(a) measurements at different times may be more clinically beneficial in refining risk prediction. Further studies are warranted to elucidate standard protocol for Lp(a) measurement.

The latest ACC/AHA 2018 Blood Cholesterol guidelines stated that Lp(a) ≥ 50 mg/dL or 125 nmol/L...
(it is preferable to use an assay that reports Lp[a] levels in nmol/L) is considered a risk-enhancing factor with increasing significance at higher levels.2 Remarkably, the National Heart Lung and Blood Institute reported (2018) that an estimated 1.4 billion people globally have Lp(a) levels ≥ 50 mg/dL, with a prevalence ranging from 10% to 30% and possibly higher in patients with established ASCVD, calcific aortic valve disease, or chronic kidney disease,35 making Lp(a) a promising biomarker to further risk-stratify patients.34 In fact, measuring serum Lp(a) is of clinical significance as it has been shown to reclassify about 40% of individuals into either lower or higher risk groups.35 For instance, in the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes) trial, patients with controlled LDL-C had 89% higher risk of ASCVD with Lp(a) > 50 mg/dL compared with those with optimal levels.36 In a meta-analysis of 126,634 participants from 36 prospective studies, elevated Lp(a) was associated with a logarithmic increase in myocardial infarction and cardiovascular death (risk ratio 1.13, 95% CI 1.09−1.18).29 For example, patients had a risk ratio of coronary heart disease adjusted for age and sex of 1.16 per 3.5-fold elevation in Lp(a).29

To date, there are no US Food and Drug Administration-approved therapies that directly target elevated Lp(a); however, novel agents are in late stage clinical trials (National Clinical Trial [NCT]04023552). Nevertheless, the effect of currently available lipid-lowering agents on Lp(a) is modest and clinically not significant.31,37 For instance, in a systematic review and meta-analysis38 comparing ezetimibe to placebo in patients with primary hypercholesterolemia, there were minimal to no changes in Lp(a) levels. While proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to reduce Lp(a) levels by around 20% to 30%,39 this reduction is probably insufficient to reach targeted Lp(a) concentrations (< 50 mg/dL) in many patients.37 On the other hand, lipid apheresis has been shown to decrease Lp(a) by 50% to 75%. However, this procedure is expensive and needs to be performed every 1 to 2 weeks.37 Recently, ligand-conjugated antisense oligonucleotides have shown promising efficacy and safety in reducing Lp(a) in phase I/II clinical trials. Antisense oligonucleotides are short, single-stranded oligonucleotides that target mRNA of Lp(a) and degrade it by activating an enzyme called RNase H1 (ribonuclease H1). Pelacarsen, formerly known as AKCEA-APO-(a)LRx, is one example of an antisense oligonucleotide that was shown to reduce Lp(a) by up to 92% in phase II clinical trials with excellent safety profiles.30,40 The HORIZON trial (Assessing the Impact of Lipoprotein [a] Lowering With Pelacarsen [TQJ230] on Major Cardiovascular Events in Patients With CVD)41 is a phase III, double blinded, placebo-controlled ongoing clinical trial investigating the effect of pelacarsen on cardiovascular outcomes in patients with established ASCVD. It has currently enrolled nearly 4,000 participants globally (more than 50% enrollment target) (NCT04023552).41

■ CASE 4

A 52-year-old African American female with a history of hypertension, diabetes, chronic kidney disease stage IV, coronary artery bypass graft 5 years ago, and a non-ST-segment elevation myocardial infarction 2 months ago, presented to the clinic for a follow-up visit. She was concerned about her cardiovascular risk after her 45-year-old brother suffered a massive myocardial infarction a few weeks prior and unfortunately passed away. Her medications included aspirin 81 mg, atorvastatin 80 mg, amlodipine 10 mg, and a multivitamin. On physical examination, her blood pressure was 137/74 mm Hg. Cardiac auscultation revealed a regular rhythm, no murmurs. Her ankle-brachial index was 0.60 (reference range 1−1.4) and lipid panel was as follows: LDL-C (92 mg/dL), HDL-C (49 mg/dL), and triglycerides (220 mg/dL). How would you further reduce this patient’s risk of future cardiovascular events?

A. Add ezetimibe therapy
B. Add a PCSK9 inhibitor
C. Add a PCSK9 inhibitor and ezetimibe
D. Continue current management

Answer: A

■ RATIONALE

In case 4, the patient has established ASCVD. Thus it is recommended to aggressively control her lipid profile to reduce her risk of future cardiovascular events. While she is on maximally tolerated statin therapy, her LDL-C is still above 70 mg/dL. Hence, the next reasonable step would be to add ezetimibe 10 mg/day. After 6 to 8 weeks, the patient would be re-evaluated for treatment efficacy. When the targeted LDL-C goal of < 70 mg/dL is not reached, the addition of a PCSK9 inhibitor is indicated. Obtaining a CAC score in such cases would not add valuable clinical information or alter treatment plans.
EVIDENCE

Beyond statins
Statins remain the foundation of LDL-C reduction in secondary prevention. However, in patients with established cardiovascular disease, maximally tolerated doses of statins are not sufficient to reach the targeted goal of < 70 mg/dL or at least 50% reduction in serum LDL-C from baseline. Hence, in such patients, especially in patients with a history of multiple ASCVD events who are at high risk of future disease, the use of non-statin medications is indicated. The first option to be considered as an adjunctive therapy is ezetimibe. Ezetimibe inhibits the uptake of cholesterol by interacting with the Niemann-Pick C1-like protein. Consequently, less cholesterol will be delivered to the liver, upregulating hepatocytic LDL-C receptors and leading to a decrease in serum LDL-C. Ezetimibe monotherapy decreases LDL-C by 18%; however, this percent reduction increases up to 27% when combined with a high-intensity statin regimen. Results from the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International) trial favor the addition of ezetimibe to high-intensity statins if patients do not reach the LDL-C target with statin monotherapy. The most important finding from this trial is that lower LDL-C levels achieved in the simvastatin plus ezetimibe group translated into further reduction in major adverse cardiovascular events that were more prominent in patients with diabetes as well as those over age 75. Thus, patients at highest ASCVD risk derive the greatest benefit from LDL-C-lowering therapies.

Furthermore, if LDL-C remains above 70 mg/dL despite the use of dual lipid-lowering therapy, it is recommended to start PCSK9 inhibitors. To date, there are two US Food and Drug Administration-approved PCSK9 inhibitors, alirocumab and evolocumab. The approval was based on two major randomized controlled trials that evaluated efficacy and safety of PCSK9 inhibitors: the FOURIER and the ODYSSEY trials. In the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial, patients had a baseline LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL. At follow-up (median, 2.2 years), evolocumab significantly reduced composite ASCVD (15% relative risk reduction). These results were replicated in the ODYSSEY (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial that investigated efficacy and safety of alirocumab in secondary prevention of patients on maximally tolerated statins. Although both trials did not reveal major adverse effects (< 3 years), the absence of longitudinal data raises concern over long-term safety profiles of these agents. While no trials to date have investigated whether the addition of ezetimibe or PCSK9 inhibitors to maximally tolerated statins is better, the use of ezetimibe as a second-line treatment before PCSK9 inhibitors is reasonable. First, ezetimibe is less costly and is now available in generic forms. Second, the long-term safety profile of this drug is well established. Finally, the combination of ezetimibe and high-intensity statins would be enough to reach LDL-C reduction target in the majority of patients.

TAKE-HOME POINTS

- In patients with low or moderate 10-year ASCVD risk and low-density lipoprotein cholesterol (70–189 mg/dL), an assessment of potential risk-enhancing factors may be useful to clinicians in risk-stratifying patients and further directing medical therapy.
- The CAC score may be used for patients with borderline or intermediate risk of ASCVD to guide statin initiation.
- Lp(a) is an important risk factor for ASCVD with promising therapies in late-stage clinical trials.
- The addition of ezetimibe or a PCSK9 inhibitor or both is proven to further reduce the risk of ASCVD when target LDL-C cannot be achieved with high-intensity statin monotherapy.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES


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Cirrhotic coagulopathy: A rebalanced hemostasis

ABSTRACT
Cirrhosis has been regarded as a hypocoagulable state associated with an increased risk of bleeding. But patients with cirrhosis also have a high incidence of thrombotic complications, challenging this dogma. We now recognize that in cirrhosis there is a simultaneous decrease in both clotting and anticlotting factors, leading to a new equilibrium. Conventional coagulation tests such as the platelet count and prothrombin time do not assess the reduced anticoagulation factors in cirrhosis and overestimate the bleeding risk, and any intervention based on these test results can lead to thrombotic complications. This article reviews the changes in hemostasis associated with cirrhosis, newer tests for assessing coagulation, and preprocedural minimization of coagulopathy.

KEY POINTS
The rebalanced hemostasis of cirrhosis is a delicate equilibrium of antithrombotic and prothrombotic changes associated with decreased synthetic liver function, inflammation, and endothelial and platelet activation related to cirrhosis.

Coagulopathy—characterized by prolonged prothrombin time, elevated international normalized ratio (INR) of the prothrombin time, prolonged activated partial thromboplastin time, low fibrinogen levels, and low platelet counts—is a hallmark of advanced cirrhosis. Traditionally, cirrhosis has been considered a hypocoagulable state in which the risk of life-threatening bleeding complications is increased.1–3 Evidence of this comes from the PRO-LIVER study,4 which prospectively followed 280 patients with cirrhosis for a median of 1,129 days. Significant bleeding events occurred in 5.45% of patients per year.5 The bleeding rate is higher in patients with advanced liver disease who need to be admitted to the hospital because of acute decompensation of their liver disease, or for patients with cirrhosis who need to be admitted to the intensive care unit for any reason.1,5 Most of these bleeding events are gastrointestinal and most are thought to be related to elevated portal pressures.5 Importantly, markers of coagulopathy such as elevated INR, thrombocytopenia, and low fibrinogen levels have not been shown to correlate with or predict the risk of bleeding events accurately.6

However, patients with cirrhosis also have a high incidence of thrombotic complications such as portal vein thrombosis and venous thromboembolism, which are independently associated with significant morbidity, acute hepatic decompensation, and death.7,8 The incidence of portal vein thrombosis in patients with cirrhosis has varied widely in different studies, owing to differences in the populations studied, but it is higher than in patients...
without cirrhosis.\textsuperscript{9,10} A rate ranging between 3.2\% and 4.1\% at 1 year after diagnosis is often cited and increases over time.\textsuperscript{11,12}

In a large case-control study, the relative risk of venous thromboembolism in patients with cirrhosis was found to be 1.74 (95\% confidence interval [CI] 1.54–1.95) compared with patients without liver disease.\textsuperscript{13} These findings were echoed by data from the Multiple Environmental and Genetic Assessment study,\textsuperscript{14} which showed that in hospitalized patients, liver disease was associated with significantly increased risk of venous thromboembolism (adjusted odds ratio [OR] 1.7, 95\% CI 1.0–2.9).\textsuperscript{14}

This increased risk of thrombotic events challenges the notion that patients with cirrhosis are “autoanticoagulated” and highlights the need for a more nuanced evaluation of the coagulopathy of cirrhosis.

In fact, the liver synthesizes most proteins of the coagulation system. Cirrhosis results in a simultaneous decrease in both procoagulant and anticoagulant factors, resulting in a delicate state of rebalanced hemostasis, metaphorically illustrated in Figure 1. This coagulation profile is unique to the individual patient and is influenced by the etiology of liver disease, disease severity, acute illnesses, and ongoing therapy.\textsuperscript{15,16} Conventional coagulation tests such as prothrombin time, INR, and platelet count measure procoagulant
factors but not the anticoagulation factors, and therefore they are inadequate to accurately assess bleeding risk and guide management.2,11

The purpose of this review is to elucidate the current understanding of coagulopathy of cirrhosis, how to assess it, and how to manage bleeding risk in patients about to undergo invasive procedures.

■ PATHOPHYSIOLOGY OF HEMOSTASIS

The normal hemostatic process comprises 3 phases (Figure 2):

- Platelet activation: When the vessel wall is injured, subendothelial collagen and tissue factor are exposed, triggering platelet activation and primary hemostasis with adhesion of the initial platelet plug through interactions with von Willebrand factor, factor VIII, glycoprotein IIb/IIIa receptors, and fibrinogen.
- Coagulation: Sequential activation of prothrombotic coagulation factors leads to thrombin activation, thrombus formation, and thrombus stabilization through conversion of fibrinogen to fibrin and cross-linking of fibrin polymers.
- Fibrinolysis or clot dissolution.

Cirrhosis affects all 3 phases, leading to a delicate new equilibrium—the rebalanced hemostasis of cirrhosis. This new balance is easily disturbed and tipped toward either bleeding or thrombosis by acute events such as infection, renal failure, and invasive procedures with or without prophylactic transfusions.

A new balance in platelet activation

Fewer platelets. Thrombocytopenia is common in cirrhosis and portal hypertension, likely due to increased platelet destruction, reduced hepatic synthesis of thrombopoietin, and increased splenic aggregation (which further increases thrombopoietin clearance).18 Tripodi et al19 found that platelet counts as low as 60 × 10⁹/L in plasma from patients with cirrhosis were still sufficient to yield in vitro thrombin generation similar to that in plasma from healthy controls with normal platelet counts. This highlights the importance of qualitative alterations in platelet activation beyond the quantitative decrease in platelet counts in cirrhosis.

Figure 2. The 3 phases of coagulation, involving a range of clotting factors (as Roman numerals).

HK = high-molecular-weight kininogen; tPA = tissue plasminogen activator; uPA = urokinase plasminogen activator
More von Willebrand factor. In contrast to the coagulation factors synthesized by the liver, von Willebrand factor is produced, stored, and released by the vascular endothelium. Its levels are preserved or even increased in cirrhosis. Levels of von Willebrand factor have also been shown to progressively increase with more advanced liver disease. Lisman et al. reported that, compared with healthy controls, patients with Child-Pugh class A cirrhosis had von Willebrand factor antigen levels 380% higher, those with class B cirrhosis had levels 500% higher, and those with class C cirrhosis had levels 760% higher. Similarly, von Willebrand factor levels were 790% higher in patients with acute liver failure.

Less ADAMTS13. ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13) is a potent inhibitor of von Willebrand factor and is reduced in cirrhosis. However, data are conflicting as to the magnitude of this decrease and its correlation with disease severity, perhaps partly because ADAMTS13 is difficult to measure and results vary with different assays.

Thus, the data suggest that in patients with cirrhosis, thrombocytopenia is countered by a simultaneous increase in von Willebrand factor and a decrease in ADAMTS13, resulting in only mildly decreased or even increased platelet activity. Indeed, the excess risk of thrombosis observed in patients with biliary cirrhosis has been attributed to platelet activation.

Rebalanced coagulation vs anticoagulation
The coagulation cascade is driven by procoagulant factors and inhibited by anticoagulant factors. As both types of factors are predominantly produced in the liver, this phase is rebalanced in cirrhosis.

Procoagulation factors are decreased. Release of tissue factor from the endothelium activates factor VII, forming the tissue factor-VIIa complex, which leads to activation of factors V, IX, and X and ultimately to conversion of prothrombin to thrombin. As all coagulation factors except for factor VIII (produced in hepatic sinusoidal endothelial cells) are synthesized in hepatocytes, conventional coagulation tests that assess procoagulant factors tend to suggest a hypocoagulable state in conditions of hepatic synthetic dysfunction such as cirrhosis or liver failure: eg, the prothrombin time will be prolonged and the INR will be high.

Anticoagulation factors are also decreased. Anticoagulation factors, in contrast, exert their effect in the endothelium and are difficult to quantify in vitro. For example, tissue factor pathway inhibitor forms a complex with activated factor X. It inhibits the tissue factor-factor VIIa complex and facilitates degradation of factors V and VIIIa. Tissue factor pathway inhibitor has been shown to be reduced in cirrhosis.

Moreover, the key anticoagulant proteins activated protein C and protein S have been similarly shown to be reduced in cirrhosis. Activated protein C with protein S as a cofactor inhibits activated factors V and VII and thus thrombin formation. The activity of protein C is regulated in the endothelium by thrombomodulin, and “thrombomodulin resistance” has been demonstrated in plasma from patients with cirrhosis. This affirms the hypercoagulable effect of decreased hepatic synthesis of proteins C and S in vitro.

In fact, the thrombin generation potential in plasma from cirrhotic patients has been demonstrated to be similar to that of noncirrhotic patients, confirming the rebalanced state of hemostasis in cirrhosis.

Decreased fibrinolysis
Plasmin-mediated fibrinolysis and clot dissolution is the final step in hemostasis. Plasmin is activated from plasminogen by fibrin, as well as by tissue plasminogen activator, urokinase plasminogen activator, and activated factor XII. Conversion of plasminogen to plasmin is inhibited by thrombin activatable fibrinolysis inhibitor and plasminogen activator inhibitor. A decrease in the plasmin activation pathway results in a hypofibrinolytic state, while an increase results in a hyperfibrinolytic state.

Cirrhosis has been shown to be associated with both quantitative and qualitative changes in the fibrinolytic pathway. Plasminogen levels are reduced in patients with cirrhosis, likely due to the combined effects of decreased production and increased consumption related to the frequent activation of the coagulation cascade from ongoing inflammation. Oxidative stress, leading to modifications of fibrin, and increased sialic acid content and altered calcium binding lead to decreased clot permeability and impaired fibrinolysis. Together these qualitative and quantitative changes result in a net decrease in fibrinolysis in cirrhosis.

Inflammation and infection can tip the balance
Systemic inflammation is an important factor in the development and progression of chronic liver disease, acute liver failure, and acute-on-chronic liver failure. Moreover, patients with liver disease are at increased risk of both primary and secondary infections, which in turn contribute to disease progression.
### Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Normal range</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>R time</td>
<td>Latent time from test initiation to initial clot formation and is approximately equal to the rate of thrombin formation</td>
<td>15–23 minutes (whole blood) 5–10 minutes (kaolin added)</td>
<td>Prolongation shows deficiency or inhibition of clotting factors (anticoagulants or autoimmune inhibitors)</td>
</tr>
<tr>
<td>Alpha angle</td>
<td>Measures rate of clot progression Determined by fibrin sheath buildup and cross-linking</td>
<td>22–38 degrees (whole blood) 53–67 degrees (kaolin added)</td>
<td>Narrow or reduced angle suggests deficiency of fibrinogen or its decreased activity Low platelets counts or dysfunction in conditions like uremia, cirrhosis can also decrease the angle</td>
</tr>
<tr>
<td>K time</td>
<td>Time required to achieve a particular clot strength, ie, 20-mm amplitude</td>
<td>5–10 minutes (whole blood) 1–3 minutes (kaolin added)</td>
<td>Prolonged in fibrinogen deficiency or decreased function</td>
</tr>
<tr>
<td>Maximum amplitude (MA)</td>
<td>Ultimate strength of the platelet clot</td>
<td>47–88 mm (whole blood) 59–68 mm (kaolin added)</td>
<td>Low indicates low platelet number or function or decreased fibrinogen levels or function; can also be affected by other factors such as factor XIII deficiency</td>
</tr>
<tr>
<td>Coagulation index</td>
<td>Composite indicator of the coagulation profile</td>
<td>−3 to 3</td>
<td>Increased in hypercoagulable states, decreased in hypocoagulable states</td>
</tr>
<tr>
<td>Clot lysis at 30 minutes (LY)</td>
<td>Percentage decrease in amplitude 30 minutes after MA; indicates fibrinolysis</td>
<td>0–7.5%</td>
<td>Decreased in hypercoagulable states, increased in hyperfibrinolytic states</td>
</tr>
</tbody>
</table>

**Figure 3.** Thromboelastography is a promising test of coagulation. The horizontal axis represents time, the vertical axis represents deflection of the thromboelastography probe. The R time is also assessed by tests such as the prothrombin time (PT), the activated partial thromboplastin time (aPTT), and the activated clotting time (ACT). D-dimer is used to assess fibrinolysis.

Several mechanisms link inflammation and coagulopathy. Inflammatory cytokines lead to direct activation of platelets and the endothelium, and endothelial activation in turn prompts the release of tissue factor and von Willebrand factor. Tissue factor activates the extrinsic coagulation cascade, and increasing levels of von Willebrand factor further promote platelet activation and adhesion. Increased levels of fibrinogen, an acute-phase reactant, can tip the balance toward a more hypercoagulable state. Similarly, inflammation-induced expression of plasminogen activator inhibitor 1 further inhibits fibrinolysis. Eventually, prolonged activation of a systemic inflammatory response can result in exhaustion of thrombotic and thrombolytic systems, leading to a state of consumptive coagulopathy.

These mechanisms highlight the complexity of coagulopathy of advanced liver disease and emphasize the importance of individualized assessment and management of coagulopathy in patients with cirrhosis and liver failure, particularly in patients with systemic inflammation or sepsis, or both.

### ASSESSING CLOTTING AND ANTICLOTTING IN CIRRHOSIS

An accurate assessment of the coagulation system is paramount in the clinical management of cirrhosis. An ideal test should evaluate both the clotting and the anticlotting pathways to provide an accurate assessment of hemostasis to guide therapy.

#### Conventional tests assess only clotting and may overestimate bleeding risk

The conventional tests for assessing coagulation are the prothrombin time, INR, platelet count, and fibrinogen level. These tests cannot assess the impact of the anticoagulant mechanisms outlined above and may overestimate the bleeding risk in cirrhosis. Prolongation of the prothrombin time and activated partial thromboplastin time indicates a decrease in hepatic synthesis of procoagulation factors and correlates with hepatic function, but this does not adequately quantify bleeding risk.

Of importance is that the INR is standardized and validated using plasma from patients receiving vitamin K antagonists such as warfarin. There is no standard reference plasma that could be used in clinical practice to express a normalized ratio of the prothrombin time for patients with cirrhosis.

Similarly, the quantitative decrease of platelet counts and fibrinogen levels in cirrhosis is balanced by qualitative changes in platelet activation and fibrinolysis, making the absolute values difficult to interpret in the context of the rebalanced state of hemostasis.

#### Viscoelastic tests are promising but need more study

Viscoelastic tests such as thromboelastography and rotational thromboelastometry provide a holistic evaluation of the coagulation process, assessing clot formation, clot propagation, maximum clot strength, and fibrinolysis as a reflection of shear stress in vitro. Viscoelastic tests are performed using whole blood, assessing coagulation in a more global, functional, and potentially clinically relevant fashion than individual coagulation parameters.

Thromboelastography is performed with a torsion pin suspended in an oscillating cup containing whole blood. As the blood begins to clot, the initial platelet clot and fibrin strands move this pin. The deflection of the pin is proportional to clot strength and is displayed graphically. The pattern is altered in patients with abnormal hemostasis. Thromboelastography is considered less vulnerable to movement and vibration.

Viscoelastic tests were developed as point-of-care tests to provide rapid results during surgery or in the trauma bay—in 15 to 20 minutes, compared with conventional tests, which require significantly longer turnaround times (eg, 45–60 minutes for prothrombin time and INR).

Viscoelastic testing is well established in trauma care and cardiothoracic surgery, where its use has significantly reduced blood product utilization and has led to improved outcomes. It has been shown to predict the need for massive transfusions during liver transplant, and transfusion protocols guided by viscoelastic testing during liver transplant surgery have been shown to reduce the intraoperative use of blood products without an associated increased rate of bleeding.

Viscoelastic testing is highly reproducible and routinely shows normal coagulation profiles in patients with cirrhosis in stable condition. For example, in 273 patients with compensated cirrhosis, Stravitz...
found that the thromboelastography parameters were within the normal range, even though the prothrombin time and INR were prolonged. Similarly, only 14 (27%) of 51 patients with stable cirrhosis had abnormal clotting times on rotational thromboelastography in a study by Tripodi et al.45

However, the coagulopathy of liver disease is dynamic, and thromboelastography displays a more hypocoagulable profile with increasing severity of liver disease as well as in the setting of acute decom-

![Figure 4. Results of thromboelastography in various conditions.](image)

<table>
<thead>
<tr>
<th>Tracing</th>
<th>Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Normal" /></td>
<td><strong>Normal</strong>&lt;br&gt;R time, K time and alpha angle normal</td>
</tr>
<tr>
<td><img src="image" alt="Anticoagulant use or hemophilia" /></td>
<td><strong>Anticoagulant use or hemophilia</strong>&lt;br&gt;(factor deficiency)&lt;br&gt;R time and K time prolonged&lt;br&gt;Maximum amplitude, alpha angle decreased</td>
</tr>
<tr>
<td><img src="image" alt="Use of platelet blockers" /></td>
<td><strong>Use of platelet blockers</strong>&lt;br&gt;(thrombocytopenia, thrombocytopathy)&lt;br&gt;R time normal, K time prolonged&lt;br&gt;Maximum amplitude decreased</td>
</tr>
<tr>
<td><img src="image" alt="Use of fibrinolytic drugs" /></td>
<td><strong>Use of fibrinolytic drugs</strong>&lt;br&gt;(urokinase, streptokinase, tissue plasminogen activator)&lt;br&gt;R time normal&lt;br&gt;Maximum amplitude shows continuous decrease&lt;br&gt;Clot lysis at 30 minutes &gt; 7.5%&lt;br&gt;Clot lysis at 60 minutes &gt; 15.0%</td>
</tr>
<tr>
<td><img src="image" alt="Hypercoagulation" /></td>
<td><strong>Hypercoagulation</strong>&lt;br&gt;R time and K time decreased&lt;br&gt;Maximum amplitude and alpha angle increased</td>
</tr>
<tr>
<td><img src="image" alt="Disseminated intravascular coagulation" /></td>
<td><strong>Disseminated intravascular coagulation</strong>&lt;br&gt;Stage 1: Hypercoagulable state with secondary fibrinolysis&lt;br&gt;Stage 2: Hypocoagulable state</td>
</tr>
</tbody>
</table>
CIRRHOTIC COAGULOPATHY

De Pietri et al.46 compared the coagulation profiles of 261 patients with decompensated cirrhosis and Model for End-Stage Liver Disease scores between 15 and 40 with those of 40 healthy participants. The latency time between test initiation and clot formation (R time) was prolonged in 41.5% of the patients, and the ultimate strength of the clot (maximal amplitude) was weaker in 79.3% patients with cirrhosis.46

Further, Lloyd-Donald et al.47 reported that 34 critically ill patients with Child-Pugh class C cirrhosis had longer R times, weaker clot strength, and reduced clot lysis compared with 157 healthy controls. This further supports the dynamicity of liver disease and the impact of underlying cirrhosis on coagulability.

However, certain limitations restrict widespread clinical implementation of viscoelastic testing. The normal limits are not standardized, and clinical trials have used different cutoff values as indications for treatment.48–51 Moreover, the impact of concomitant conditions such as sepsis or acute kidney injury on these results has not been studied.51

Accordingly, the current guidelines from the American Association for the Study of Liver Diseases11 and a technical review from the American Gastroenterology Association52 state that though viscoelastic tests are promising, their clinical utility in predicting bleeding risk in patients with liver disease is yet to be firmly established. The current Society for Critical Care Medicine guidelines53 recommend the use of viscoelastic testing over the conventional tests in patients with cirrhosis in the intensive care unit. The clinical applicability of these tests is detailed in the next section.

### PROPHYLACTIC OPTIMIZATION OF COAGULOPATHY

Coagulopathy in cirrhosis is widely interpreted as a risk factor for bleeding after an invasive procedure. The need to minimize the risk of coagulopathy before procedures is a common dilemma for practitioners.

The risk of bleeding is mainly determined by the type of procedure, the clinical scenario, comorbidities, use of ultrasonographic guidance, and operator experience.54 Various procedures are classified as high-, intermediate-, or low-risk (Table 1).2,55

Traditional coagulation tests do not predict post-procedural bleeding complications.56 A meta-analysis

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Bleeding risk associated with invasive procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk procedures</strong></td>
</tr>
<tr>
<td>All major surgeries (cardiac, intra-abdominal, orthopedic, brain, spine)</td>
</tr>
<tr>
<td>Intracranial pressure catheter insertion</td>
</tr>
<tr>
<td>Endoscopy: large polypectomy with endoscopic mucosal resection or submucosal resection</td>
</tr>
<tr>
<td><strong>Moderate-risk procedures</strong></td>
</tr>
<tr>
<td>Lumbar puncture</td>
</tr>
<tr>
<td>Percutaneous or transjugular liver biopsy</td>
</tr>
<tr>
<td>Transarterial or percutaneous therapies for hepatocellular carcinoma</td>
</tr>
<tr>
<td>Transjugular intrahepatic portosystemic shunt</td>
</tr>
<tr>
<td>Endoscopy for percutaneous gastrostomy placement, biliary sphincterotomy</td>
</tr>
<tr>
<td><strong>Low-risk procedures</strong></td>
</tr>
<tr>
<td>Paracentesis</td>
</tr>
<tr>
<td>Thoracocentesis</td>
</tr>
<tr>
<td>Dental extraction</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
</tr>
<tr>
<td>Central line placement</td>
</tr>
<tr>
<td>Endoscopy for diagnosis, variceal band ligation, uncomplicated polypectomy</td>
</tr>
</tbody>
</table>

**Note:** Risk is calculated based on relative vascularity, expected vascular breech, and potential clinical consequences. Risk should always be defined by the clinician performing the procedure.

of 29 studies including 13,276 patients found that neither elevated INR (OR 1.52, 95% CI 0.99–2.33) nor thrombocytopenia (OR 1.24, 95% CI 0.55–2.77) significantly increased the risk of bleeding in patients with cirrhosis. Moreover, the mean INR did not significantly differ between patients with bleeding complications and those without. However, there was significant heterogeneity ($I^2 = 51$%) in the pooled results, likely attributable to differences in the severity of thrombocytopenia in various studies. The risk of bleeding was associated with the type of invasive procedure, but not with the results of conventional tests of coagulopathy.

Paracentesis, the most commonly performed procedure in patients with cirrhosis, is considered low-risk and can be done safely even if the results of conventional coagulation tests are abnormal. In a study of 1,100 therapeutic paracenteses in 628 patients, of whom 513 had cirrhosis of the liver and in whom the mean INR was 1.7, no patients received prophylactic preprocedural correction of INR, and no significant bleeding events (defined as bleeding requiring hospitalization) were reported. By comparison, a study of 2,740 percutaneous liver biopsies reported an increased risk of bleeding in patients with INR greater than 1.3 and platelet counts less than $60 \times 10^9/L$. This area clearly needs further study.

**Transfusion may not reduce bleeding, and it has its own risks**

Furthermore, no studies have shown that giving prophylactic transfusions of fresh frozen plasma to correct an elevated INR reduces the risk of procedure-related bleeding in patients with cirrhosis. Also, in vitro experiments have demonstrated that transfusion of fresh frozen plasma does not increase coagulation potential in patients with cirrhosis, as it supplies both procoagulant and anticoagulant factors in equal amounts. As a result, the increase in plasma levels of procoagulant factors may correct an elevated INR, but thrombin-generating potential does not change, or may even decrease.

The current standard of practice is prejudiced toward the hypocoagulable state of coagulopathy and disregards the risks associated with blood product transfusion. Acutely ill patients with cirrhosis are at increased risk for transfusion-related lung injury and complications from transfusion-related circulatory overload. In a small classic study, every 100 mL of volume expansion increased the portal pressure by 1.4 cm H$_2$O (1.03 mm Hg). It is estimated that lowering the INR from 2.0 to 1.5 requires transfusion of 1.5 L, which would raise the portal pressure by approximately 15.5 mm Hg. This is important, since an elevated hepatic venous pressure gradient (> 12 mm Hg) is associated with an increased risk of variceal hemorrhage.

Large-volume blood product transfusions aimed at correcting an elevated INR can therefore translate to increased bleeding complications. This is supported by a recent multicenter retrospective study, which found that transfusion of fresh frozen plasma to manage acute variceal bleeding increased the risk of death within 42 days (OR 9.41, 95% CI 3.71–23.90). Notably, patients who received fresh frozen plasma had a higher INR at baseline evaluation, and the patients who had died by 42 days had received a median of 3 units of fresh frozen plasma, compared with 0 units in those who were alive at 42 days.

Accordingly, the current recommendations advise against routine preprocedural correction of INR or thrombocytopenia in patients with cirrhosis, particularly for low-risk procedures.

**Can viscoelastic testing reduce transfusions?**

As reviewed, viscoelastic tests may more accurately assess the global coagulation status. Recent randomized controlled trials have evaluated the impact of thromboelastography-guided prophylactic transfusion protocols compared with the standard of care for the use of blood products and bleeding complications for invasive procedures and in the setting of variceal and nonvariceal gastrointestinal bleeding. In all the studies, thromboelastography-guided therapy significantly reduced transfusion of blood products (fresh frozen plasma and platelets) compared with the standard of care, while the incidence of postprocedure-related bleeding between the groups was similar.

However, several limitations need to be considered when interpreting these findings. Most importantly, in these trials, the standard of care aimed to “correct” the INR and platelet counts to arbitrary near-normal thresholds. This is not in line with current restrictive recommendations for transfusion. Furthermore, transfusion thresholds in the thromboelastography-based protocols varied among trials, and there are currently no uniform and well-established transfusion thresholds for viscoelastic tests. It remains unclear if a restrictive transfusion strategy based on viscoelastic testing is superior to a restrictive strategy based on conventional tests. The small number of patients and the very low bleeding rates observed in these trials further limit their generalizability, as they may therefore be underpowered to detect true differences between the 2 strategies.
In sum, viscoelastic tests are promising tools to both assess the coagulopathy of cirrhosis and guide preprocedural management of hemostasis, but their current use is limited by a lack of validated transfusion thresholds and limited clinical availability outside of the operating room or research setting. Further large-scale studies are needed to establish such thresholds to facilitate translation into general clinical practice.

**DISCLOSURES**

Dr. Lindenmeyer has disclosed authorship for Merck Manuals. The other authors have disclosed no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

**REFERENCES**


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