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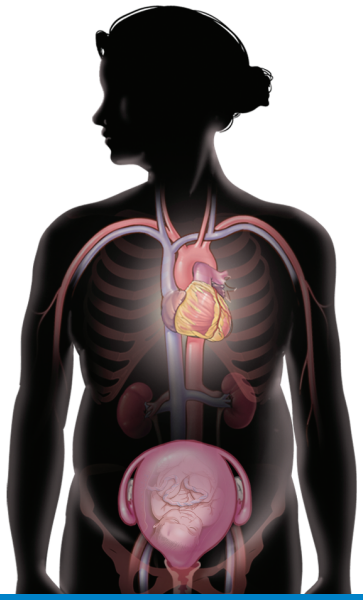

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# Upcoming Features

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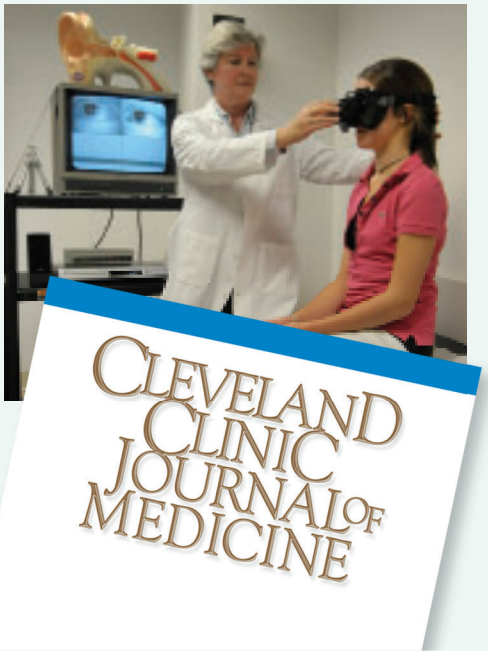

# Modifying genetic diseases: Promises to be realized?

In some genetic disorders, there is a total absence of a protein: the absence of adenosine deaminase (ADA) in severe combined immunodeficiency, enzyme deficiency in some lysosomal storage diseases, protein deficiency in several coagulopathies, and lack of uricase in humans, leading to hyperuricemia and gout. In other disorders, the genome dictates the translation of defective proteins or proteins that interfere with normal functioning of the wild-type protein, such as in sickle cell disease.

There is a myriad of mechanisms by which our genome directly or indirectly contributes to disease or disruption of homeostasis. Monogenic disorders are the most straightforward and have been targeted in trials of directed gene therapy. Successes have been few but significant, including treatments for a devastating retinal dystrophy, ADA deficiency, and spinal muscular atrophy.

Strategies have been tried for genetic disorders characterized by deficiency of a necessary protein. Protein replacement therapy is currently available for several disorders, but routine success is hampered by immunogenicity of the replacement protein, as well as challenges in getting the protein or enzyme to the organs where it is most needed. Attempts to mask enzymes from the immune system by encasing them in artificial membranes or molecules of polyethylene glycol (pegylation) have met with limited success.

Organ transplant as a replacement source for the missing or defective protein has been used with variable success in some diseases. As discussed in 2 papers in the current issue of the *Journal* (by Onimoe and Rotz on page 19 and by Curtis and Shah on page 28), bone marrow transplant has provided clinical benefit in patients with sickle cell disease. But the need for "conditioning chemotherapy" before transplant and the possibility of graft-vs-host disease afterward pose significant challenges for the individual patient, and limited suitable donor availability and the technological demands of the procedure remain challenges on a societal level.

For some diseases, a biochemical work-around can be used. A missing biochemical product from a genetically defective pathway can sometimes be provided, or a mechanism for sopping up an excess of abnormal product can be introduced (eg, monoclonal antibody, soluble receptor, enhanced cellular receptor function). And in sickle cell disease, the pathologic sickling process can be at least transiently ameliorated with transfusion of normal red blood cells or with hydroxyurea or voxelotor therapy.

But arguably the most elegant approach is to remove a dysfunctional gene and replace it with a normal one, or to add a missing gene to the genome. While this may not always prevent the generation of protein-neutralizing antibodies, successful gene replacement may only need to be done once, and may not require ongoing medication.

The ethical and pragmatic technical concerns and challenges for this approach have thus far been significant and limiting. There are ethical reservations regarding the possibility of affecting germline DNA, with unknown consequences to potential offspring. There have been complications associated with viral gene delivery vectors,

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and challenges remain with how to target the gene-bearing viral Trojan horse to only the desired organ and cell locations.

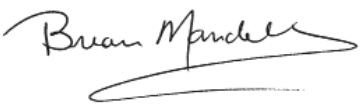
And that brings us to the CRISPR-Cas9 technology of gene engineering.[1] The guts of the technology lie in a prokaryotic endonuclease (Cas9) that carries with it a guidance RNA strand that can target and bind a specifically defined DNA sequence. Once bound, the endonuclease can cause double-strand breaks in the DNA. The awesome power of this technology is that the guidance RNA strand can be manipulated almost at will to provide pinpoint targeting within the genome. Using information gleaned from the Human Genome Project, virtually any gene can be spliced out, including incorporated viral DNA (think human immunodeficiency virus, Epstein-Barr virus, hepatitis B). It is intriguing to me that this "primitive" prokaryotic adaptive immune response to viral infection is effective in mammalian cells, where the enzyme-RNA complex is required to traverse the nuclear membrane in order to access the genome.

The therapeutic possibilities are striking. The nuclease portion of the molecular complex can be modulated to block gene promoters similar to the action of inhibitor RNAs. Controlling the DNA repair process after the Cas9 endonuclease-specific binding and genomic clipping also permits the possibility of introducing new base-pair sequences to provide an alternative gene product to the original problematic genome. Preclinical studies have already demonstrated the power of this approach to gene replacement in several animal models of human disease.[2]

This technology is not cheap, and it may still suffer from challenges of getting the protein-RNA complex to the right cells while avoiding the wrong ones, and the durability and fidelity of the genome modifications in humans remain to be demonstrated. There may also be binding efficiency issues based on the transcriptional state of the specific gene to be targeted due to coiling of chromatin and other factors, and concerns regarding "off-target" binding remain. But the box (hopefully not Pandora's) of promises is yet only partially unwrapped.

After a year filled with derision, division, and far too many tragedies, it is nice to begin the New Year writing of a promise of hope for patients and families with diseases for which there was previously little.

From all of us at CCJM, best wishes for a happy, healthy, and peaceful 2020. Please take some time to visit our new and evolving website (ccjm.org) and let us know what you think of it.



BRIAN F. MANDELL, MD, PhD
Editor in Chief

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# Is diabetes still a compelling indication for renin-angiotensin-aldosterone system inhibitors?

SEPTEMBER 2019

**TO THE EDITOR:** The recent review by Momoniat et al, "ACE inhibitors and ARBs: Managing potassium and renal function," provides a thorough overview of these important medication classes.[1] The authors state, "In general, a renin-angiotensin-aldosterone system inhibitor is recommended if the patient has diabetes; stage 1, 2, or 3 chronic kidney disease; or proteinuria." The sentence suggests that patients with diabetes alone, even without nephropathy, are to receive renin-angiotensin-aldosterone system inhibitors.

We take issue with this statement. The current literature no longer supports the notion that diabetes mellitus is a compelling indication for use of renin-angiotensin-aldosterone system blockers in the absence of associated nephropathy. In a systematic review and meta-analysis of 19 randomized controlled trials that enrolled 25,414 participants with diabetes for a total of 95,910 patient-years of follow-up, we demonstrated that inhibitors of the renin-angiotensin-aldosterone system were not superior to other antihypertensive drug classes in patients with diabetes.[2] Specifically, renin-angiotensin-aldosterone system blockers were not superior to thiazides, calcium channel blockers, or beta-blockers at reducing the risk of hard cardiovascular and renal end points.[2] Current guidelines from the American Diabetes Association,[3] European Society of Cardiology,[4] and Joint National Committee[5] also do not give preference to these drug classes in patients with diabetes without nephropathy.

Perhaps the word "diabetes" could be removed in the above-referenced sentence. Furthermore, heart failure with reduced ejection fraction could be added to the list of conditions that are indications for inhibition of the renin-angiotensin-aldosterone system irrespective of initial blood pressure level.

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doi:10.3949/ccjm.87c.01001

**IN REPLY:** We would like to thank Dr. Fakheri and colleagues for their extremely helpful comments on our recent review of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).[1] We agree entirely with their suggestion on the lack of current data on any superiority of ACE inhibitors or ARBs in patients with diabetes without proteinuria and diabetes with "normal" renal function.[2,3] As mentioned, the sentence perhaps lacks clarity.

In the United Kingdom, ACE inhibitors and ARBs are commonly prescribed for diabetic microalbuminuria, proteinuric renal disease, and hypertension, as well as after myocardial infarction and in heart failure.[4] We therefore also concur that heart failure with reduced ejection fraction could be added

to the list of conditions that are indications for inhibition of the renin-angiotensin-aldosterone system irrespective of the initial blood pressure level.

Interestingly, chronic kidney disease is associated with significantly increased risk of cardiovascular disease and cardiovascular death.[5,6] Studies of patients with chronic kidney disease have noted an increased relative risk of coronary heart disease, heart failure, and stroke compared with those without chronic kidney disease.[7,8] We recognize that additional randomized controlled studies and a better understanding of these differences in risk are required to guide optimal therapy and improve outcomes, and we wonder if ACE inhibitors and ARBs might be useful in this high-risk population even before proteinuria is established, as alluded in the heart failure group.

Finally, although the data are not available, we wonder if over a longer period of follow-up, one may in the future see a benefit from reduced intraglomerular hyperfiltration, but we concede this is mere speculation, and more recent data have challenged the hyperfiltration model of renal damage.

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doi:10.3949/ccjm.87c.01002

# How should diabetic dyslipidemia be treated?

SEPTEMBER 2019

**TO THE EDITOR:** The case presented by Hsueh and colleagues[1] is interesting and illustrative. The options for fibric acid derivatives are equally listed as gemfibrozil and fenofibrate. It should be noted, however, that current multisociety guidelines recommend statin treatment for most patients with diabetes,[2] and fenofibrate is the preferred fibric acid derivative to use in combination with a statin. Gemfibrozil has been associated with a higher risk of muscle-related toxicity when combined with statin therapy due to inhibitory effects on the statin metabolic pathway and subsequent increases in plasma statin concentrations.[3] US Food and Drug Administration labeling includes this precaution and states that the benefits of combination use of gemfibrozil and statins do not outweigh the risks.

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doi:10.3949/ccjm.87c.01003

**IN REPLY:** We agree that statin therapy is first-line treatment for primary prevention of atherosclerotic cardiovascular disease for patients with diabetes mellitus who are 40 to 75 years of age.[1] However, severe hypertriglyceridemia (fasting triglycerides ≥ 500 mg/dL and especially > 1,000 mg/dL) in diabetic patients, such as our patient,[2] may warrant pharmacologic therapy with fibric acid derivatives, fish oil, or both to reduce the risk of acute pancreatitis.[3] Thus, lifestyle modifications, glycemic control with oral hypoglycemic agents, and fenofibrate therapy were initially prescribed to our patient.[2]

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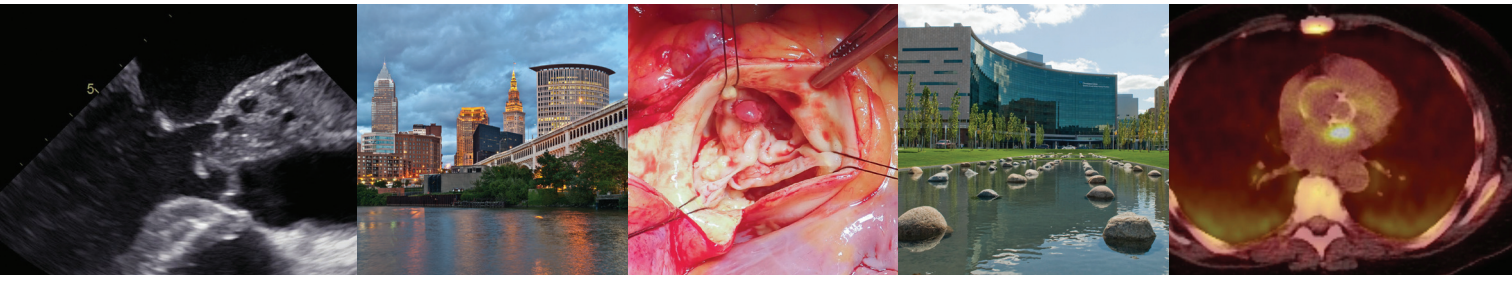

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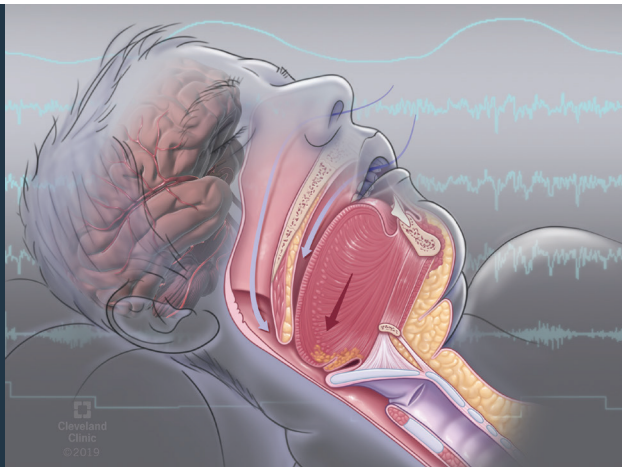


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# Giant uric acid stone in the bladder

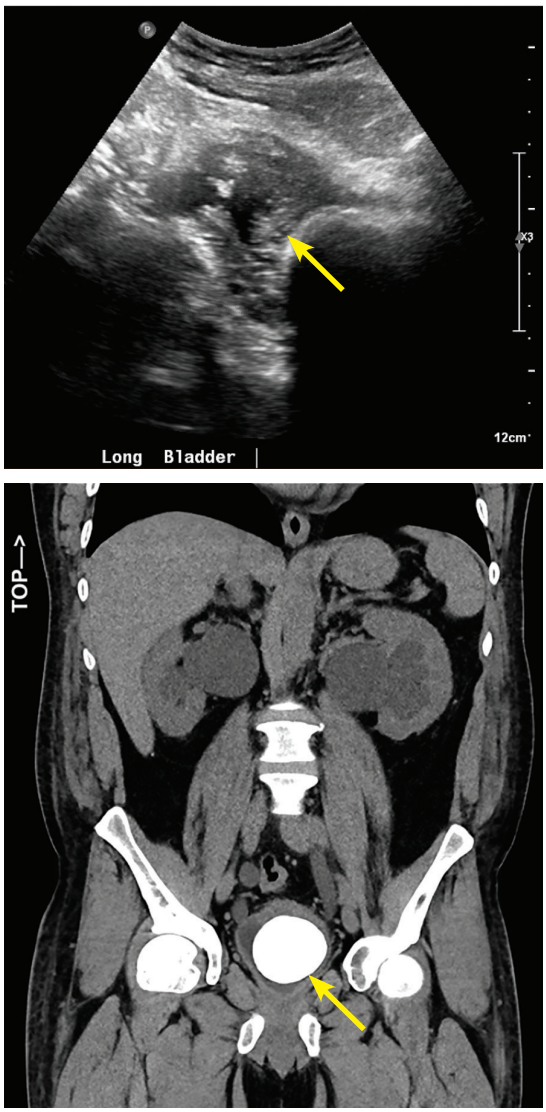


**Figure 1.** Renal ultrasonography (top) revealed a decompressed bladder (arrow). Computed tomography (bottom) showed a bladder stone occupying the entire bladder (arrow).

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**The patient said he had to urinate 30 to 40 times a day, but only a small volume each time**

A 45-YEAR-OLD MAN presented with 2 weeks of dysuria and urinary frequency. He said he had to urinate 30 to 40 times a day, but only a small volume each time. He also said he drank ten 750-mL bottles of wine daily. He had no history of nephrolithiasis, genitourinary infection, or pelvic surgery.

He had no abdominal or costovertebral angle tenderness. The bladder was not palpable, and there were no palpable masses. The prostate was not enlarged on digital rectal examination.

The serum creatinine was 4.3 mg/dL (reference range 0.58–0.96), up from 3.1 mg/dL several weeks earlier. Urinalysis showed a pH of 5.5 (4.5–8.0), 1+ protein (0), 8 red blood cells (0–5 per high-power field), and 42 white blood cells (0–3 per high-power field), with no granular casts. Urine culture was negative. The initial fractional excretion of sodium was 3.9%.

Attempts at urinary catheterization for strict output measurement were abandoned as the procedure caused the patient intense pain, especially during balloon inflation. Bladder scans showed a residual volume of 10 mL. The serum creatinine level peaked at 6.3 mg/dL on hospital day 3. Renal ultrasonography revealed severe bilateral hydronephrosis and a decompressed bladder, and computed tomography showed a radiopaque bladder stone occupying the entirety of the bladder (**Figure 1**).

He underwent bilateral percutaneous nephrostomy tube placement followed by open cystolithotomy, and a large calculus (6.9 × 4.8 × 4.5 cm) was removed (**Figure 2**). Analysis of the stone revealed 100% uric acid composition and no evidence of a foreign body nidus. A 24-hour urine collection showed normal excretion of uric acid, calcium, citrate, phosphorus, and potassium. The acute kidney injury

resolved, and his serum creatinine level came down to 1.9 mg/dL.

## GIANT BLADDER STONES

Giant bladder stones are rare and a rare cause of acute kidney injury.[1] They are usually solitary and associated with urinary stasis in the setting of neurologic injury, neobladder reconstruction, or benign prostatic hypertrophy. They can also occur in chronic infections with urease-splitting bacteria or secondary to an iatrogenic foreign body.[1,2]

While this patient did not have any of these risk factors, computed tomography noted a small bladder diverticulum, a possible nidus of urinary stasis and calculus formation.[1]

There are case reports of retained surgical material and foreign bodies as a nidus for giant bladder calculi development.[1] However, in our patient, no foreign body was identified during stone bisection.

Uric acid bladder stones have been associated with acidic urinary pH.[3] Our patient's initial urine pH was 5.5, which we attributed to chronic ketosis from alcoholism. It increased to 7.0 during his hospitalization with alcohol cessation, but it was again found to be 5.5 on urinalysis at follow-up visits after hospital discharge.

Bladder calculi account for only 5% of all urinary stones; they often arise in the setting of bladder outlet obstruction and are rarely associated with upper tract calculi.[1,4] The earliest giant bladder stone was found in the skeleton of a 7,000 year-old Egyptian mummy, and the prevalence of these stones has dramatically decreased in the developed world due to modernization of diets.[1] No specific nutritional deficiency has been causally linked to bladder stone formation, though these calculi remain most common in North Africa, the Middle East, and India in chronically undernourished children with diets low in animal protein and phosphate.[1,5]

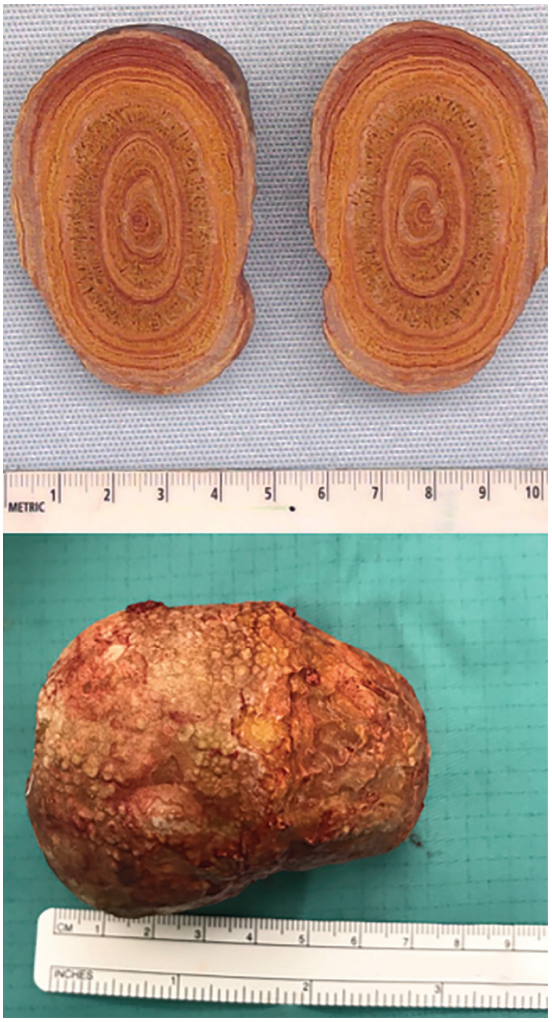


**Figure 2.** The bladder stone measured 6.9 cm × 4.8 cm × 4.5 cm.

Most giant bladder stones are composed of calcium phosphate or struvite, rarely uric acid. Studies suggest that only 7% of bladder calculi in men are composed of uric acid, with far more composed of calcium oxalate or struvite.[6]

***Acknowledgment**: The authors thank Dr. Juan Paredes Magaña for his care of this patient.*

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COMMENTARY

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# Are we all clear? Unintended shocks to caregivers during cardiopulmonary resuscitation

Although training in basic life support and advanced cardiac life support emphasizes the importance of ensuring that caregivers are "clear" before shock delivery, there will inevitably be circumstances when they are not. However, to our knowledge, device manufacturers do not address how to manage cases of unintended shock either in their training programs or service manuals. Therefore, the management of caregivers who appear asymptomatic after receiving an unintended shock from a defibrillator remains undefined.

**Little has been published in the last decade, and no formal guidelines exist on how to manage this event**

## WE DON'T KNOW HOW OFTEN IT OCCURS

Reports of unintended shock from defibrillator use during cardiopulmonary resuscitation (CPR) are limited, perhaps because there is no clear avenue for reporting. Also, caregivers may be reluctant to report shocks because they are embarrassed about failing to follow proper protocol.

In one study,[1] the rate of injury was 1 per 1,700 shocks for paramedics and 1 per 1,000 shocks for emergency medical technicians. The incidence for hospital caregivers may be higher, as more caregivers are involved in the code process. Regardless, the paucity of literature and the limited extent of reporting does not allow us to estimate current injury rates.

The use of defibrillators has likely increased since 2015, when the American College of Cardiology and American Heart Association (ACC/AHA) updated their guidelines on cardiopulmonary resuscitation.[2] The guidelines recommend delivering shock within 2 minutes of recognizing a dysrhythmia that is amenable to defibrillation. The ACC/AHA guidelines also stress the importance of continuing chest compressions during defibrillator charge time.[2] In addition, automated external defibrillators are now common in public areas and can be used by people who are not medically trained.

## EFFECTS OF ACCIDENTAL SHOCK

Defibrillators are designed to affect electrical activity in the patient's heart, and potentially can affect the caregiver's heart as well. Earlier reports describe a tingling sensation and electrical burns in those who are shocked.[3] However, little has been published within the last decade on this topic, and no formal guidelines or recommendations exist on how to manage this event.

### How much exposure?

The electric exposure of the individual largely affects how one perceives the shock and its effects on the body.

The minimal perceptible current detected by the central nervous system is approximately 1 mA but is insufficient for skeletal or cardiac muscle stimulation via transcutaneous exposure. A 1- to 5-mA current is generally perceptible but considered harmless and is un-

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likely to transcutaneously stimulate cardiac or skeletal muscle or burn the skin. A current of 100 to 300 mA, however, will affect skeletal and cardiac muscle and thus can externally induce ventricular fibrillation if present during cardiac repolarization (T wave).

Biphasic defibrillators deliver shock energy up to 360 J. The minimum amount of transcutaneous energy required to induce ventricular fibrillation ranges from 10 to 50 J.

The energy delivered to both the patient and the unsuspecting caregiver depends on the resistance to the current; this is referred to as shock impedance and is measured in ohms. Various factors affect impedance and therefore the amount of shock energy delivered. Clothing and gloves are insulating (have high impedance) and can protect the exposed caregiver from shock energy. Conductive media such as human tissue, metallic objects, or fluids have low impedance and can facilitate shock delivery.

Subcutaneous automated implantable defibrillators are generally ineffective for cardiac defibrillation at shock impedance values over 100 ohms. In a study of 321 patients, the mean impedance on effective shocks that terminated the lethal arrhythmia was 85 ohms vs 104 ohms on ineffective shocks.[4] However, ventricular fibrillation induction is feasible for exposures occurring at lower outputs when timed with ventricular repolarization (T wave), or atrial fibrillation when occurring during atrial repolarization (QRS complex).

Along with the amount of energy supplied, there is a high degree of variability in the level of caregiver exposure. A caregiver could receive a large amount of energy if his or her hand were touching the conductive surface of a paddle, or a small amount if touching a more distal area of the patient with a barrier in place such as gloves. Either way, if the caregiver perceives a sense of electrical impulse, then the caregiver received some unintended degree of energy.

### Do gloves protect against shock?

All caregivers should wear personal protective equipment, including gloves, during emergency resuscitation. This helps ensure that if a current is unintentionally conducted through the caregiver's body, the most likely source of entry will be through the gloved hand, which will minimize any current that is shunted from the patient to the caregiver.

A 2016 study examining interruptions in CPR and the utilization of hands-on defibrillation (HOD) reported limited data on emergency personnel being shocked by contact with a patient receiving defibrillation therapy.[5]

Another study examining the conduction of electricity through nitrile gloves found that they did not offer adequate protection from electricity delivered during defibrillation.[6] In an opposing study, it was found that the nitrile pad and neoprene gloves prevented 99% of shocks detectable by the caregiver.[7]

The most common result of these shocks is a tingling sensation and brief paresthesias with associated muscle soreness lasting up to 24 hours.[8] The lack of a perceived current in HOD with exposure to electricity may not ensure that the provider did not receive a shock, which raises questions about the safety of HOD.[9]

## HOW TO MANAGE ACCIDENTAL SHOCK

We believe that unintended shocks are highly underreported and may cause more than nuisance-type central nervous system stimulation. Atrial or ventricular fibrillation is possible if the transmitted current density is sufficiently high and the timing is inopportune (ie, during the T wave for ventricular fibrillation, and during QRS for atrial fibrillation). The risk of fibrillation may be further increased in the context of prior cardiac dysrhythmia or underlying structural heart disease. The actual risk is, however, undefined despite a perception that a small amplitude shock is of minimal risk.

**We believe shocks are highly underreported and can cause atrial or ventricular fibrillation**

Therefore, we advocate for a systematic approach for all caregivers who have received an accidental shock, regardless of severity. This should include a focused history and a limited physical examination to include vital signs, skin assessment, cardiac auscultation, and an electrocardiogram.

Current recommendations in the emergency medicine literature call for an electrocardiogram, urinalysis, complete blood cell count, and a basic metabolic panel[10] to help assess the degree of nonvisible injury. Further imaging studies are recommended based on symptoms.[10] Late arrhythmias have not been shown to be an issue based on current data, and long-term monitor-

ing does not appear to be of great utility.[11] This approach is reasonable for caregivers with obvious injury or residual symptoms, including pain or muscular discomfort, following a shock.

## FURTHER RESEARCH NEEDED

Accidental caregiver shock from defibrillator use during CPR is likely to be grossly underreported. Guidance is needed for the systematic reporting of these cases and for proper medical management. Further clinical research and studies are needed to fully understand the risks and consequences of these events, as they may represent a public health concern and certainly an occupational hazard for healthcare providers.

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REVIEW

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# Sickle cell disease: A primary care update

## ABSTRACT

Sickle cell disease (SCD) is the most common hemoglobinopathy in the United States and causes significant disease-related morbidity including multiorgan damage, chronic anemia, and debilitating pain crises. Primary care physicians play a key role in the medical home model of care for adults with SCD. This review focuses on current recommendations for health maintenance and provides a brief summary of disease complications and current updates.

## KEY POINTS

Because SCD is a chronic debilitating condition, there is a need for anticipatory guidance as part of comprehensive care.

Primary care physicians are fundamental to the multidisciplinary approach to improving SCD care.

Disease-modifying therapies, newer hematopoietic stem cell transplant techniques, and gene therapies offer the potential for cure and improved quality of life.

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Approximately 100,000 people live with sickle cell disease (SCD) in the United States, and 1 of every 350 black children is born with the disease.[1] Advances in health maintenance and therapy mean that more young patients are surviving to adulthood, requiring care in the adult primary care setting.

*See related editorial, page 28*

While the survival rate has improved for adults with SCD, their life expectancy is still more than 2 decades shorter than in the general population, as complications of chronic SCD interact with age-related non-SCD conditions and add to the disease morbidity.[2–5] An alliance of patient, primary care physician, hematologist, and other caregivers is crucial to optimizing disease outcomes, and the primary care physician is an important partner in providing optimal care of these patients.

Here, we review mechanisms of sickle cell disease, common complications and their management based on current guidelines, and current approaches to health maintenance.

## UNDERLYING MECHANISMS

The characteristic mutation of SCD at the sixth codon of the beta-globin gene causes a substitution of valine for glutamic acid, resulting in an abnormal hemoglobin tetramer with poor solubility when deoxygenated. The polymerization of deoxygenated hemoglobin S is central to vaso-occlusive phenomena, and this cascades into secondary processes including inflammation, hemolysis, anemia, vasculopathy, and oxidative stress affecting many organs.[1] Other pathways include increased adherence to vascular endothelium, changes in red blood cell membrane structure and func-

TABLE 1

## Acute complications of sickle cell disease

| | |
|---|---|
| **Hepatic** | Hepatic crisis: right upper quadrant pain, fever, jaundice, nausea, tender hepatomegaly, jaundice |
| | Hepatic sequestration: abdominal pain, tender hepatomegaly, and acute anemia, but absence of cholestasis or transaminitis |
| | Acute cholecystitis |
| **Splenic sequestration** | Sudden enlargement of spleen due to trapping of the red cell mass |
| | Presents with left-sided abdominal pain, abdominal distention, pallor, acute anemia, hypovolemic shock |
| **Stroke** | Focal seizures, hemiparesis, speech deficits; hemorrhagic stroke more common in adults |
| **Acute ocular conditions** | Hyphema, central retinal artery occlusion, orbital infarction, orbital compression syndrome |
| **Acute chest syndrome** | Fever, respiratory symptoms, chest pain, new infiltrate on chest radiography, hypoxia, acute anemia |
| **Acute anemia** | Decline of the hemoglobin level of 2 g/dL below the baseline value |
| | Etiology includes red cell aplasia, delayed hemolytic transfusion reaction, acute bleeding (surgery), spleen sequestration |
| **Priapism** | Painful sustained penile erection; urinary retention may occur |
| **Fever** | Repeated splenic infarctions from vaso-occlusion result in hyposplenism and functional asplenia, leading to increased susceptibility to infection from encapsulated organisms; sickle cell fever, defined as temperature > 38.3°C (101.5°F), should prompt rapid evaluation and initiation of antibiotics |
| **Pain** | Acute excruciating pain, most commonly in the extremities, chest, and back; onset may be gradual, duration may be hours to days; triggers include stress, exposure to cold, and infectious illness |
| **Multisystem organ failure** | Usually occurs during a vaso-occlusive crisis |
| | Presents with fever, rapid fall in hematocrit and platelet count, and altered sensorium; respiratory, hepatic, and kidney failure |

Data from American Society of Hematology. Management of Acute Complications of Sickle Cell Disease: A Pocket Guide for the Clinician. www.hematology.org/Clinicians/Guidelines-Quality/Quick-Ref/3466.aspx.

**Impaired urinary concentrating ability in sickle cell disease can lead to enuresis, polyuria, and dehydration**

tion, and ordered cell-volume control.[6]

SCD genotypes common in the United States include SS, SC, sickle–beta zero thalassemia, and sickle–beta plus thalassemia. The most prevalent and severe genotype is homozygosity of the hemoglobin SS mutation, accounting for 60% to 70% of US cases. Sickle cell–beta zero thalassemia (ie, no hemoglobin A production) has a clinical course as severe as homozygous SCD. While other sickle cell variants tend to have a milder clinical course, a broad range of disease severity can be seen within individual genotypes.

## GENERAL MANAGEMENT STRATEGIES

Current management strategies include prophylactic penicillin and immunizations to decrease the occurrence of pneumococcal infections, hydroxyurea (a disease-modifying agent), blood transfusions (for symptomatic acute anemia, stroke management, preoperative optimization), and bone marrow transplant. In 2017, the US Food and Drug Administration (FDA) approved L-glutamine oral powder for reducing acute complications of SCD, and many other drugs are in develop-

ment and undergoing clinical testing. Gene therapy is also progressing, with a recently reported successful outcome in 1 patient.[7]

The National Heart, Lung and Blood Institute (NHLBI) has developed guidelines for the care of SCD patients; the most recent version was published in 2014.[8] The American Society of Hematology has developed new guidelines on the management of SCD complications (https://ashpublications.org/bloodadvances/article/3/23/3867/429210/American-Society-of-Hematology-2019-guidelines-for).

## ACUTE COMPLICATIONS

Acute complications of SCD (**Table 1**) include hepatic crisis, cholecystitis, splenic sequestration, stroke, acute chest syndrome, acute anemia, priapism, pain, and multisystem organ failure.

## CHRONIC COMPLICATIONS

In addition to chronic pain, common complications of SCD include organ damage (kidney, liver, heart, lung), avascular necrosis, cerebral infarction, retinopathy, leg ulcers, and chronic anemia. Though the incidence of these complications increases with older age, onset can occur much earlier.

### Kidneys

Chronic kidney disease occurs in 4% to 18%, and early identification is crucial to improved outcomes. Deteriorating renal function contributes to the risk of death after age 40, and progressive glomerular fibrosis is associated with a declining glomerular filtration rate, falling erythropoietin levels, and a gradual decline in total hemoglobin.[9]

Impaired urinary concentrating ability is common in SCD and can lead to enuresis, polyuria, and dehydration.

### Liver

Chronic hepatobiliary complications include gallstone disease, viral hepatitis, and cholangiopathy.

### Heart and lungs

In adults with SCD, the prevalence of pulmonary hypertension—defined as tricuspid valve regurgitation jet velocity of at least 2.5 m/sec on Doppler echocardiography—has been reported to be as high as 30%.[10] Pulmonary hypertension is often associated with left ventricular diastolic dysfunction. These patients also have a high prevalence of asthma, frequent pain crises, and acute coronary syndrome, and a higher risk of death.[11]

### Avascular necrosis

Avascular necrosis resulting from bone necrosis secondary to ischemia affects the femoral and humeral heads most often. Avascular necrosis is typically asymptomatic until late-stage disease, but once it becomes symptomatic, there is a rapid progression to collapse, especially in avascular necrosis secondary to SCD.

### Brain

Adults with SCD are prone to new and ongoing silent cerebral infarctions.[12,13] These may lead to decreased intellectual performance and may also become progressive, leading to clinically overt stroke.[12]

### Eyes

In SCD, retinopathy triggered by vaso-occlusion of the small vessels of the eye is classified as proliferative or nonproliferative sickle cell retinopathy.[14] Proliferative sickle cell retinopathy is a major contributor to vision loss, leading to visual impairment in 10% to 20% of affected eyes.[15] Sickle cell retinopathy occurs most often in patients with the hemoglobin SC genotype.[15]

### Leg ulcers

Leg ulcers occur in 8% to 10% of adults with SCD. The pathogenesis is complex and includes mechanical obstruction by dense red blood cells, venous incompetence, and bacterial infection.[16] Leg ulcers tend to occur in areas with less subcutaneous fat, with thin skin, and with decreased blood flow. The most common site is the lateral malleoli. Less common sites are the anterior tibial area, dorsum of the foot, and Achilles tendon.[16,17]

### Thrombosis

SCD is a hypercoagulable state, and various mechanisms are involved, such as enhanced platelet function, activation of the coagulation cascade, and impaired fibrinolysis.[18] Venous thromboembolism affects nearly a quarter of adult patients and appears to be a risk factor for death in SCD.[18–20]

**Immunization status should be reviewed to ensure compliance with vaccinations**

TABLE 2

## Sickle cell disease: Recommended screening and interventions

**Nephropathy**
Screen annually for albuminuria: spot urine test to estimate protein-to-creatinine ratio
If micro- or macroalbuminuria is present: 24-hour urine test
If protein excretion rate > 300 mg/24 hours, refer to a nephrologist
Consider angiotensin-converting enzyme inhibitor therapy

**Pulmonary**
Assess for respiratory problems
Pulmonary function testing
If findings suggest pulmonary hypertension, refer for cardiology evaluation

**Hypertension**
Screen; treat to ≤ 130/80 mm Hg[a]

**Retinopathy**
Refer to an ophthalmologist for a dilated eye examination[b]; rescreen in 1–2 years if normal
Refer to a retinal specialist for suspected retinopathy

**Stroke**
Screening limited to children
Blood transfusion: simple or exchange
Hydroxyurea[c]

**Leg ulcers**
Inspect lower extremities for active and healed ulcers
Treat with debridement, wet-to-dry dressings, topical agents
Chronic recalcitrant deep leg ulcers: evaluate for osteomyelitis, consult wound care specialist

**Reproductive counseling**
Reproductive life plan
Refer partners for hemoglobinopathy status testing if status is unknown
Test women anticipating pregnancy for red blood cell alloantibodies
Discuss contraception choices with no restrictions for use in sickle cell disease: progestin-only contraceptives, barrier methods; reinforce the need for barrier methods for patients on hydroxyurea

**Avascular necrosis**
Elicit from history and physical examination
Confirm with radiography and magnetic resonance imaging
Refer for physical therapy, orthopedic clinic

[a] Systolic value based on updated American Society of Hematology guidelines on sickle cell disease management: https://ashpublications.org/bloodadvances/article/3/23/3867/429210/American-Society-of-Hematology-2019-guidelines-for.
[b] Sickle cell retinopathy is more common in the SC variant, but other genotypes carry a risk.
[c] While hydroxyurea has been shown to be comparable to transfusion therapy in the prevention of stroke, chronic transfusions have remained an efficient method of reducing the occurrence of secondary stroke.

From National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: Expert panel report, 2014. www.nhlbi.nih.gov/guidelines.

**Enuresis secondary to hyposthenuria can occur, exacerbating dehydration; adult patients may not divulge enuresis voluntarily**

### Reproductive concerns

Pregnancy in patients with SCD carries serious risks. It is associated with an increased incidence of painful crises, infections, pulmonary complications, thromboembolic events, and antepartum bleeding.[21,22] The risk of maternal death is 6 times higher than in controls, and the risks for preeclampsia, stillbirth, preterm delivery, and infants small for gestational age[21,23] are markedly increased.

Though SCD affects fertility in both males and females, males are more often affected. Fertility problems in men result from erectile dysfunction (from priapism), primary gonadal failure, delayed sexual maturation, and sperm abnormalities.[24,25]

## THE MEDICAL HOME MODEL OF CARE

Establishing a medical home—comprehensive care based on a partnership between the patient, family, primary care physician, and other medical staff—is of paramount importance to the care of the SCD patient.

Typically, care is provided by a hematologist in collaboration with the primary care physician. In some instances, a single setting is used, such as a comprehensive sickle cell clinic. Often, a primary care physician knowledgeable in the care of SCD functions as the sole provider. Referral to subspecialists is used as needed to manage disease complications.

### Regular medical evaluations

Regular medical evaluations are essential in assessing disease severity and progression. A detailed history and physical examination enable the clinician to note deviations from the previous clinical status and to identify new stressors.

The regular visit is also an opportunity to address chronic complications (**Table 2**), as discussed in the following sections. Efforts should be made to perform a yearly comprehensive review to screen for chronic complications of SCD and to facilitate specialty referrals.

### Immunization

Immunization status should be reviewed to ensure compliance with vaccinations (**Table 3**).

### Albuminemia

Microalbuminemia screening is done through urinalysis and is confirmed with an albumin-creatinine ratio. For micro- or macroalbuminuria with no other known cause, the NHLBI guidelines recommend angiotensin-converting enzyme (ACE) inhibitor therapy. Since the standard calculations of glomerular filtration rate cannot be used reliably in patients with SCD and in the acute setting, an increase in creatinine of 0.3 mg/dL should prompt an avoidance of nephrotoxic agents.

**TABLE 3**

**Recommended immunizations in sickle cell disease**

| Vaccine | Recommendation |
|---|---|
| ***Haemophilus influenzae*** | 1 dose, if not administered previously |
| **Meningococcal** | Meningococcal conjugate vaccine, then a booster every 5 years<br>Serogroup B meningococcal vaccine (2 doses, 2 months apart) |
| **Pneumococcal** | PCV 13 (if vaccine-naïve), then PSV 23 8 weeks later<br>Repeat PSV 23 5 years after initial dose |
| **Hepatitis B** | 3-dose series: 0, 1, and 6 months |
| **Tetanus booster** | Every 10 years |

PCV 13 = pneumococcal conjugate vaccine; PSV 23 = pneumococcal polysaccharide vaccine

From the US Centers for Disease Control and Prevention. General best practice guidelines for immunizations: Altered immunocompetence. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html.

### Enuresis

Enuresis secondary to hyposthenuria (dilute urine) can occur, exacerbating dehydration. Adult patients may not wish to divulge this information voluntarily.

### Pulmonary hypertension

Pulmonary hypertension and acute chest syndrome are major causes of death in SCD. Guidelines for screening in SCD patients by the American College of Chest Physicians and the Pulmonary Hypertension Association recommend echocardiography or testing for plasma N-terminal pro-brain natriuretic peptide. However, the frequency of screening has not been established.[26]

### Osteopenia

Osteopenia with or without osteoporosis, defined by decreased bone mineral density, has been reported in up to 80% of adults with SCD. Significant vitamin D deficiency was associated with a higher prevalence of fracture history, secondary hyperparathyroidism, and increased bone turnover.[27] Studies have shown the potential benefit of vitamin D in reducing the number of pain days in SCD.[27,28]

### Avascular necrosis

Avascular necrosis can reduce the ability to

**Early involvement of a physical therapist and orthopedic specialist can improve function and help assess the need for surgical intervention**

**TABLE 4**

## Management of pain in sickle cell disease

**Acute pain**
Parenteral opioids
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Frequent reevaluation for pain relief

**Chronic pain**
NSAIDs, gabapentin, antidepressants (tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors)
Opioids: for pain not relieved by nonopioids and nonpharmacologic interventions
Refer to mental health professional as needed for depression, anxiety, dependence on pain medication
Nonpharmacologic: cognitive behavioral therapy, massage, meditation, relaxation techniques, transcutaneous electrical nerve stimulation
Collaborate with patient to develop a written individualized treatment plan
Educate patient to increase oral hydration and use stool softeners as needed

From National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: Expert panel report, 2014. www.nhlbi.nih.gov/guidelines.

perform activities of daily living. Though there is no standardized approach to prevention or therapy, early involvement of a physical therapist and orthopedic specialist can improve function and help assess the need for surgical intervention.

### Antibiotic prophylaxis

It has been recommended that patients with SCD who have a history of splenectomy or an invasive pneumococcal infection be placed on indefinite prophylaxis with penicillin.[8]

### Chronic pain syndrome

Chronic pain syndrome is described as pain that persists for at least 3 months. It is usually described as pain that is deep, nagging, achy, and constant.[29] Neuropathic pain resulting from peripheral or central nervous system dysfunction manifests as allodynia and hyperalgesia.[29]

Opioids are the mainstay of SCD pain management and may be used in conjunction with nonpharmacologic interventions (**Table 4**). Clinicians need to be wary of stigmatizing these patients as drug-seekers, as this can result in delayed treatment and undertreatment. A doctor-patient relationship based on respect and trust will optimize pain management in these patients, and establishing this type of relationship should be a priority, as well as more frequent monitoring of disease status.

While detailed management of chronic pain and pain crises in SCD is beyond the scope of this article, it should be noted that individualized pain management plans crafted with the participation of the patient or caregiver may help facilitate adherence. Concerns about drug-seeking behavior should be addressed after treatment of acute episodes.

Effects of chronic opioid use (tolerance, dependence, and addiction) occur, and the provider may need to involve a pain management expert for collaboration in patient care.

### Neurocognitive effects of sickle cell disease

Neurocognitive dysfunction should be assessed with a focused history (memory deficits, work-school challenges, difficulties with medication adherence), followed by neuropsychiatric evaluation as appropriate. Vichinsky et al[30] reported that adult patients with SCD who did not have neurologic symptoms remained at risk for neurocognitive performance deficits; their anemia may induce neurocognitive impairment secondary to cerebral hypoxemia undetected on standard neuroimaging. Early identification of patients with difficulties on specific measures of neurocognitive function may encourage earlier enrollment in cognitive rehabilitation programs.[30]

### Reproductive health

**The regular evaluation should include discussion of fertility, contraception, erectile dysfunction, and available treatment options**

The regular evaluation should include discussion of fertility, contraception, erectile dysfunction, and available treatment options.

Before conception, genetic counseling should be offered to address modes of disease inheritance and transmission, as well as options for preimplantation genetic diagnosis. Pregnancy in SCD patients is a high-risk condition and warrants care from a team of specialists including a perinatologist, adult hematologist, and specialists involved in the management of SCD-related complications.

### Medication adherence

Adherence to medications is a major challenge for patients with SCD. It can be improved during clinic visits by reviewing missed doses and providing tools to aid daily compliance, such as smartphone medication apps, pillboxes, and calendar reminders.

### Intravenous access

Patients with SCD undergo repeated interventions that require intravenous access (laboratory analysis, fluid resuscitation, transfusions), and over time, peripheral venous access becomes difficult.[31] Central venous access is often required, and it is important to educate the patient about the proper care of these devices and potential complications such as thrombosis and infection.

### Psychosocial support

Patients with chronic illness face psychosocial stressors, and access to psychosocial support (psychologist, counselor, social worker) is of paramount importance in sustaining effective health maintenance strategies. Assistance can be provided for acquiring health insurance and transportation, joining support groups, and addressing educational and vocational goals.

## DISEASE-MODIFYING THERAPIES

### Hydroxyurea

Hydroxyurea, a fetal hemoglobin-modifying agent, has been in use for several decades in SCD but is underused because of patient and caregiver reluctance to provide consent due to misconceptions about drug side effects gleaned from Internet websites.

Current guidelines recommend starting hydroxyurea in adults with SCD in the following situations:

- 3 or more episodes of moderate to severe vaso-occlusive pain in a 12-month period
- Chronic kidney disease in patients already on erythropoietin to improve anemia
- Chronic SCD-associated pain that interferes with activities of daily living or quality of life
- Severe symptomatic chronic anemia
- Severe or recurrent acute chest syndrome.

During the regular evaluation, educating the patient about the benefits of hydroxyurea and the importance of regular monitoring for adverse effects may affect the patient's choice of initiating therapy.

### L-glutamine

L-glutamine, the second drug used to reduce acute complications of SCD, was approved by the FDA in 2017 for use in patients over age 5. Results of a phase 3 trial[32] showed that treatment with L-glutamine led to a statistically significant reduction in the frequency of pain crises and rates of hospitalization. L-glutamine is available as an orally reconstituted powder, administered twice daily, with weight-based dosing.

### Emerging drug therapies

Studies are under way to target the various mechanisms underlying SCD. One approach to therapy is reduction of reactive oxygen species by blockade of cellular adhesion, inhibition of hemoglobin S polymerization, and reactive oxygen species-reducing antioxidants.[33]

The role of anticoagulants and platelets in SCD is also being studied.[34] Leukocytes, platelets, and multiple proinflammatory pathways contribute to the pathophysiology of SCD. Hence, several approaches are being studied to determine whether downregulation of inflammatory pathways will ameliorate aspects of SCD.[34]

Crizanlizumab, a monoclonal antibody against P-selectin glycoprotein that is expressed on activated endothelial cells and platelets, and which acts to reduce the frequency of vasco-occlusive crises,[35] was granted a breakthrough therapy designation in January 2019 for the prevention of vaso-occlusive crises in patients with SCD. On November 20, 2019, the FDA approved crizanlizumab for use in SCD patients age 16 and older.

In January 2018, the FDA granted a breakthrough therapy designation to the hemoglobin S polymerization inhibitor voxelotor after preliminary clinical evidence indicated the potential for substantial improvement over available therapies.[36] On November 25, 2019, the FDA granted accelerated approval to voxelotor for SCD patients age 12 and older.

### Hematopoietic stem cell transplant

The first stem cell transplant for SCD was reported in 1984 in a child who developed acute myeloid leukemia and was cured of both diseases.[37] To date, more than 1,000 stem cell transplants have been performed for patients with SCD, with an estimated 5-year event-free survival of 91.4%, and an overall survival rate of 92.9%.[38] However, these data encompass patients who had a matched sibling donor, and only 18% of patients with SCD have

**Psychosocial support (psychologist, counselor, social worker) is paramount to sustaining effective health maintenance strategies**

a matched sibling donor.[39]

Trials of matched unrelated donors in SCD have been limited by high rates of graft-vs-host disease.[40] In many cases, families are willing to accept the risk,[41] but the availability of newer disease-modifying agents and techniques has limited the use of matched unrelated donors.

In 2012, Bolaños-Meade et al published data on a cohort of SCD patients who underwent haploidentical stem cell transplant,[42] in which the donor is a "half match" to the patient, ie, a mother, father, child, sibling, or cousin. In haploidentical transplant, post-transplant cyclophosphamide is used to significantly reduce the risk of graft-vs-host disease. Patients undergoing haploidentical transplant were, however, at high risk for graft loss, resulting in recurrence of sickle cell hematopoietic stem cells.

Since this initial cohort study, changes have been made to haploidentical protocols, leading to a decreased rate of graft loss. At present, more than 2 dozen clinical trials of haploidentical and other stem cell transplant techniques in SCD are enrolling patients. However, given the small number of stem cell transplants performed for SCD, the challenge for any study is to accrue a sufficient number of patients for meaningful results.

### Gene therapy in SCD

Despite the success of stem cell transplant in SCD, questions remain about donor sources, graft loss, and graft-vs-host disease. SCD is caused by a single base-pair substitution, and gene therapy offers an attractive mechanism to repair the abnormal beta-globin gene product. Hematopoietic stem cells may be mechanically selected using apheresis techniques from patients with SCD, and therapeutic ex vivo gene transfer can occur in the laboratory prior to reinfusion of cells.

In 2017, Ribeil et al reported on a 13-year-old patient who underwent gene therapy.[7] At 15 months after infusion, the patient had no further sickle cell crises, and the level of anti-sickling beta-globin was greater than 50%, indicating a reduction in sickling properties and disease complications.

With this proof-of-concept study published, further protocols (NCT02186418, NCT03282656, NCT02140554, NCT02247843) have opened to explore different methods of gene transfer, and results are anxiously awaited. With the CRISPR/Caspase 9 gene-editing technique, SCD would seem to be an almost ideal candidate for gene editing of hematopoietic stem cells. Various techniques using CRISPR are plausible, and preclinical studies are under way.[43]

## TAKE-HOME MESSAGES

- With new advances, health maintenance and curative therapies are available.
- A team approach including the patient, caregivers, primary care physician, and hematologists is crucial to optimizing disease outcomes.
- The primary care physician is an important partner in providing optimal care to adults with SCD.

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# Gene therapy in sickle cell disease: Possible utility and impact

In developed countries, 95% of children with sickle cell disease (SCD) survive into adulthood, yet the median age of death remains in the mid-40s,[1] highlighting the clear need for curative therapies for this disease.

*See related article, page 19*

At present, the only potentially curative option is allogeneic stem cell transplant (ie, bone marrow transplant), which requires human leukocyte antigen (HLA) matching of a suitable healthy donor. But a lack of donors, the risk of graft-vs-host disease and graft failure, and long-term toxicities related to pretransplant conditioning regimens are major drawbacks.

Gene therapy may provide an option for SCD patients without a suitable bone marrow donor. However, questions remain as to its cost, its long-term efficacy, and whether it can be done with less-toxic conditioning regimens.

**CRISPR-Cas9 makes it possible to edit the patient's own genes**

## THE ONGOING CHALLENGES OF BONE MARROW TRANSPLANT

HLA-matched sibling donor transplants have a 5-year overall survival rate of 95% for children under age 16 and 81% for those age 16 and older, with a 5-year graft-vs-host disease-free survival rate of 86% for those under age 16 and 77% for those age 16 and older.[2]

The timing of bone marrow transplant plays an important role in the chance of overall success, as each additional year of delay increases the hazard ratio of death by 10%.

Only 18% of people with SCD have an HLA-matched sibling who does not have SCD. Other patients have to rely on the unrelated-donor registry to find a suitable HLA match, but only 16% to 18% of African Americans have a full HLA-matched unrelated donor option in the national donor pool, and unrelated donor transplants are associated with a higher rate of graft-vs-host disease than HLA-matched sibling donor transplants.[3]

To meet these challenges, the donor pool has been expanded to include partial-matched healthy unrelated, half-matched (ie, haploidentical) donors, and partial-matched cord blood units as options when a suitable sibling or full-match donor is not available. However, these options carry increased risk of graft-vs-host disease and graft failure.[4]

Another challenge is that bone marrow transplant requires conditioning chemotherapy to destroy the recipient's bone marrow before the infusion of healthy donor cells. Previously, for patients with SCD, transplant was preceded by myeloablative conditioning with high-dose chemotherapy and radiotherapy, which was associated with immediate and long-term complications including transplant-related infertility and death. More recently, regimens using reduced-intensity or nonmyeloablative conditioning are being used and have decreased the risks of immediate and long-term complications, with success rates similar to those for matched-sibling donor transplant for SCD. A similar approach is being evaluated in a study of unrelated-match donor grafts.[5]

In summary, while advances in allogeneic bone marrow transplant offer higher rates of survival and disease cure, the procedure still has the serious limitations of the lack of suitable donors, the risk of graft-vs-host disease and graft rejection associated with use of related or unrelated partial-matched donors, and long-term adverse effects of myeloablative conditioning.

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## GENE THERAPY

Gene therapy is emerging as a second curative option for SCD, apart from allogeneic bone marrow transplant. Marrow cells are removed, genetically modified, and then reinserted into the patient, mitigating the risk that the gene modification could affect other somatic or germline cells.

The new gene is inserted by using lentivirus vectors or by using clustered regularly interspaced short palindromic repeats (CRISPR). In the lentivirus vector approach, new genetic material is inserted into a cell's DNA, causing the altered cell to replicate and express the new gene. In CRISPR therapy, short palindromic DNA repeats are recognized by an enzyme called Cas9, which then removes those sequences from the DNA.[6] Then, during the DNA repair process, new corrected sequences are added, resulting in normal genetic function.

Gene therapy does not correct the genetic mutation that causes SCD; instead, it adds additional genes or modifies the regulation of other genes. A variety of genes are being added or altered in gene therapy studies for the treatment of SCD to prevent hemoglobin sickling, to add a beta-hemoglobin gene, or to induce the production of hemoglobin F.[7]

Major advantages of gene therapy are that it uses the patient's own cells, eliminating the need for an HLA-matched donor and the risk of graft-vs-host disease. But myeloablative conditioning is still required so that the genetically modified stem cells are not rejected by the patient's own marrow. Studies are examining the possiblity of less toxic conditioning regimens.[8]

Most studies of gene therapy for SCD are in early phases with short follow-up times, and questions about gene persistence and potential long-term toxicities are as yet unanswered.[7] Further, many of the outcomes targeted by current gene therapy trials are reproducible without gene therapy: hydroxyurea increases hemoglobin F, the oral agent voxelotor reduces sickling, and blood transfusion adds normal hemoglobin. And although these treatments can improve disease status, they are not curative.[9] Even though gene therapy also offers a curative option for SCD, we need to see its long-term persistence and effectiveness. A key advantage of gene therapy is that it can achieve these outcomes with a one-time treatment instead of requiring a lifetime of medication or transfusions.

## GENE THERAPY IN SCD: THE BOTTOM LINE

In SCD, gene therapy may prove to be a good option for those without an HLA-matched donor. On the other hand, gene therapy still requires a toxic conditioning regimen, and the long-term efficacy is not yet known. Finally, the cost of this curative gene therapy option is still unknown. Most would agree that a one-time curative option with a hefty price tag may be a good option compared with continuous lifelong management of a chronic disease. However, it is still unclear how expensive gene therapy will be, and whether it will be available to those not living in developed countries.

There is a need for more curative therapies for SCD other than allogeneic bone marrow transplant for patients with a suitable donor option, and gene therapy may provide a good curative option for those who do not have a suitable bone marrow donor. However, questions remain as to the affordability and the long-term efficacy of gene therapy, and whether it can be done with less toxic conditioning regimens. ■

**Questions remain about cost, long-term efficacy, and less toxic conditioning regimens**

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# 2020

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January 17–19
Las Vegas, NV

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**ASH REVIEW**
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# Fever in a traveler returning from Ethiopia

A 44-YEAR-OLD MAN presented to an outpatient clinic after 11 days of fever, chills, headache, and nausea. He was a coffee roaster by trade, and his symptoms had started about 10 days after returning from a 3-week trip to buy coffee in Ethiopia. He said his fever would come and go, and the last episode was 2 days earlier. He denied any diarrhea, constipation, rash, or lymphadenopathy.

The patient appeared lethargic. Examination of his heart, lungs, and abdomen was unremarkable. His vital signs were:

- Temperature 38.9°C (102.0°F)
- Heart rate 80 beats per minute
- Respiratory rate 14 breaths per minute
- Blood pressure 142/80 mm Hg
- Oxygen saturation 97% on room air.

He had been treated for malaria in Tanzania when he fell sick there a few years earlier. He said he took chloroquine to prevent malaria every time he went abroad, as directed for his earlier trips. He had received the yellow fever virus vaccine because of his frequent travel to the tropics and was up-to-date on his routine childhood and pretravel immunizations. On his last trip, he had not been exposed to local domestic or wild animals, had not had any sexual encounters, had not drunk any unclean water, and had not eaten any raw or improperly cooked food.

## DIFFERENTIAL DIAGNOSIS OF FEVER IN A RETURNING TRAVELER

**1** What is the most likely cause of this patient's fever?

- ☐ Malaria
- ☐ Typhoid fever
- ☐ Influenza
- ☐ Yellow fever
- ☐ Meningococcemia
- ☐ Measles

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The differential diagnosis for fever with a medium to long incubation period in a returning traveler is broad. Providers should consider the infections endemic to the region where the patient traveled (wwwnc.cdc.gov/travel).

Thwaites and Day[1] proposed a risk-based approach using the Quick Sepsis-Related Organ Failure Assessment (qSOFA) score, signs of severe disease (cyanosis, meningism, peritonism, digital gangrene), and possibility of a highly transmissible infection (eg, Middle East respiratory syndrome-coronavirus [MERS-CoV], Ebola) as an initial assessment to identify and treat life-threatening causes of fever. A detailed history of exposure to unclean water, animals, insects, bites, or raw or improperly cooked food is crucial in building a robust differential diagnosis.[2]

**The differential diagnosis is broad for fever with a medium to long incubation in a returning traveler**

### Malaria

Fever in a traveler returning from an area where malaria is endemic (see www.cdc.gov/malaria/travelers/country_table/) is an emergency. Major clinical features of malaria are fever (present in 92% of cases in 1 study), chills (78%), headache (64%), and nausea and vomiting (35%)—and our patient had all of these. Other possible symptoms such as myalgia (53%) and diarrhea (26%) are sometimes mistaken for symptoms of influenza or infectious gastroenteritis.[3]

In another study,[4] *Plasmodium falciparum* malaria was the most common cause of fever in US residents returning from sub-Saharan Africa (accounting for 12.78% of cases), followed by acute unspecified diarrhea (9%), acute bacterial diarrhea (5.59%), and giardiasis (4.23%).

TABLE 1

## Incubation periods of common travel-related infections[a]

| Short (< 10 days) | Medium (10–21 days) | Long (> 21 days) |
|---|---|---|
| Bacteria | Bacteria | Bacteria |
| Typhoid and paratyphoid | Typhoid and paratyphoid | *Rickettsia* species |
| Bacterial diarrhea | *Brucella* species | *Brucella* species |
| Bacterial pneumonia | *Rickettsia* species | Bartonellosis |
| *Neisseria meningitidis* | | **Tuberculosis** |
| *Brucella* species | Spirochete | |
| *Rickettsia* species | Leptospirosis | Spirochetes |
| | | Leptospirosis |
| Spirochetes | Viruses | Syphilis |
| Relapsing fever (*Borrelia recurrentis*) | Hemorrhagic fevers[b] | |
| Leptospirosis | Human immunodeficiency virus (acute) | Viruses |
| | Cytomegalovirus | HIV (acute) |
| Viruses | Hepatitis A | Hepatitis B, hepatitis C |
| Hemorrhagic fevers[b] | Rabies | Epstein-Barr virus |
| Respiratory viruses | **Measles** | Cytomegalovirus |
| **Influenza**, **Middle East respiratory syndrome coronavirus (MERS-CoV)** | **Chicken pox (varicella)** | Rabies |
| **Measles** | Protozoa | **Measles** |
| Protozoa | Malaria | Protozoa |
| Malaria | Giardia | Malaria |
| African trypanosomiasis | Toxoplasma | Leishmaniasis |
| Amoebic dysentery | African trypanosomiasis | African trypanosomiasis |
| Parasite | Parasite | Parasites |
| Fascioliasis | Babesia | Filariasis |
| | | Leishmaniasis |
| | | Amebic liver abscess |
| | | Babesia |

[a] Bold-face type indicates a serious transmissible infection; isolation precaution is mandatory when such infections are suspected.

[b] Viruses that cause hemorrhagic fevers in humans comprise 5 distinct families:

- Arenaviridae (lymphocytic choriomeningitis virus, Junin virus, Machupo virus, **Lassa virus**, Guanarito virus, Sabia virus, Chapare virus, Lujo virus)
- Bunyaviridae (orthobunyavirus, phlebovirus [eg, Rift Valley fever virus], nairovirus [eg, **Crimean-Congo hemorrhagic fever**], hantavirus)
- Flaviviridae (yellow fever, dengue fever, Japanese encephalitis, West Nile virus, Zika virus)
- Filoviridae (cuevavirus, **Marburgvirus**, **Ebolavirus**)
- Paramyxoviridae (measles, mumps, Newcastle disease virus, Hendra virus, Nipah virus).

**Fever in a traveler returning from a malaria-endemic area is an emergency**

Malaria is transmitted by the bite of a female *Anopheles* mosquito.[5] Most *Anopheles* mosquitoes are not exclusively anthropophilic (preferring to feed on humans). However, the primary malaria vectors, *A gambiae* and *A funestus*, are strongly anthropophilic and are the two most efficient malaria vectors worldwide.

Our patient's symptoms were consistent with malaria. Moreover, although he was taking malaria chemoprophylaxis, he was not taking the right one, as there is a high incidence of chloroquine-resistant *P falciparum* malaria in Africa. The prolonged incubation period also points to malaria (**Table 1**).

Finally, although our patient's pulse rate of 80 beats per minute seems normal, it is actually lower than expected, given his fever. Assessing vital signs for relative bradycardia is a great tool to discern several medical conditions, and malaria is one of the causes (**Table 2**). However, the most common cause of relative bradycardia is the use of beta-blockers.[6,7]

### Typhoid fever

Typhoid fever, caused by *Salmonella typhi*, is a common cause of travel-related fever. In 2002, an estimated 408,837 cases of typhoid fever occurred in Africa.[8] However, precise numbers are not available, since many hospitals in Africa do not have laboratories capable of performing the blood cultures essential for the di-

**TABLE 2**

## Causes of relative bradycardia

**Diseases that cause relative bradycardia[a]**

Infections
- *Legionella*
- Psittacosis
- Q fever
- Typhus (*Rickettsia typhi, Orientia tsutsugamushi*)
- Typhoid fever (*Salmonella typhi*)
- Babesiosis
- Malaria
- Leptospirosis
- Yellow fever
- Dengue
- Viral hemorrhagic fevers
- Rocky Mountain spotted fever

Noninfectious causes
- Beta-blockers
- Drug fever
- Central nervous system lesions
- Lymphomas
- Factitious fever

**Diseases not associated with relative bradycardia**

Infections
- *Mycoplasma pneumoniae*
- *Streptococcus pneumoniae*
- Salmonella (nontyphoidal)

[a]A median increase in heart rate of less than 10 beats per minute for every increase of 1°C in body temperature.

agnosis of typhoid fever. In addition, typhoid fever is often mistaken for malaria.

Typhoid fever has an incubation period of about 1 week, which makes it less likely to be the cause of this patient's illness. However, in rare cases, the incubation period can be as long as 3 weeks.[9]

The patient said he had no diarrhea or constipation, which also makes typhoid fever less likely. Moreover, typhoid fever is more commonly associated with high unremitting fever, which is inconsistent with the patient's fever pattern.

### Influenza

Influenza is uncommon in warm-weather months; however, the seasons are reversed in the Southern and Northern hemispheres.

**TABLE 3**

## Diseases that mosquitoes carry

***Anopheles***
Malaria (*Plasmodium* species)
O'nyong'nyong

***Aedes***
Dengue fever
Yellow fever (Africa)
West Nile fever
Chikungunya
Eastern equine encephalitis
Zika virus

***Culex***
West Nile virus
Japanese encephalitis
St. Louis encephalitis

***Haemogogus***
Yellow fever (South America)

Also, physicians should suspect influenza at any time of year in travelers returning from the tropics, where influenza can occur year-round.[10] However, the incubation period of influenza is typically 1 to 4 days, which was inconsistent with our patient's history.

**Influenza can occur year-round in the tropics**

### Yellow fever

Yellow fever should be suspected if an unvaccinated traveler returns from sub-Saharan Africa or forested areas of Amazonia with fever, jaundice, hemorrhage, and renal failure.

The mosquito vectors of yellow fever are *Aedes* species in Africa and *Haemogogus* species in South America. *Aedes* mosquitoes are also vectors for dengue virus (symptoms: high fever, sudden-onset skin rash, myalgia, headache, and mild hemorrhagic manifestations), West Nile virus, Chikungunya (symptoms: high fever, headache, myalgia, and moderate to severe arthralgia), eastern equine encephalitis virus, and Zika virus (symptoms: low-grade fever, descending rash, myalgia, conjunctivitis, headache, edema, and vomiting) (**Table 3**).[11]

Our patient had relative bradycardia, which can be seen in yellow fever. However, the incubation period for yellow fever is short, 3 to 6 days (median 4.3 days) after the bite of an infected mosquito.[12] Moreover, he had been vaccinated against yellow fever.

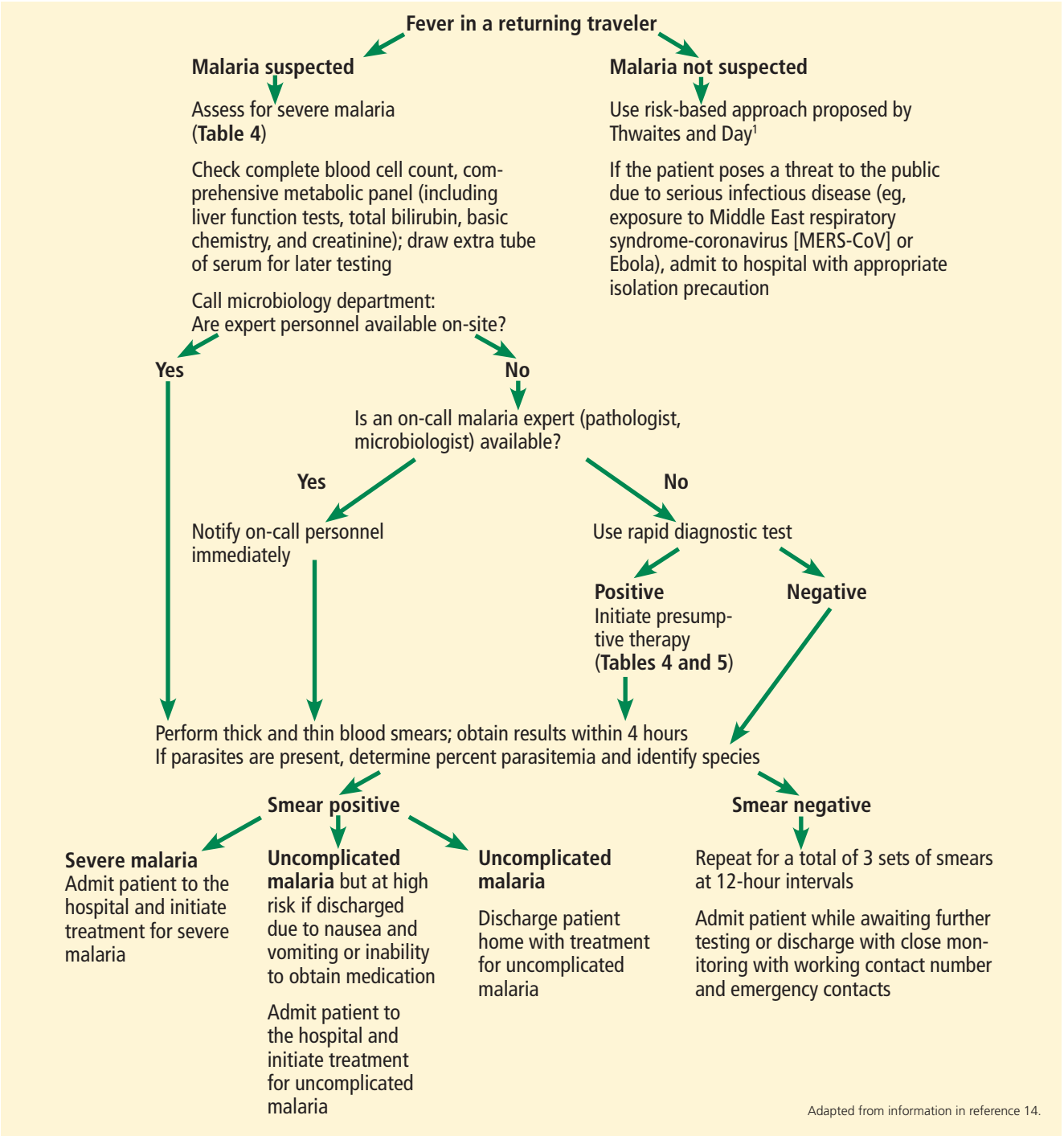


**Figure 1.** Workup of fever in a returning traveler.

### Meningococcemia

Meningococcemia, caused by *Neisseria meningitides* serogroups A, B, C, W, X, and Y, is a life-threatening illness if not treated promptly. Travelers returning from the "meningitis belt" of sub-Saharan Africa who have symptoms consistent with this diagnosis should be suspected of having it, especially during the dry season (December–June). Symptoms generally surface 1 to 10 days after exposure (which is a short incubation period) and present as meningitis half of the time. The clinical

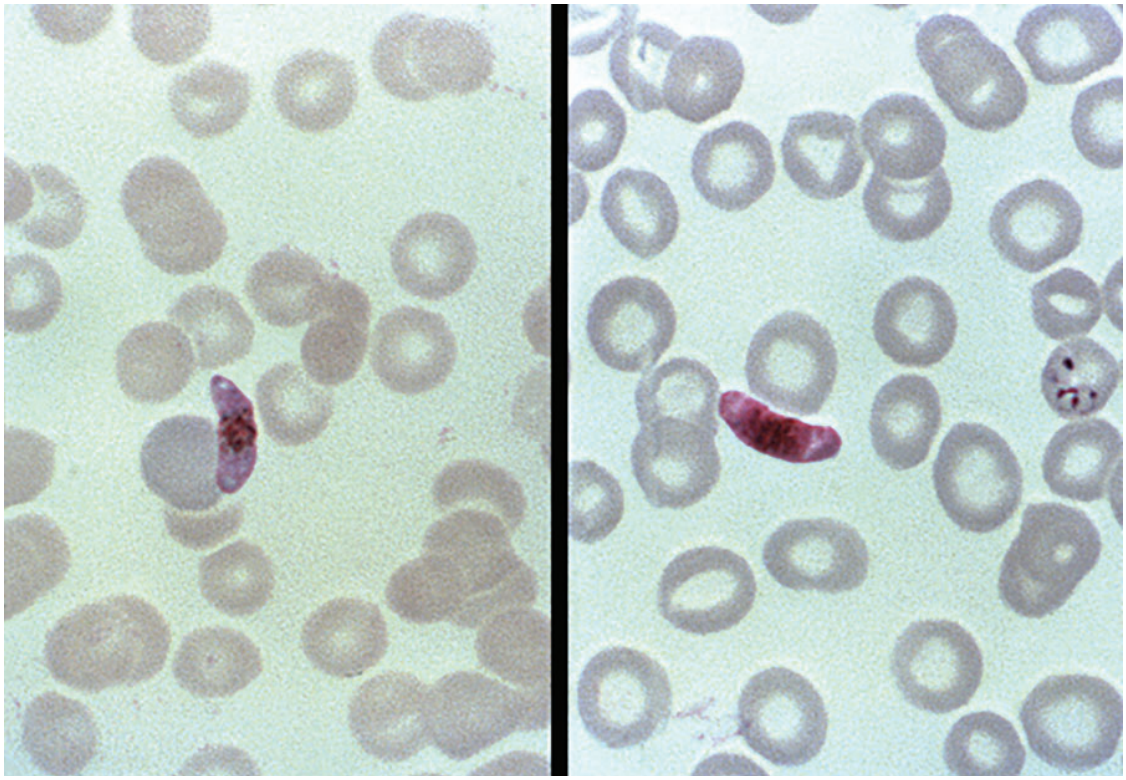

**Figure 2.** Two Giemsa-stained, thin-film blood smear photomicrographs. Left, a *Plasmodium falciparum* macrogametocyte; right, a microgametocyte. Image by US Centers for Disease Control and Prevention, Steven Glenn, Laboratory & Consultation Division 1979.

manifestations include sudden onset of headache, fever, neck stiffness, and petechial or purpuric rash, which did not fit our patient's presentation.

### Measles

Measles is considered the most contagious viral disease known, and its incidence in Ethiopia is high, with 49 cases per million population in 2016.[13] The incubation period ranges from 7 to 21 days from exposure to onset of fever. A clinical diagnosis of measles can be made from the clinical features of generalized maculopapular rash lasting for 3 or more days, temperature of 38.3°C (100.9°F) or higher, and cough, coryza, and conjunctivitis.

These clinical features did not fit our patient's presentation; moreover, he had been vaccinated against measles.

All of the infections discussed above can be prevented with appropriate pretravel vaccinations and chemoprophylaxis.

## DIAGNOSTIC TESTING FOR MALARIA

**2** If a pathologist or microbiologist is not available on call, how is the diagnosis of malaria made?

- ☐ Blood culture
- ☐ *Plasmodium* species polymerase chain reaction (PCR)
- ☐ *Plasmodium* species rapid diagnostic test, then thick and thin blood films when an expert is available to look at them
- ☐ *Plasmodium* serologic study

The best choice in this situation is *Plasmodium* species rapid diagnostic test, followed by thick and thin blood films.

### Light microscopy is the gold standard

Light microscopy of blood smears with Giemsa staining (to give parasites a distinctive appearance) remains the gold standard for malaria diagnosis if qualified staff are available to do it immediately (**Figure 1**). The thick film is used to screen for parasites using hypotonic

**Measles is the most contagious viral disease known**

saline to lyse red blood cells. The thin film is then used to identify the species of *Plasmodium*. Blood films should be prepared and read immediately by experienced personnel.

### Rapid diagnostic tests

If expert personnel are not readily available to examine a blood smear, a rapid diagnostic test should be performed immediately (**Figure 2**).[14]

There are two types of rapid diagnostic tests for malaria. The first is based on detection of *Plasmodium* histidine-rich protein-2 (HRP-2), which is closely associated with the development and proliferation of the parasite. The only test of this type approved and available in the United States is BinaxNOW Malaria (www.alere.com/en/home/product-details/binaxnow-malaria.html), which has a reported sensitivity of 96% and specificity of 99% for *Plasmodium* infection compared with microscopy.[15] This test is approved for use by hospital and commercial laboratories, not by individual clinicians or by patients themselves.

However, HRP-2 tests have limitations. Common causes of false-negative results include:

- *P falciparum* strains that do not express HRP-2
- Nonfalciparum species (*P vivax*, *P ovale*, *P malariae*, *P knowlesi*)
- Low-level parasitemia (100–1,000/µL).

The second type of rapid diagnostic test, which is not available in the United States, is based on detection of *P falciparum*-specific lactate dehydrogenase and pan-*Plasmodium* lactate dehydrogenase. It has a sensitivity of 80% and a specificity of 98% for *Plasmodium* infection compared with microscopy.[15]

Rapid diagnostic tests take only 2 to 15 minutes and are highly specific; hence, a positive result should prompt immediate treatment. However, a negative result still requires a blood smear to detect low-level parasitemia or nonfalciparum species. Therefore, regardless of the rapid diagnostic test result, microscopy must always be performed afterward (**Figure 2**).[14]

### Polymerase chain reaction

Although PCR testing for *Plasmodium* is available in commercial laboratories, the turn-around time may be unfavorable when an immediate medical decision is needed. It can, however, be beneficial in identifying the *Plasmodium* species (eg, *P vivax* and *P ovale*), which may further guide the need for presumptive antirelapse therapy (previously known as terminal prophylaxis).

### Serologic testing

Serologic *Plasmodium* testing only assesses past exposure and has no utility in the acute setting.

### Blood culture

Malaria diagnosis cannot be established through blood culture. Hence, that is not the correct answer to the question. However, if a provider suspects a bacterial coinfection with bacteremia (eg, *Salmonella* species or *Escherichia coli*), obtaining blood culture should be considered. In a small study of 67 adults hospitalized for *P falciparum*, 13% (95% CI 5.3%–21.6%) were bacteremic on admission.[16]

**CDC malaria hotline**
**770-488-7788;**
**after hours**
**770-488-7100**

## CASE CONTINUED: LABORATORY RESULTS

A rapid diagnostic test was ordered for our patient and was positive for *P falciparum*. On-call expert personnel were available to read the blood film. The level of parasitemia was 4% of red blood cells infected. Results of other blood tests were as follows:

- Hemoglobin 10 g/dL (reference range 13.0–17.0)
- White blood cell count 15.0 × $10^9$/L (3.70–11.00)
- Platelet count 150 × $10^9$/L (150–400)
- Glucose 60 mg/dL (65–100)
- Carbon dioxide 20 mmol/L (23–32)
- Creatinine 1.5 mg/dL (0.70–1.40)
- Total bilirubin 1.2 mg/dL (0.2–1.0).

The patient was immediately transferred to the emergency department to be treated and monitored.

## TREATMENT OF MALARIA

**3** What treatment should this patient receive?

- ☐ Chloroquine phosphate
- ☐ Hydroxychloroquine
- ☐ Primaquine
- ☐ Atovaquone-proguanil

**TABLE 4**

## Severe malaria definition and treatment[a]

| Definition | Treatment |
|---|---|
| Positive blood smear and at least one of the following criteria: | Intravenous artesunate is available under an expanded-access investigational new drug protocol (call the US Centers for Disease Control and Prevention) |
| Impaired consciousness or coma | and |
| Severe normocytic anemia (hemoglobin < 7 g/dL) | Artemether-lumefantrine, atovaquone-proguanil, doxycycline (clindamycin in pregnant women); if no other options, mefloquine |
| Acute kidney injury | |
| Acute respiratory distress syndrome | |
| Hypotension | |
| Disseminated intravascular coagulation | |
| Spontaneous bleeding | |
| Acidosis | |
| Hemoglobinuria | |
| Jaundice | |
| Repeated generalized convulsions | |
| Parasitemia ≥ 5% | |

[a] Severe malaria is most often caused by *Plasmodium falciparum*.

Our patient appeared to have uncomplicated *P falciparum* infection from a chloroquine-resistant region. A patient who presents with symptoms of malaria and a positive malaria test without features of severe malaria is considered to have uncomplicated malaria (**Table 4**). Given this information, he should receive atovaquone-proguanil (**Table 5**).

Most severe malaria cases are caused by *P falciparum*. Fortunately, our patient appeared to have uncomplicated *P falciparum* malaria. This could be thanks to acquired immunity from earlier infection, which does not provide sterilizing immunity against parasitemia but may inhibit the development of symptomatic and severe disease. This immunity increases with age, cumulative number of malarial infections, and time spent living in a malaria-endemic area.[17] Nevertheless, acquired immunity is usually short-lived without continuous exposure. It is a misconception that prior infection causes lifelong immunity against malaria; in fact, immigrants visiting friends and relatives constitute the most significant group for malaria importation in developed countries.[18] **Table 6** lists other risk factors for malarial acquisition.

If chloroquine phosphate, hydroxychloroquine, quinine, atovaquone-proguanil, or mefloquine is used to treat *P vivax* or *P ovale* infection, either primaquine or tafenoquine must be given as presumptive antirelapse therapy (also known as terminal prophylaxis) to prevent late-onset or relapsing disease due to hypnozoites (the liver stage of the parasite) of *P vivax* or *P ovale*, which can occur 17 to 255 days after the initial infection.[19]

The patient was treated with atovaquone-proguanil and recovered.

**Most severe malaria cases are caused by *P falciparum*, which is widely resistant to chloroquine in Africa**

## STAYING HEALTHY ABROAD

**4** What can clinicians do to prevent malaria at the present time?

- ☐ Give chemoprophylaxis that is appropriate to the area the traveler will visit
- ☐ Instruct patients to take measures to avoid being bitten by mosquitoes
- ☐ Give the malaria vaccine
- ☐ Release genetically modified *Anopheles* to reduce the mosquito population

TABLE 5

## Treatment of uncomplicated malaria

| Plasmodium species | Region | Recommended medication |
|---|---|---|
| ***P falciparum*** **or species not identified** | Chloroquine-resistant (all areas except Central America or the Caribbean) or unknown | Atovaquone-proguanil |
| | | Artemether-lumefantrine |
| | | Quinine sulfate + doxycyline, clindamycin, or tetracycline |
| | | Mefloquine[a] |
| | Chloroquine-sensitive (Central America or the Caribbean) | Chloroquine phosphate |
| | | Hydroxychloroquine |
| ***P malariae*** **or** ***P knowlesi*** | All | Chloroquine phosphate |
| | | Hydroxychloroquine |
| ***P vivax*** **or** ***P ovale*** | Chloroquine-sensitive | Chloroquine phosphate + primaquine phosphate or tafenoquine |
| | | Hydroxychloroquine + primaquine phosphate or tafenoquine |
| ***P vivax*** | Chloroquine-resistant (Papua New Guinea or Indonesia) | Quinine sulfate + doxycyline or tetracycline + primaquine phosphate or tafenoquine |
| | | Atovaquone-proguanil + primaquine phosphate or tafenoquine |
| | | Mefloquine + primaquine phosphate or tafenoquine |
| **Alternatives for pregnant women** | Chloroquine-sensitive | Chloroquine phosphate |
| | | Hydroxychloroquine |
| | Chloroquine-resistant *P falciparum* and *P vivax* | Artemether-lumefantrine (2nd or 3rd trimester only) |
| | | Quinine sulfate + clindamycin (all trimesters) |
| | | Mefloquine (all trimesters)[a] |

[a]Do not use in mefloquine-resistant areas (eg, Thailand, Myanmar, Cambodia, Vietnam).

### Malaria prevention

It is essential to give appropriate chemoprophylaxis, taking into account the regions where malarial organisms are resistant to chloroquine, and to instruct patients to take measures to avoid being bitten by mosquitoes.

Risk assessment of travelers to malaria-endemic areas is important (**Table 6**).[20,21] Education of travelers and physicians about chloroquine-resistant areas is essential. Failure to take appropriate precautions may result in death due to severe malaria.[22]

The US Centers for Disease Control and Prevention (CDC) website provides information on areas with malaria, estimated relative risk of malaria for US travelers, drug resistance, malaria species, and recommended chemoprophylaxis (**Table 7**). Some chemoprophylaxis regimens need to be started 1 to 2 weeks before travel to malaria-endemic areas.

Other measures to prevent malaria infection are use of mosquito repellent containing 20% to 35% *N*,*N*-diethyl-meta-toluamide (DEET), wearing permethrin-treated clothes, sleeping under insecticide-treated bed nets, and staying in air-conditioned buildings.

TABLE 6

**Risk factors for acquiring malaria**

| Risk factors | Not risk factors |
|---|---|
| Rural setting | Urban setting |
| Camping | Air-conditioned environment |
| Longer duration of stay | Shorter duration of stay |
| Altitude of destination (< 2,000 m above sea level) | High altitude (≥ 2,000 m above sea level) |
| Inappropriate chemoprophylaxis | Appropriate chemoprophylaxis with good adherence |
| Visiting friends and relatives (eg, immigrants who return to home country to visit friends and relatives) | |

### Vaccinations

The CDC provides information about vaccinations according to the destination country at wwwnc.cdc.gov/travel. For example, for a traveler going to Ethiopia, vaccinations against cholera, hepatitis A, hepatitis B, meningococcal disease, polio, rabies, typhoid, and yellow fever are recommended.

Certain countries require proof of vaccination against yellow fever to enter, especially if traveling from a country where yellow fever is endemic. Due to limited availability of yellow fever vaccine in the United States, travelers may need to schedule appointments well in advance and visit a nonlocal travel clinic.

Saudi Arabia requires visitors and Hajj and Umrah pilgrims to be vaccinated against meningococcal disease.

### Obtaining care abroad

Medical evacuation insurance can be helpful when traveling to a remote destination or to a place where medical care is not up to US standards. Supplemental travel health insurance is recommended as well if the current travel and medical insurance has inadequate coverage.

The US embassy in the destination country (www.usembassy.gov/) can assist in locating medical services and notifying friends and family in the event of an emergency. Other sources such as the International Association for Medical Assistance to Travelers (www.iamat.org/medical-directory; requires free membership login) or International Society of Travel Medicine (www.istm.org/AF_CstmClinicDirectory.asp) can also help you find travel clinics around the globe.

## WHAT'S NEW IN MALARIA?

### No more quinidine

On March 28, 2019, the CDC issued new guidance for the treatment of severe malaria in the United States. The change in treatment protocol was necessary because quinidine, the only approved intravenous antimalarial drug in the United States, was discontinued by its sole manufacturer, Lilly USA. Previously available lots have now passed their expiration date of March 2019.

### Artesunate

Artesunate, the first-line treatment for severe malaria recommended by the World Health Organization, is now the first-line treatment for severe malaria in the United States. However, US clinicians must call the CDC malaria hotline (770-488-7788) to obtain intravenous artesunate.

### Malaria vaccine

In 2019, public health programs in Ghana, Kenya, and Malawi began vaccinating young children against *P falciparum* malaria using the RTS,S/AS01 (RTS,S) vaccine, the first malaria vaccine provided to young children through routine immunization. In an intention-to-treat analysis of a controlled clinical trial, children 6 weeks to 17 months old who received this vaccine had an infection rate of 1.9% compared with 2.8% in a control group that received a nonmalaria comparator vaccine ($P < .001$), with a number needed to treat of 111 to prevent 1 case of severe malaria.[23]

**In 2019, public health programs in Ghana, Kenya, and Malawi began vaccinating young children against *P falciparum* malaria**

TABLE 7

## Chemoprophylaxis for malaria

| Drug | Adult dosage | Adverse effects and cautions | Price[a] |
|---|---|---|---|
| **Chloroquine phosphate**[b] | 500 mg (300 mg base) once every week<br>Start 1–2 weeks before travel; stop 4 weeks after leaving malaria-endemic area | Hypoglycemia, potential retinopathy from prolonged use<br>Only in chloroquine-sensitive areas (Central America and Caribbean) | $23.11–$55.60 (7 tablets) |
| **Atovaquone-proguanil** | 250 mg/100 mg daily<br>Start 1–2 days before travel; stop 1 week after leaving malaria-endemic area | Diarrhea, dreams, oral ulcers, headache<br>Take with food or whole milk<br>Contraindicated in severe renal impairment (creatinine clearance < 30 mL/min) | $64.10–$86.02 (30 tablets) |
| **Doxycycline** | 100 mg daily<br>Start 1–2 days before travel; stop 4 weeks after leaving malaria-endemic area | Drug-induced esophagitis, photosensitivity<br>Do not use in children < 8 years old or in pregnant women | $13.65–$52.23 (30 tablets)[c] |
| **Mefloquine**[b,d] | 250 mg once every week<br>Start 2 or more weeks before travel; stop 4 weeks after leaving malaria-endemic area | Do not use in individuals with cardiac conduction abnormalities, history of seizures, or serious psychiatric illnesses<br>Do not use in first trimester of pregnancy | $30–$46.97 (8 tablets) |
| **Primaquine phosphate** | 30 mg daily<br>Start 1–2 days before travel; stop 1 week after leaving malaria-endemic area | Contraindicated in glucose-6 phosphate dehydrogenase (G6PD) deficiency and women who breastfeed G6PD-deficient infants | $37.68–$47.73 (28 tablets) |
| **Tafenoquine** | Loading: 200 mg daily starting 3 days before travel<br>Maintenance: 200 mg/week while in malaria-endemic area, starting 7 days after the last loading dose<br>Terminal prophylaxis: 200 mg once, 7 days after the last maintenance dose | Contraindicated in G6PD deficiency and women who breastfeed G6PD-deficient infants<br>Contraindicated in patients with history of psychotic disorders or current psychotic symptoms | $37.52–$42.41 (2 Krintafel 150-mg tablets) |

[a]Drug price obtained from www.goodrx.com on 10/25/19 at 11:33 AM.
[b]Can be used in pregnancy.
[c]Doxycyline monohydrate.
[d]Do not use if traveling to mefloquine-resistant areas (eg, Thailand, Myanmar, Cambodia, Vietnam).

### *Plasmodium* and the intestinal microbiome

The intestinal microbiome may influence the development and treatment of malaria. Ippolito et al,[24] in a systematic review, discussed how *Plasmodium* infection may cause intestinal dysbiosis, which correlates with more severe disease outcomes and frequent bacterial coinfection. Moreover, intestinal microbiota may also influence the metabolism of antimalarial agents, susceptibility to *Plasmodium* infection, and skin microbiome determinants of mosquito attraction.[24]

### 'Gene-driving' mosquitoes to be less of a threat

On July 1, 2019, the first release of genetically modified *Anopheles* mosquitoes in Africa took place in Burkina Faso. This "gene drive" approach, under development at the nonprofit consortium Target Malaria (tar-

getmalaria.org/), is designed to spread mutations through the wild population that knock out key fertility genes or reduce the proportion of female insects that transmit the disease. Researchers released about 10,000 genetically sterilized males to observe their survivability and dispersion in the wild and to introduce the concept of genetically modified mosquitoes to regulators and community members.

### Tafenoquine

Tafenoquine was recently approved for treating malaria of all species. It can be used for chemoprophylaxis against all *Plasmodium* species and, as a single dose, for presumptive antirelapse therapy.[25,26] Patients must be tested for glucose-6-phosphate dehydrogenase deficiency before receiving tafenoquine.

## CASE CONCLUDED

Our patient recovered from his illness and received education about the importance of malaria chemoprophylaxis when he travels to malaria-endemic areas in the future. The most recent event did not deter him from further travel to buy coffee in South America or Africa; however, he is now an advocate for malaria prevention.

## TAKE-HOME POINTS

- Fever in a traveler returning from a malaria-endemic area is an emergency.
- Clinical features of malaria are nonspecific and include fever, headache, weakness, and profuse night sweats.
- *P falciparum* is chloroquine-sensitive in some areas of Central America and the Caribbean and resistant in all other areas.
- A blood smear is the gold standard for diagnosing malaria. However, a rapid diagnostic test can be used if a microbiologist or pathologist is not readily available.
- Treatment of malaria depends on the severity and the sensitivity or resistance of the organism in the malaria-endemic area.

## Malaria resources

Treatment should be in collaboration with an infectious disease physician and an infectious disease pharmacist

**US Centers for Disease Control and Prevention (CDC)**

Vaccines. Medicines. Advice
wwwnc.cdc.gov/travel

Malaria information and prophylaxis, by country
www.cdc.gov/malaria/travelers/country_table/

CDC malaria hotline
770-488-7788 (M–F, 9 AM–5:00 PM, Eastern time)
770-488-7100 (after hours; ask to speak with a CDC malaria expert)

Malaria treatment (United States)
www.cdc.gov/malaria/diagnosis_treatment/treatment.html

Dosing details
www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf

**United States embassies**
www.usembassy.gov/

**International Association for Medical Assistance to Travelers**
www.iamat.org/medical-directory

**International Society of Travel Medicine**
www.istm.org/AF_CstmClinicDirectory.asp

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**Santa with CPAP Riding a Motorcycle**

Artist: Nick; Student at Monarch Center for Autism; Shaker Heights, Ohio

REVIEW

ABIM CME MOC ACCREDITED

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# Cardio-obstetrics: Recognizing and managing cardiovascular complications of pregnancy

## ABSTRACT

Pregnancy can exacerbate known cardiovascular disorders and unmask previously unrecognized problems. Patients with congenital heart disorders, valvular disease, primary pulmonary hypertension, hypertensive disorders of pregnancy, and acquired peripartum cardiomyopathy need a collaborative interdisciplinary team that includes a cardiologist with specialty training in obstetrics.

## KEY POINTS

Several trends are increasing cardiovascular risk in pregnancy. The average maternal age at first pregnancy is increasing, survival in congenital heart disease has improved, and cardiovascular risk factors are developing at younger ages.

Maternal morbidity and mortality are increasing, with cardiovascular diseases accounting for over one-quarter of peripartum and postpartum deaths.

Rates of maternal mortality from cardiovascular disease are highest among low-income women and women of color.

The emergence of new cardiovascular complications during pregnancy is often considered a failed stress test and can increase the risk of future cardiovascular disease. Women should be monitored closely after pregnancy in order to improve maternal outcomes and prevent the development of future cardiovascular disease.

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Cardiovascular complications during and after pregnancy are on the rise, but traditional cardiology and obstetric training programs do not adequately cover this topic. As a result, many family clinicians, obstetricians, and cardiologists are uncomfortable managing pregnant women with cardiovascular conditions.

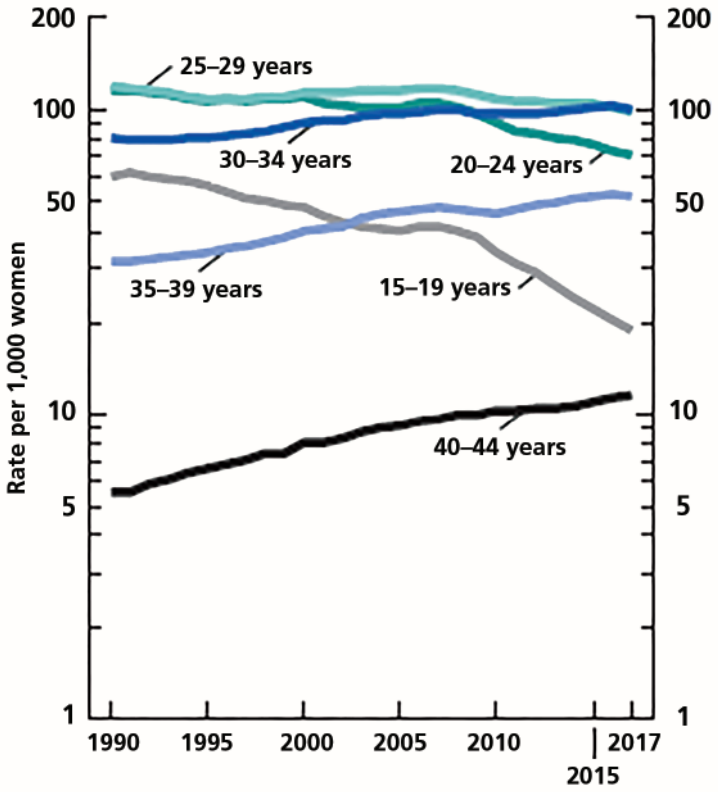
In this review, we describe populations of women at risk for heart disease in pregnancy and discuss the most commonly encountered preexisting and incident types, with a focus on recognition, risk assessment, and management.

## MATERNAL MORTALITY RATES RISING

In the United States, between the years 2000 and 2014, the maternal death rate increased by 6.6%.[1] In the years 1998–2005, the rate of death during or within 1 year of pregnancy attributed to cardiovascular causes was 3.48 per 100,000 live births[2]; in 2006–2010 it was 4.23.[3,4]

A study in Hawaii from 1991 to 2007 found that 4.2% of all deaths occurred within 1 year of pregnancy, and heart disease was the leading cause of pregnancy-associated death (20.5%). The most prominent causes of maternal death were peripartum cardiomyopathy, myocardial infarction, and arrhythmias.[5] Similar findings were reported in a 2002–2006 review in California.[6]

Ethnic and racial disparities in maternal outcomes exist in the United States: eg, in black women, the risk of pregnancy-related death is 3 times higher than in women of oth-




NOTE: Rates are plotted on a logarithmic scale.
Source: NCHS, National Vital Statistics System, Natality.

**Figure 1.** Birth rates by selected age of mother, United States, 1900–2017.

From reference 12.

er races.[3] This may partially be due to higher rates of preexisting cardiovascular disease and higher rates of new-onset hypertension of pregnancy and peripartum cardiomyopathy.[7,8] Disparities may also result from poorer quality of care and provider bias.[9,10]

## REASONS FOR THE INCREASE IN CARDIOVASCULAR RISK

Three major trends are contributing to the increase in maternal cardiovascular risk.

### Older women are having children

Women are waiting longer to have children (**Figure 1**).[11,12] Between 2000 and 2015, pregnancy rates increased from 40 to 52.3 per 1,000 in women ages 35 to 39 and from 8 to 11.6 per 1,000 in women ages 40 to 45.[13,14] The average age of first-time mothers in the United States rose from 24.9 in 2000 to 26.8 in 2017.[12,14] This trend is not limited to the United States—the mean age for first pregnancies is increasing around the world.[15]

Reasons for delaying pregnancy likely include increased availability and efficacy of contraception, more women pursuing higher education and careers, and economic uncertainty among younger women.[16]

### More children with congenital heart disease now survive into adulthood

Thanks to advances in surgery and medical care, most children with congenital heart disease now survive to childbearing age.[17]

An estimated 1% of women giving birth in the United States have congenital heart disease.[18] Between 2000 and 2010, the prevalence of maternal congenital heart disease increased from 6.4 to 9.0 per 10,000 hospitalizations for childbirth.[19]

Congenital heart diseases in adults range in severity from simple abnormalities such as atrial septal defects (17%) and ventricular septal defects (14%) to moderate ones such as repaired tetralogy of Fallot (11%) and more severe disease such as transposition of the great arteries (5%) and Ebstein anomaly (2%).[20]

### Cardiovascular risk factors are increasing in young people

Rates of obesity, diabetes, hypertension, and atherosclerosis are increasing in the United States in younger adults,[21] including women of childbearing age, placing them at risk of pregnancy complications.

## PREGNANCY INCREASES CARDIOVASCULAR RISK

Hemodynamic and hormonal factors in pregnancy contribute to cardiac risk and exacerbate preexisting conditions.

### Increased cardiac output

During pregnancy, plasma volume expands, leading to increased stroke volume, which may increase cardiac output by 30% to 50%.[22] Cardiac output is further increased during labor—by 15% in the first stage, and by up to 50% in the second stage, due to pain, anxiety, and "autotransfusion" of blood into the circulation during uterine contractions, increasing the circulating volume by 300 to 500 mL (**Table 1**).[23] Cardiac output also increases by 25% to 40% after delivery in addition to the increases during pregnancy and delivery, due to

reduced vena cava compression and to uterine contractions, and then declines rapidly over the next hours.[24]

Other hemodynamic changes of pregnancy include increased heart rate, reduced systemic vascular resistance, and complex changes in systolic blood pressure, all of which contribute to a rise in cardiac output.[25]

### Physiologic anemia

In conjunction with increased cardiac output, blood volume increases by about 1.5 L during pregnancy. Although red blood cell mass also increases, the increase is not proportionate to the plasma volume, resulting in physiologic anemia.[26]

### Hormonal changes

Estrogen and progesterone levels rise during pregnancy, which increases sympathetic tone and can increase the risk for plaque rupture and thrombosis.[27]

## CONGENITAL HEART DISEASE AND PREGNANCY

Congenital heart disease accounts for about 75% of cases of heart disease in pregnancy,[28] and this percentage is increasing.

While some congenital heart problems (eg, atrial septal defect, patent ductus arteriosus) may be well tolerated during pregnancy, complex syndromes such as pulmonary hypertension from Eisenmenger physiology are associated with a risk of maternal death as high as 50%.[29]

Metabolic and physiologic changes of pregnancy may precipitate new heart failure or exacerbate existing cardiac disease, especially in women who underwent repair of congenital heart lesions as children. Even if the defect has been repaired, a patient can still be vulnerable to later complications such as heart failure, arrhythmia, pulmonary hypertension, and residual structural concerns.

Congenital heart disease also increases the risk of medical and obstetric complications during delivery.[19]

### Management guidelines available

The 2008 American College of Cardiology and American Heart Association guidelines for managing adults with congenital heart disease include topics in pregnancy such as frequency of follow-up, stress testing, anticoagulation, anesthesia, monitoring during delivery, pregnancy counseling, genetic evaluation, review of medications, and fetal echocardiography.[30] The following are a few highlights:

**TABLE 1**

**Physiologic changes of pregnancy**

**Arterial compliance** increases throughout pregnancy

**Cardiac output** begins to increase by 5 weeks and plateaus at 20 weeks

**Heart rate** increases throughout pregnancy

**Systolic blood pressure** increases at 20 weeks

**Systemic vascular resistance** decreases early on, continues to decrease, and plateaus toward the end of pregnancy

**Stroke volume** peaks at 24 weeks

**Relative anemia:** Red blood cell mass increases but relatively less than plasma volume, which expands by 10% to 15% by 6–12 weeks

**During labor:** Cardiac output increases 15% to 50% with contractions, and circulating volume increases

**General risk.** In general, if a patient's functional class and systolic function are normal or near-normal, pregnancy tends to be uncomplicated. Nonetheless, all women with congenital heart disease who are considering pregnancy should be seen by an adult congenital heart disease specialist before conceiving.

**Anticoagulation.** The risks and benefits of continuing anticoagulation during pregnancy should be discussed with the patient. Warfarin is teratogenic and should be avoided during the first trimester. Warfarin should also be avoided during delivery, given the increased risk of fetal intracranial hemorrhage; low molecular weight heparin and unfractionated heparin should be used instead. The efficacy and safety of the direct-acting oral anticoagulants in pregnancy are still unknown, as data are scarce.[31]

**Delivery method.** In general, vaginal delivery is preferable for women with congenital heart disease unless cesarean delivery is indicated for obstetric reasons.

**Breastfeeding** is considered safe in patients with heart disease, although many cardiac medications may cross into breast milk. These issues should be discussed with the patient before restarting medications after delivery.

**Traditional training does not adequately cover pregnant women with cardiovascular conditions**

## PREEXISTING ACQUIRED HEART DISEASE IN PREGNANCY

The prevalence of preexisting acquired heart disease (eg, valvular heart disease, pulmonary hypertension, arrhythmia) in pregnancy is difficult to ascertain, given that pregnancy can unmask previously unknown disease. A nationwide 2003–2012 study found 81,295 women with heart disease, representing 0.2% of all pregnant women in the sample. Of these women, 30.9% had valvular heart disease and 6.5% had pulmonary hypertension, both of which require specific management during pregnancy.[32]

### Acquired valvular disease

Acquired valvular disease can lead to complications during pregnancy owing to hemodynamic changes. In some situations, valvular disease is first diagnosed during pregnancy, when hemodynamic changes may cause heart failure and arrhythmias.

Women with a stenotic valve can safely undergo balloon dilation by percutaneous catheter; cardiac surgery should be considered only in severe cases.[33]

### Primary pulmonary hypertension

**In 2017, the average age of first-time US mothers was 26.8**

Primary pulmonary hypertension can cause right heart failure. Women with severe pulmonary hypertension have the highest maternal death rate, approaching 50%, which is attributed to high fixed pulmonary vascular resistance and an inability to increase pulmonary blood flow.[34] Given the high risk, most providers and guidelines recommend against pregnancy for women with established pulmonary hypertension.

**Pregnancy management.** A woman who decides to continue her pregnancy should be followed closely with at least monthly visits. Given the dearth of data, it is unknown if patients with lower pulmonary pressures have a lower risk of complications; even some women with mild to moderate pulmonary hypertension deteriorate during pregnancy. Efforts should be made to reduce oxygen demand with rest and to use supplemental oxygen when indicated. Frequently, patients with severe pulmonary hypertension are admitted to the hospital in the second trimester and followed as inpatients.

It is often recommended that women continue their pulmonary hypertension medications during pregnancy, except for bosentan, a dual endothelin receptor antagonist with teratogenic effects. Other advanced therapies such as prostacyclin analogues and sildenafil are considered safe.[35]

**Delivery.** The preferred delivery method in patients with pulmonary hypertension is highly debated. Vaginal delivery increases cardiac output, and pushing during the second stage of labor can reduce venous return to the right side of the heart, both of which may be particularly dangerous for these patients. Additionally, because patients with pulmonary hypertension tend to go into labor early, induction of labor may be associated with increased length of labor and a likelier need for an emergency cesarean delivery, which entails additional risks.

For these reasons, many institutions (including ours) recommend elective cesarean delivery to avoid emergency procedures and minimize blood loss. General anesthesia is not recommended because of reports of cardiac failure owing to adverse effects of intubation and positive pressure ventilation on venous return. Instead, regional anesthesia with a combination of epidural and low-dose spinal anesthesia is preferred to avoid vasodilation and the associated risk of hypotension. During delivery, it is imperative to closely follow arterial and venous hemodynamics including blood pressure; in addition, the mother should be observed in the hospital after delivery for several days until stable.[36–38]

### Preexisting hypertension

A physiologic drop in blood pressure in pregnancy may allow women with preexisting hypertension to avoid medication use early in pregnancy, although they should be monitored closely. Those who require ongoing medication should switch to a drug deemed safer for pregnancy such as labetalol, metoprolol, or a calcium channel blocker; labetalol and nifedipine are most commonly used. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and direct renin inhibitors are contraindicated in pregnancy.

Hypertensive patients of African or Caribbean family origin should be treated with a calcium channel blocker as a first-line agent[39] and should be carefully monitored for progression to preeclampsia or eclampsia.[40]

## INCIDENT CARDIOVASCULAR DISEASE IN PREGNANCY

Cardiovascular disease can arise during pregnancy in women without preexisting conditions.

### Hypertensive disorders of pregnancy

New-onset hypertension and maternal placental disorders such as preeclampsia occur in 1% to 5% of pregnancies. They are defined as blood pressure higher than 140/90 mm Hg arising after 20 weeks of gestation.

Risk factors for hypertensive disorders of pregnancy include genetics[41,42] and, for preeclampsia, elevated body mass index (> 24 kg/m$^2$).[43]

**Future risk.** Developing a hypertensive disorder of pregnancy has been compared to failing a stress test, in that it often presages later cardiovascular disease.[44] Underlying or unrecognized risk factors may contribute not only to the development of hypertensive conditions in pregnancy, but also to subsequent cardiovascular disease.

Hypertensive disorders in pregnancy have been shown in numerous studies to increase the risks for metabolic syndrome, subsequent diagnosis of hypertension, and lifetime risk of cardiovascular disease.[45–48] Problems may reveal themselves soon after giving birth: a study of all births in New York City from 1995 to 2004 found that women with gestational hypertension had a higher rate of hospitalizations in the year after delivery related to heart failure (adjusted odds ratio 2.6), and women with preeclampsia had higher rates of hospitalization for cardiovascular disease and stroke.[49]

The American Heart Association considers preeclampsia to be a cardiac risk factor and recommends monitoring women with preeclampsia for the first few years after delivery.[50,51] Women with this condition have at least double the risk of stroke, cardiac ischemia, or venous thromboembolism for up to 20 years after pregnancy.

### Peripartum cardiomyopathy

Peripartum cardiomyopathy occurs in about 1 in 1,000 to 4,000 live-birth pregnancies. Proposed causes include autoimmunity, genetics, nutritional deficiencies, and vascular dysfunction.[52] Advanced maternal age, preeclampsia, gestational hypertension, multiparity, and African American race have been identified as risk factors.

**Presentation.** Peripartum cardiomyopathy classically presents during the first 6 months after delivery, but it may also present during the second or third trimester of pregnancy. The typical presentation is consistent with that of heart failure (eg, orthopnea, paroxysmal nocturnal dyspnea, significant peripheral edema, elevated jugular venous distention). This is often difficult to distinguish from signs and symptoms of normal pregnancy, especially during the third trimester, so a high index of suspicion is required.

**Diagnosis.** Other possible causes of heart failure (ie, ischemic, congenital) should first be ruled out. Echocardiography is required for evaluation.[52]

**Pregnancy management.** Patients are managed similarly to pregnant women with other forms of heart failure in pregnancy: beta-blockers and volume control agents, including diuretics, to reduce afterload are the mainstays of therapy.

**Postpartum care.** After delivery, patients should be managed with standard therapy consisting of beta-blockers, angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, and diuretics. Patients with severe hemodynamic compromise and depressed left ventricular function may require inotropic support or mechanical circulatory devices.[53]

**Prognosis.** Most women recover from peripartum cardiomyopathy. The Investigations of Pregnancy-associated Cardiomyopathy study found that after 12 months, left ventricular ejection fraction had increased to greater than 50% in more than two-thirds of women. However, 13% had major events or persistent heart failure (ejection fraction < 35%).[54] Even with full left ventricular recovery, there is a risk of recurrence with subsequent pregnancies, and this risk is higher in women with persistent left ventricular dysfunction. There are currently no firm recommendations to guide women on subsequent pregnancies,[55] but they should be advised of the risks.[52]

**Most children with congenital heart disease now survive to childbearing age**

### Ischemic heart disease

New ischemic heart disease of pregnancy, which includes plaque rupture and thrombosis, spontaneous coronary artery dissection, coro-

TABLE 2

**The Cardiac Disease in Pregnancy (CARPREG II) modified risk score**

| Predictor | Points |
|---|---|
| Prior cardiac events or arrhythmias | 3 |
| Baseline New York Heart Association functional class II or III heart failure or cyanosis | 3 |
| Mechanical valve | 3 |
| Ventricular systolic dysfunction | 2 |
| High-risk left-sided valve disease or left ventricular outflow obstruction | 2 |
| Pulmonary hypertension | 2 |
| Coronary artery disease | 2 |
| High-risk aortopathy | 2 |
| No prior cardiac intervention | 1 |
| Late pregnancy assessment | 1 |

| Total points | Risk |
|---|---|
| 0–1 | 5% |
| 2 | 10% |
| 3 | 15% |
| 4 | 22% |
| > 4 | 41% |

Data from reference 62.

nary embolism, and vasospasm, is estimated to occur in 1 to 6.2 per 100,000 deliveries,[56] a rate 3 to 4 times higher than in nonpregnant women of comparable age.[57] The most common causes of new ischemic heart disease are coronary artery dissection and coronary artery thrombosis.

**Spontaneous coronary artery dissection.** Pregnancy-related spontaneous coronary artery dissection occurs by intimal rupture causing medial dissection, or by a spontaneous disruption of the vasa vasorum, which causes intramedial hemorrhage and separation within the arterial wall. Proposed underlying causes include hormonally mediated structural changes of decreased collagen synthesis and increased polysaccharide content, which weakens the tunica media, predisposing it to dissection; underlying connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome; and inflammatory conditions such as lupus erythematosus. Such factors, when combined with the increased hemodynamic effects of pregnancy and labor, are thought to precipitate spontaneous artery dissection.[58]

**Risk factors for ischemic heart disease** during pregnancy are similar to those outside of pregnancy, ie, smoking, diabetes, family history, hyperlipidemia, and chronic hypertension. While rare, women with preexisting but undiagnosed coronary atherosclerosis have the greatest risk of myocardial ischemia during pregnancy,[59] followed by those with pregnancy after age 40.[60] Patients with congenital heart disease (eg, uncorrected anomalous origins of the coronary arteries) or severe aortic stenosis or those who have undergone previous surgical coronary manipulation are also at increased risk for ischemia.[61]

**Pregnancy management.** The goal of managing ischemic heart disease during pregnancy is to reduce oxygen demand to avoid progression to infarction. In the absence of ST-segment elevation acute coronary syndrome, patients can be managed with watchful waiting and medical therapy with beta-blockade and low-dose aspirin.

**Infarction management.** Should myocardial infarction occur, percutaneous coronary intervention is advised, given the risk of hemorrhage with thrombolysis. After percutaneous coronary intervention, routine management with dual antiplatelet inhibitors and beta-blockers is generally well tolerated. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are contraindicated due to embryonic toxicity.

**Delivery.** Vaginal delivery is preferred over cesarean delivery to avoid the hemodynamic changes of anesthesia and the potential for blood loss. Epidural analgesia is advised for pain control, given its effects on reducing afterload, pain, stress, and anxiety.

## RISK ASSESSMENT

Several tools have been developed to estimate morbidity and mortality risk in pregnant women with cardiac disease.

**The Cardiac Disease in Pregnancy Study (CARPREG) risk score,** developed in 1997, has been validated in several retrospective studies and is widely used. Applicable to pregnant wom-

en with acquired or congenital heart disease, the score stratifies risk according to the presence of poor functional class (New York Heart Association class III or IV), cyanosis, arrhythmias, prior cardiovascular events (heart failure, transient ischemic attack, stroke), left heart obstruction, and ejection fraction less than 40%.[19]

**The CARPREG II study** refined the initial score in 2018 by incorporating general characteristics with lesion-specific risk estimates (such as systemic right ventricle or peripartum cardiomyopathy with residual left ventricular dysfunction) to improve predictive accuracy (**Table 2**).[62]

**The Pregnancy in Women With a Congenital Heart Defect (ZAHARA) risk score** was developed in 2010 based on data from a retrospective study of 1,300 pregnancies (**Table 3**).[63] It differs from the original CARPREG score by incorporating more specific details of prepregnancy cardiac disease, including valvular heart disease, and cardiac medications.

**The World Health Organization (WHO) risk classification** (**Table 4**), devised by the Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology,[40] the Working Group on Pregnancy and Contraception, and others, integrates congenital and acquired heart disease data with other comorbidities. It may better reflect the diversity of at-risk pregnant women and thus be more useful. One especially useful feature of the WHO score is that it has a 100% negative predictive value of cardiovascular events for class I patients (ie, uncomplicated or mild defect, repaired simple lesions, isolated premature ventricular beats and atrial ectopic beats), indicating that risk of pregnancy for that group is considered equivalent to that of the general population.

Based on studies comparing the 3 scores, the WHO's appears to best estimate the risk of cardiovascular events in pregnant women with preexisting heart disease. However, studies were performed using the first CARPREG model, so it is unclear how the CARPREG II model compares.[64,65]

**TABLE 3**

**The Pregnancy in Women With a Congenital Heart Defect (ZAHARA) risk score**

| Predictor | Points |
|---|---|
| History of arrhythmias | 1.5 |
| Cardiac medication before pregnancy | 1.5 |
| New York Heart Association functional class before pregnancy ≥ II | 0.75 |
| Left heart obstruction (peak gradient > 30 mm Hg, or aortic valve area < 1.0 $cm^2$) | 2.5 |
| Systemic aortic valve regurgitation (moderate or severe) | 0.75 |
| Mechanical heart prosthesis | 4.25 |
| Cyanotic heart disease (corrected or uncorrected) | 1.0 |

| Total points | Risk |
|---|---|
| 0–0.5 | 2.9% |
| 0.51–1.50 | 7.5% |
| 1.51–2.50 | 17.5% |
| 2.51–3.50 | 43.1% |
| > 3.50 | 70.0% |

Data from reference 63.

## SUBSEQUENT PREGNANCIES

Many women with cardiovascular complications in pregnancy, regardless of severity, desire additional pregnancies. The provider should engage the patient in shared decision-making with the goal of making as informed a decision as possible. Predicting outcomes for subsequent pregnancies can be challenging, and other than for preeclampsia and peripartum cardiomyopathy, few data exist regarding recurrent pregnancies in the setting of cardiac disease. With no firm guidelines or recommendations, guidance must rely heavily on a patient's diagnosis and previous experience.

Women with structural or congenital heart disease that has remained stable can be managed similarly through subsequent pregnancies.

**Preeclampsia.** Published rates of recurrent preeclampsia range widely, from 5% to nearly 50%. Blood pressure and proteinuria should be monitored during subsequent pregnancy for early detection and consideration of aspirin use.[48,51]

**Peripartum cardiomyopathy.** Risk of relapse may be as high as 20% to 50% and is highest in patients with persistent left ventricular dysfunction from prior pregnancies. To reduce the risk of additional complications,

TABLE 4

## World Health Organization classes of pregnancy risk

**Class 1: Risk is considered equivalent to that in the general population**

Uncomplicated, small, or mild pulmonary stenosis, patent ductus arteriosus, mitral valve prolapse

Repaired simple lesions, eg, atrial septal defect, ventricular septal defect, patent ductus arteriosus, total anomalous pulmonary vein drainage

Isolated premature ventricular beats and atrial ectopic beats

**Class 2: Small increased risk of morbidity and death**

Unoperated atrial septal defect

Repaired tetralogy of Fallot

Most arrhythmias

**Class 2 or 3: Moderate increased risk of morbidity and death, depending on the patient**

Mild left ventricular impairment

Hypertrophic cardiomyopathy

Native or tissue valvular heart disease (not including class IV valvular disease)

Marfan syndrome without aortic dilation

Heart transplant

**Class 3: Significantly increased risk of morbidity and death**

Mechanical valves

Systemic right ventricle (ie, repaired congenital lesions)

Cyanotic heart disease

Post-Fontan operation

Complex congenital heart disease

**Class 4: Pregnancy contraindicated**

Pulmonary hypertension

Severe systemic ventricular dysfunction (left ventricular ejection fraction < 30%)

Severe left heart obstruction

Marfan syndrome with dilated aorta (> 40 mm)

Previous peripartum cardiomyopathy with residual impaired left ventricular function

Adapted from information in reference 33.

women should be advised to wait until their left ventricular function has completely recovered before attempting pregnancy again.[55]

## IMPROVING MATERNAL OUTCOMES

Cardiologists with expertise in managing cardiovascular disease in pregnancy are increasingly needed, as are multidisciplinary teams that can facilitate care for complex patients.

Lacking specific guidelines for pregnant women with a cardiovascular disorder, clinical practice varies, and knowledge is limited regarding best practices for detection and management. More research and opportunities for shared learning are needed, including establishing registries of pregnant women at risk of heart disease or with a known condition. Clinical trials of effective management approaches should be done.

Academic institutions should promote learning opportunities (eg, conferences, didactics, or specialized cross-disciplinary training). Our program at Yale has a monthly management conference attended by specialists in maternal fetal medicine, adult congenital heart disease, and cardiology.

The American College of Cardiology and American Heart Association recommend that patients with congenital heart disease be closely followed by a specialized team of providers, including specialists in adult congenital heart disease and maternal-fetal medicine, to assist in managing their pregnancies.[30] Hospitals should organize and support collaborative multidisciplinary pregnancy care teams that include clinicians from the fields of family medicine, pediatrics, obstetrics, cardiology, endocrinology, and emergency medicine to facilitate care of complex patients.

In view of racial disparities in rates of maternal death, with especially high rates in black women, focused efforts are needed that engage health systems, providers, and communities to understand breakdowns in care.

Finally, better care systems need to be developed to focus on maternal health after delivery. Typically, medical attention tends to pivot toward the baby, resulting in missed opportunities for education, surveillance, and possible intervention for women at risk.

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REVIEW

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ABIM CME MOC ACCREDITED

# Sepsis and septic shock: Guideline-based management

## ABSTRACT

Sepsis is a life-threatening organ dysfunction that results from the body's response to infection. It requires prompt recognition, appropriate antibiotics, careful hemodynamic support, and control of the source of infection. With the trend in management moving away from protocolized care in favor of appropriate usual care, an understanding of sepsis physiology and best practice guidelines is critical.

## KEY POINTS

Tools such as the Systemic Inflammatory Response Syndrome criteria and the quick version of the Sequential Organ Failure Assessment can help with early diagnosis and triage.

The initial antibiotic should be broad-spectrum, based on local sensitivity patterns, with daily assessment of appropriate antibiotic de-escalation and cessation.

Resuscitation with initial fluid boluses should be followed by weighing benefits and risks of additional fluid administration based on dynamically assessed volume status, and then aggressive fluid removal during recovery.

During resuscitation, a goal mean arterial pressure of 65 mm Hg is preferred, using norepinephrine (with vasopressin if needed) to achieve it.

Glucocorticoids are not recommended if fluid resuscitation and vasopressors are sufficient to restore hemodynamic stability.

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Sepsis and particularly septic shock should be recognized as medical emergencies in which time matters, as in stroke and acute myocardial infarction. Early recognition and rapid institution of resuscitative measures are critical. But recognizing sepsis can be a challenge, and best management practices continue to evolve.

This article reviews guidance on the diagnosis and management of sepsis and septic shock, with attention to maximizing adherence to best practice statements, and controversies in definitions, diagnostic criteria, and management.

## COMMON AND LIFE-THREATENING

Sepsis affects 750,000 patients each year in the United States and is the leading cause of death in critically ill patients, killing more than 210,000 people every year.[1] About 15% of patients with sepsis go into septic shock, which accounts for about 10% of admissions to intensive care units (ICUs) and has a death rate of more than 50%.

The incidence of sepsis doubled in the United States between 2000 and 2008,[2] possibly owing to more chronic diseases in our aging population, along with the rise of antibiotic resistance and the increased use of invasive procedures, immunosuppressive drugs, and chemotherapy.

The cost associated with sepsis-related care in the United States is more than $20.3 billion annually.[3]

## DEFINITIONS HAVE EVOLVED

**In 1991,** *sepsis* was first defined as a systemic inflammatory response syndrome (SIRS) due

to a suspected or confirmed infection with 2 or more of the following criteria[4]:

- Temperature below 36°C or above 38°C
- Heart rate greater than 90/minute
- Respiratory rate above 20/minute, or arterial partial pressure of carbon dioxide less than 32 mm Hg
- White blood cell count less than $4 \times 10^9$/L or greater than $12 \times 10^9$/L, or more than 10% bands.

*Severe sepsis* was defined as the progression of sepsis to organ dysfunction, tissue hypoperfusion, or hypotension.

*Septic shock* was described as hypotension and organ dysfunction that persisted despite volume resuscitation, necessitating vasoactive medication, and with 2 or more of the SIRS criteria listed above.

**In 2001,** definitions were updated with clinical and laboratory variables.[5]

**In 2004,** the Surviving Sepsis Campaign guidelines adopted those definitions, which led to the development of a protocol-driven model for sepsis care used worldwide.[6] The US Centers for Medicare and Medicaid Services (CMS) followed suit, defining sepsis as the presence of at least 2 SIRS criteria plus infection; severe sepsis as sepsis with organ dysfunction (including serum lactate > 2 mmol/L); and septic shock as fluid-resistant hypotension requiring vasopressors, or a lactate level of at least 4 mmol/L.[7]

**Appropriate antimicrobials should be started within an hour of recognizing sepsis**

**In 2016,** the Sepsis-3 committee[8] issued the following new definitions:

- *Sepsis*—A life-threatening condition caused by a dysregulated host response to infection, resulting in organ dysfunction
- *Septic shock*—Circulatory, cellular, and metabolic abnormalities in septic patients, presenting as fluid-refractory hypotension requiring vasopressor therapy with associated tissue hypoperfusion (lactate > 2 mmol/L).

The classification of severe sepsis was eliminated.

### Multiple definitions create confusion

Both the CMS and international consensus definitions are currently used in clinical practice, with distinct terminology and different identification criteria, including blood pressure and lactate cutoff points. The CMS definition continues to recommend SIRS for sepsis identification, while Sepsis-3 uses sequential organ failure assessment (SOFA) or the quick version (qSOFA) to define sepsis (described below). This has led to confusion among clinicians and has been a contentious factor in the development of care protocols.

## TOOLS FOR IDENTIFYING HIGH RISK: SOFA AND qSOFA

### SOFA is cumbersome

SOFA is an objective scoring system to determine major organ dysfunction, based on oxygen levels (partial pressure of oxygen and fraction of inspired oxygen), platelet count, Glasgow Coma Scale score, bilirubin level, creatinine level (or urine output), and mean arterial pressure (or whether vasoactive agents are required). It is routinely used in clinical and research practice to track individual and aggregate organ failure in critically ill patients.[9] But the information needed is burdensome to collect and not usually available at the bedside to help with clinical decision-making.

### qSOFA is simpler…

Singer et al[8] compared SOFA and SIRS and identified 3 independent predictors of organ dysfunction associated with poor outcomes in sepsis to create the simplified qSOFA:

- Respiratory rate at least 22 breaths/minute
- Systolic blood pressure 100 mm Hg or lower
- Altered mental status (Glasgow Coma Scale score < 15).

A qSOFA score of 2 or more with a suspected or confirmed infection was proposed as a trigger for aggressive treatment, including frequent monitoring and ICU admission. qSOFA has the advantage of its elements being easy to obtain in clinical practice.

### …but has limitations

Although qSOFA identifies severe organ dysfunction and predicts risk of death in sepsis, it needs careful interpretation for defining sepsis. One problem is that it relies on the clinician's ability to identify infection as the cause of organ dysfunction, which may not be apparent early on, making it less sensitive than SIRS for diagnosing early sepsis.[10] Also, preexisting chronic diseases may influence

accurate qSOFA and SOFA measurement.[11] In addition, qSOFA has only been validated outside the ICU, with limited utility in patients already admitted to an ICU.[12]

Studies have suggested that the SIRS criteria be used to detect sepsis, while qSOFA should be used only as a triaging tool.[11,13]

## ANTIMICROBIAL THERAPY

### Prompt, broad-spectrum antibiotics

Delay in giving appropriate antibiotics is associated with a significant increase in mortality rate.[14–16] Appropriate antimicrobials should be initiated within the first hour of recognizing sepsis, after obtaining relevant samples for culture—provided that doing so does not significantly delay antibiotic administration.[17]

The initial antimicrobial drugs should be broad-spectrum, covering all likely pathogens. Multidrug regimens are favored to ensure sufficient coverage, especially in septic shock. The empiric choice of antimicrobials should consider the site of infection, previous antibiotic use, local pathogen susceptibility patterns, immunosuppression, and risk factors for resistant organisms. Double coverage for gram-negative organisms and for methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered for patients with a high likelihood of infection with such pathogens.[18] Double gram-negative coverage may be appropriate when a high degree of suspicion exists for infection with multi-drug-resistant organisms such as *Pseudomonas* or *Acinetobacter*. If a nosocomial source of infection is suspected to be the cause of sepsis, anti-MRSA agents are recommended.

Appropriate dosing is also important, as efficacy depends on peak blood level of the drug and on how long the blood level remains above the minimum inhibitory concentration for the pathogen. An initial higher loading dose may be the best strategy to achieve the therapeutic blood level, with further dosing based on consultation with an infectious disease physician or pharmacist, as well as therapeutic drug monitoring if needed.[17]

### Consider antifungals

The last few decades have seen a 200% rise in the incidence of sepsis due to fungal organisms.[19] Antifungals should be considered for patients at risk, such as those who have had total parenteral nutrition, recent broad-spectrum antibiotic exposure, perforated abdominal viscus, or immunocompromised status, or when clinical suspicion of fungal infection is high.

Risk factors for fungal infection in septic shock should trigger the addition of echinocandins or liposomal amphotericin B. Azoles are considered appropriate for hemodynamically stable patients.[20]

### De-escalation and early cessation

Antibiotics are not harmless: prolonged use of broad-spectrum antibiotics is associated with antimicrobial resistance, *Clostridium difficile* infection, and even death.[21]

A robust de-escalation strategy is needed to balance an initial broad-spectrum approach. A pragmatic strategy may involve starting with broad-spectrum antimicrobials, particularly in the setting of hypotension, and then rapidly de-escalating to an antimicrobial with the narrowest spectrum based on local sensitivity patterns. If the clinical course suggests the illness is not actually due to infection, the antibiotics should be stopped immediately. A rapid nasal polymerase chain reaction test for MRSA to guide de-escalation has been shown to be safe and to significantly reduce empiric use of vancomycin and linezolid.[22,23]

**A robust antimicrobial de-escalation strategy needs to balance an initial broad-spectrum approach**

Antibiotic de-escalation should be discussed daily and should be an essential component of daily rounds.[17] A 7- to 10-day course or even shorter may be appropriate for most infections,[24,25] although a longer course may be needed if source control cannot be achieved, in immunocompromised hosts, and in *S aureus* bacteremia, endocarditis, or fungal infections.

## FLUID RESUSCITATION

Sepsis is associated with vasodilation, capillary leak, and decreased effective circulating blood volume, reducing venous return. These hemodynamic effects lead to impaired tissue perfusion and organ dysfunction. The goals of resuscitation in sepsis and septic shock are to restore intravascular volume, increase oxygen delivery to tissues, and reverse organ dysfunction.

A crystalloid bolus of 30 mL/kg is recommended within 3 hours of detecting severe sepsis or septic shock.[17] However, only limited

data support the benefits of this recommendation, and evidence of harm from sustained positive fluid balance is growing.

Some have cautioned against giving too much fluid, especially in patients who have limited cardiorespiratory reserve.[26] Overzealous fluid administration can result in pulmonary edema, hypoxemic respiratory failure, organ edema, intra-abdominal hypertension, prolonged ICU stay and time on mechanical ventilation, and even increased risk of death.[26,27]

With this in mind, fluid resuscitation should be managed as follows during consecutive phases[28]:

- **Rescue:** During the initial minutes to hours, fluid boluses (a 1- to 2-L fluid bolus of crystalloid solution) are required to reverse hypoperfusion and shock
- **Optimization:** During the second phase, the benefits of giving additional fluid to improve cardiac output and tissue perfusion should be weighed against potential harms[27]
- **Stabilization:** During the third phase, usually 24 to 48 hours after the onset of septic shock, an attempt should be made to achieve a net-neutral or a slightly negative fluid balance
- **De-escalation:** The fourth phase, marked by shock resolution and organ recovery, should trigger aggressive fluid removal strategies.[27]

**Antibiotic de-escalation should be discussed daily**

### Assess volume with dynamic measures

Clinicians should move away from using static measures to assess volume status. Central venous pressure, the static measure most often used to guide resuscitation, has been found to be accurate in only half of cases, compared with thermodilution using pulmonary artery catheters to assess change in cardiac output with volume administration.[29] A 2017 meta-analysis[30] showed that the use of dynamic assessment in goal-directed therapy is associated with lower mortality risk, shorter ICU stay, and shorter duration of mechanical ventilation.

Dynamic measures are used to estimate the effects of additional volume on cardiac output. Two methods are used: either giving a fluid bolus or passively raising the legs. The latter method returns 200 to 300 mL of blood from the lower extremities to the central circulation and is performed by starting the patient in a semirecumbent position, then lowering the trunk while passively raising the legs.

With either method, the change in cardiac output is measured either directly (eg, with thermodilution, echocardiography, or pulse contour analysis) or using surrogates (eg, pulse pressure variation).

Alternatively, changes in cardiac output can be evaluated by heart-lung interactions in a patient on a mechanical ventilator. Changes in intrathoracic pressure are assessed during the inspiratory and expiratory cycle to detect changes in cardiac output using pulse pressure variation, stroke volume variation, and variation in inferior vena cava size.

The dynamic measures mentioned above are more accurate than static measurements in predicting preload responsiveness, so they are recommended to guide fluid management.[31,32] But they do have limitations.[33] Although giving a fluid bolus remains the gold standard for critically ill patients, indiscriminate fluid administration carries the risk of fluid overload. Heart-lung interactions are imprecise for patients with arrhythmias, those who are spontaneously breathing with active effort on the ventilator, and those with an open chest or abdomen. Thus, their use is limited in most critically ill patients.[34]

Unlike other dynamic tests, the passive leg-raise test is accurate in spontaneously breathing patients, for patients with cardiac arrhythmias, and for those on low tidal volume ventilation.[35] Due to its excellent sensitivity and specificity, the passive leg-raise test is recommended to determine fluid responsiveness.[17,32]

### Lactate level as a resuscitation guide

Lactate-guided resuscitation can significantly lessen the high mortality rate associated with elevated lactate levels (> 4 mmol/L).[36,37] A rise in lactate during sepsis can be due to tissue hypoxia, accelerated glycolysis from a hyperadrenergic state, medications (epinephrine, beta-2 agonists), or liver failure. Measuring the lactate level is an objective way to assess response to resuscitation, better than other clinical markers, and it continues to be an integral part of sepsis definitions and the Sur-

viving Sepsis Campaign care bundle.[7,8,17] Even though lactate is not a direct surrogate of tissue hypoperfusion, it is a mainstay for assessing end-organ hypoperfusion.

Central venous oxygen saturation-guided resuscitation (requiring central vascular access) does not offer any advantage over lactate-guided resuscitation.[38] Microvascular assessment devices are promising tools to guide resuscitation, but their use is still limited to clinical research.

Although optimal resuscitation end points are not known, key variables to guide resuscitation include a composite of physical examination findings plus peripheral perfusion, lactate clearance, and dynamic preload responsiveness.[17,39]

### Balanced crystalloids are preferred over isotonic solutions

Crystalloid solutions (isotonic saline or balanced crystalloids) are recommended for volume resuscitation in sepsis and septic shock. The best one to use is still debated, but over the last decade, balanced solutions have come to be favored for critically ill patients. Growing evidence indicates that balanced crystalloids (lactated Ringer solution, Plasma-Lyte) are associated with a lower incidence of renal injury, less need for renal replacement therapy, and lower mortality in critically ill patients. Moreover, isotonic saline is associated with hyperchloremia and metabolic acidosis, and it can reduce renal cortical blood flow.[40–42]

### No proven benefit from colloids

The rationale for using colloids is to increase intravascular oncotic pressure, reducing capillary leak and consequently reducing the amount of fluid required for resuscitation. But in vivo studies have failed to demonstrate this benefit.

One can consider using albumin in sepsis if a significant amount of resuscitative fluid is required to restore intravascular volume.[17] But comparisons of crystalloids and albumin, either for resuscitation or as a means to increase serum albumin in critically ill patients, have found no benefit in terms of morbidity or mortality.[43–45] When considering albumin to treat sepsis or septic shock, clinicians should remember its lack of benefit and its substantial cost—20 to 100 times as much as crystalloids, with an additional cost greater than $30,000 per case with use of albumin.[46]

Hydroxyethyl starch, another colloid, was associated with a higher mortality rate and a higher incidence of renal failure in septic patients and should not be used for resuscitation (**Table 1**).[47]

**TABLE 1**

**Randomized controlled trials of volume replacement in sepsis and septic shock**

| Author and year | Number of patients | Major findings |
|---|---|---|
| **Finfer et al,[43] 2004** | 6,997 | No reduction in mortality with albumin compared with saline |
| **Perner et al,[47] 2012** | 804 | Higher risk of death and renal replacement therapy with hydroxyethyl starch compared with Ringer solution |
| **Annane et al,[45] 2013** | 2,587 | No reduction in mortality, need for renal replacement therapy, duration of resuscitation, or length of stay with colloids compared with crystalloids |
| **Caironi et al,[44] 2014** | 1,818 | No reduction in mortality, need for renal replacement therapy, or length of stay with albumin replacement |
| **Young et al,[41] 2015** | 2,278 | No difference in incidence of acute kidney injury, need for renal replacement therapy, or length of stay with balanced solution compared with saline |
| **Semler et al,[40] 2018** | 15,802 | Lower rates of mortality and need for renal replacement therapy with balanced solutions compared with saline |

## EARLY SOURCE CONTROL

Source control is imperative in managing sepsis and septic shock. Inadequate source control may lead to worsening organ function and hemodynamic instability despite appropriate resuscitative measures.[17] A thorough examination and appropriate imaging studies should be performed to determine the optimal way to control the source and assess the risks associ-

ated with each intervention. If appropriate, source control should be achieved within 6 to 12 hours of diagnosis, once initial resuscitation is completed.[48] The source control can range from removal of infected intravascular devices to a chest tube for empyema to percutaneous or surgical intervention in cases of cholecystitis and pyelonephritis.

## RESTORING BLOOD PRESSURE

Persistent hypotension and tissue hypoperfusion after adequate fluid resuscitation are caused by loss of normal sympathetic vascular tone, leading to vasodilation, neurohormonal imbalances, myocardial depression, microcirculatory dysregulation, and mitochondrial dysfunction. Vasopressors and inotropes restore oxygen delivery to tissues by increasing arterial pressure and cardiac output respectively.

Mean arterial pressure is the preferred blood pressure to target during resuscitation. The recommended initial goal is 65 mm Hg. A higher goal of 80 to 85 mm Hg may help patients with chronic hypertension,[49] while a lower target may be better tolerated in patients with reduced systolic function, older patients, and patients with end-stage liver disease.

**The passive leg-raise test has excellent sensitivity and specificity for determining fluid responsiveness**

These recommendations are based on our understanding of autoregulation of blood flow in the vascular beds of central organs (brain, heart, kidneys). After blood pressure falls below a critical threshold, tissue perfusion decreases linearly. That critical threshold can vary between organ systems and individuals, and the target can later be personalized based on global and regional perfusion as assessed with urine output, mental status, or lactate clearance.[50]

Decisions to titrate vasopressors to achieve mean arterial pressure goals should be balanced against potential adverse effects, including arrhythmias, cardiovascular events, and ischemia.

### Norepinephrine is the first-line vasopressor

Few large, multicenter randomized controlled studies have been done to determine the most effective initial and adjunctive vasoactive agents for septic shock. Norepinephrine has shown survival benefit with lower risk of arrhythmia than dopamine.[51–53] On the other hand, 2 systematic reviews found no difference in clinical outcomes and mortality with norepinephrine vs epinephrine, vasopressin, terlipressin, or phenylephrine.[53,54]

Without convincing evidence to support other agents as first-line therapy for septic shock, norepinephrine remains the preferred vasopressor for achieving the target mean arterial pressure and is strongly recommended by the Surviving Sepsis Campaign guidelines, albeit supported by only moderate-quality data.[17,55]

### Adding a second vasopressor or inotrope

Another sympathomimetic drug such as vasopressin or epinephrine can be used to either achieve target mean arterial pressures or decrease the norepinephrine requirement. A second vasopressor is routinely added when norepinephrine doses exceed 40 or 50 µg/min.

**Vasopressin.** Septic shock involves relative vasopressin deficiency. Adding vasopressin as a replacement hormone has been shown to have a sparing effect on norepinephrine, resulting in a lower dose needed. A randomized controlled trial comparing vasopressin plus norepinephrine vs vasopressin monotherapy failed to show any survival benefit or reduction in kidney failure.[56,57] Evidence supporting the use of vasopressin over norepinephrine as a first-line agent remains limited, but vasopressin remains the preferred adjunct with norepinephrine.[56,57]

**Epinephrine** is recommended by the Surviving Sepsis Campaign guidelines as a second-line vasopressor. It has potent alpha- and beta-adrenergic activity, which increases mean arterial pressure by increasing cardiac output and vasomotor tone. Use of epinephrine is limited by significant risk of tachycardia, arrhythmia, and transient lactic acidosis.[58]

**Dopamine use is discouraged** in sepsis owing to its propensity to induce tachyarrhythmia and significantly worsen outcomes in this setting.[51,52]

**Phenylephrine** is a pure alpha-adrenergic agonist that is routinely used in septic shock, albeit with limited data on its efficacy and safety. Vail et al[59] found increased mortality associated with phenylephrine use in septic shock in a multicenter cohort study conducted during a norepinephrine shortage. Phenyl-

ephrine use should be limited to septic shock complicated by significant tachyarrhythmia or as an adjunct for refractory vasodilatory shock until there is more evidence of its benefits.[17]

**Angiotensin II** was recently approved as a vasopressor for use in septic shock. It activates angiotensin type 1a and 1b receptors to increase intracellular calcium in smooth muscle, promoting vasoconstriction. Clinical data related to its use are limited to a recent trial that showed that the addition of angiotensin II improved blood pressure in patients with refractory vasodilatory shock receiving high-dose vasopressors.[60] The data are still sparse on its safety, and its precise role in refractory shock treatment algorithms has yet to be defined.

**Inotropic agents** may be required for patients with inadequate cardiac output after fluid resuscitation due to sepsis-induced cardiomyopathy or combined shock. Data are limited suggesting an optimal inotropic agent in septic shock, but epinephrine and dobutamine are most commonly used.[61,62] A comparison of norepinephrine plus dobutamine vs epinephrine in septic shock found no difference in mortality, side effects, or shock duration.[62] Milrinone and levosimendan (not approved in the United States) have been studied, with limited data to support their use over dobutamine.[63,64] The response to use of inotropes should be monitored by measuring changes in cardiac output, central venous oxygen saturation, or other indices of tissue perfusion (**Table 2**).

TABLE 2

**Randomized controlled trials of vasopressors and inotropes in septic shock**

| Author and year | Number of patients | Major findings |
|---|---|---|
| **Annane et al,[62] 2007** | 330 | No difference in mortality with epinephrine vs norepinephrine ± dobutamine; higher lactate elevation and lower pH in epinephrine group |
| **Russell et al,[57] 2008** | 780 | No reduction in mortality with addition of vasopressin to norepinephrine<br>Survival benefit in patients with septic shock requiring norepinephrine < 15 µg/min<br>Vasopressin had norepinephrine-sparing effect. |
| **De Backer et al,[51] 2010** | 1,679 | Higher rates of mortality and arrhythmia with dopamine than with norepinephrine |
| **Gordon et al,[56] 2016** | 409 | No improvement in kidney failure-free days, use of renal replacement therapy, or mortality with vasopressin |
| **Khanna et al,[60] 2017** | 344 | Angiotensin II increased blood pressure in refractory vasodilatory shock |

## ROLE OF CORTICOSTEROIDS IS QUESTIONED

Corticosteroids downregulate the maladaptive inflammatory response seen in sepsis and help address relative adrenal insufficiency caused by adrenal suppression or glucocorticoid tissue resistance.[65] In septic shock, they have a vasopressor-sparing role and reduce the duration of shock, ventilator use, and ICU stay.

However, the evidence is not conclusive that giving corticosteroids for sepsis improves clinical outcomes or survival,[66–71] and so they are not recommended in sepsis or severe sepsis if fluid resuscitation and vasopressors are sufficient to restore hemodynamic stability. Rather, they can be added as adjunctive therapy for patients requiring higher doses of vasopressors.[17,65]

Adverse events in studies of corticosteroids were limited to hyperglycemia, hypernatremia, and hypertension, with no increase in superinfections.[71] The limited adverse events, along with a uniform demonstration of shorter shock duration, ventilator duration, and ICU stay, suggest steroids may have a role in managing refractory septic shock.[66–69]

If corticosteroids are used in septic shock, current guidelines recommend hydrocortisone 200 mg per day intravenously as a continuous drip or 50 mg bolus in 4 divided doses for at least 3 days, based on a systematic review showing a longer course of low-dose steroids is associated with a lower mortality rate.[72] There is no clear consensus on whether steroids should be tapered or if abrupt cessation is appropriate, as larger randomized clinical tri-

TABLE 3

**Randomized controlled trials of corticosteroids in septic shock**

| Author and year | Number of patients | Major findings |
|---|---|---|
| **Annane et al,[68] 2002** | 300 | Lower mortality rate and shorter duration of shock in corticotropin nonresponders with hydrocortisone + fludrocortisone, but not in all patients |
| **Sprung et al,[69] 2008** | 499 | No difference in mortality rate, but shorter duration of shock and no increased risk of superinfection with hydrocortisone |
| **Keh et al,[70] 2016** | 380 | No benefit of hydrocortisone in preventing septic shock or decreasing mortality in severe sepsis |
| **Annane et al,[66] 2018** | 1,241 | Lower mortality rate and shorter duration of shock and mechanical ventilation with addition of hydrocortisone + fludrocortisone. |
| **Venkatesh et al,[67] 2018** | 3,800 | No reduction in mortality with addition of hydrocortisone, but reduced duration of shock, mechanical ventilation and length of stay in intensive care unit |

als did not use a tapering strategy and found no difference in shock recurrence.[66,67] In most cases, steroids are stopped after cessation of vasopressors.[65]

Future research should focus on appropriate timing of glucocorticoid initiation after onset of shock and comparing a fixed duration regimen to a clinically guided one.

Etomidate as an induction agent for intubation has been associated with suppression of cortisol synthesis and a reduced response to exogenous steroids. Whether it affects outcomes is unclear. Nonetheless, clinicians should practice extreme caution with etomidate use in septic shock (**Table 3**).[73]

## BIOMARKERS

Biomarkers facilitate early diagnosis, identify patients at high risk, and monitor disease progression to guide resuscitation goals and tailor management.

**C-reactive protein and erythrocyte sedimentation rate** have been used in the past, but with limited success.[74]

**Procalcitonin** has emerged as a method to help detect bacterial infections early and to guide de-escalation or discontinuation of antibiotics.[75,76] Procalcitonin-guided de-escalation of antibiotics reduces duration of antibiotic exposure, with a trend toward decreased mortality.[77,78]

**Galactomannan and beta-D-glucan** can be used to detect infections with fungi, specially *Aspergillus*. Beta-D-glucan is more sensitive for invasive *Aspergillus*, while galactomannan is more specific.[79]

**Cytokines** such as interleukins (eg, IL-6, IL-8, IL-10), tumor necrosis factor alpha, acute-phase proteins, and receptor molecules are currently being studied to determine their utility in sepsis care.

The limited sensitivity and specificity of single biomarkers may be overcome by using a combination of biomarkers, which is a current focus of research.[80] For now, the decision to initiate, escalate, and de-escalate therapy should be based on clinical assessment, with procalcitonin or other biomarkers used as an adjunct to other clinical factors.[17]

## USUAL CARE VS PROTOCOLIZED INITIAL RESUSCITATION

In 2001, Rivers et al[61] compared usual care for severe sepsis or septic shock with a protocolized targeting of physiologic end points as goals of resuscitation for the 6 hours before admission to the ICU in a single center. They found a significantly lower mortality rate in the goal-directed therapy group. This finding heavily influenced the bundle-based, goal-directed management strategy recommended by the Surviving Sepsis Campaign in 2004.[81]

However, the protocolized approach has been challenged since then, with 3 large multicenter trials finding that usual care was not inferior to protocolized care in sepsis, with no difference in mortality or length of stay.[82–84] Further, usual care was associated with significantly reduced need for central vascular access, blood transfusions, and dobutamine. A meta-analysis involving nearly 4,000 patients at 138 hospitals in 7 countries found that usu-

al care emphasizing detecting sepsis early and rapidly implementing appropriate antimicrobial therapy and adequate fluid resuscitation was not only equivalent to protocolized care in outcomes but was more cost-effective.[85] (**Table 4**).

### Is SEP-1 appropriate?

In January 2013, the State of New York mandated that all state hospitals initiate processes for early detection and treatment of sepsis. In October 2015, the National Quality Forum and CMS implemented these processes nationwide.[7] The resultant CMS SEP-1 quality measure standardizes early management of severe sepsis and septic shock, with the goal of improving outcomes. Its elements are based on the Surviving Sepsis Campaign guidelines and consist of a series of steps that need to be completed within 3 and 6 hours after sepsis is recognized.

Steps to be performed within 3 hours include measuring the serum lactate level, drawing blood cultures, and starting appropriate antibiotics, intravenous fluid resuscitation, and vasopressor support if needed. A lactate level is repeated within 6 hours, and static and dynamic assessment of perfusion must be done to determine the need for additional fluid or vasopressors to improve end-organ perfusion.

SEP-1 overall hospital performance is publicly available on the CMS website (medicare.gov/hospitalcompare/search.html?) and has the potential to be used for financial incentives centered on SEP-1 measure compliance performance.[86]

Although SEP-1 has been adopted as a quality measure, some question its clinical relevance, as many of the core recommendations are not supported by strong evidence.[86,87] Three major trials found that the mortality rate was no lower with bundled sepsis care than with usual care.[82–84] Seymour et al[28] collected New York State Department of Health data for 49,331 patients with sepsis and septic shock and found that more rapid completion of the 3-hour bundle—particularly of antibiotic administration but not of fluids—was associated with decreased hospital mortality. A multicenter retrospective cohort study[88] found that failure to meet SEP-1 criteria for any step other than giving antibiotics did not translate to poor outcomes.

**TABLE 4**

**Randomized controlled trials evaluating early goal-directed care in septic shock**

| Author and year | Number of patients | Major findings |
|---|---|---|
| **Rivers et al,[61] 2001** | 268 | Significantly lower mortality rate with protocolized care |
| **Peake et al,[82] 2014** | 1,600 | No reduction in mortality, need for advanced respiratory or renal support, or intensive care unit length of stay with protocolized care |
| **Rowan et al,[85] 2014** | 1,351 | No reduction in mortality, need for advanced respiratory or renal support, or intensive care unit length of stay with protocolized care |
| **Mouncey et al,[83] 2015** | 1,260 | No reduction in mortality, need for advanced respiratory, cardiovascular or renal support, or intensive care unit length of stay with protocolized care |

A major concern about mandating SEP-1 is that fluids and broad-spectrum antibiotics will be overprescribed as healthcare systems try to meet CMS-mandated quality measures. Indiscriminate use of these therapies has the potential to cause harm and puts an undue strain on healthcare resources.[89]

**The lactate level remains an objective guide to assess response to resuscitation**

### A call to refine guidance

Sepsis is a multifaceted disease, and its management is complex. Simplified guidelines and quality measures based on sound evidence are needed. Electronic medical record systems show promise for assisting with early and accurate detection of sepsis and have the potential to play an important role.[90,91] Checklists that allow bedside caregivers to exercise their clinical acumen are another approach. The success of optimal care initiatives requires sustained, collaborative quality improvement across different specialties in medicine, nursing, and hospital administration.[92] ■

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