The Journal of Emergency Medicine, Vol. 56, No. 1, pp. 36–45, 2019
Published by Elsevier Inc.
0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2018.09.035

Clinical Reviews in Emergency Medicine

CONSIDERATION OF OCCULT INFECTION AND SEPSIS MIMICS IN THE SICK PATIENT WITHOUT AN APPARENT INFECTIOUS SOURCE

Marina N. Boushra, MD,* Susan N. Miller, MD,* Alex Koyfman, MD,† and Brit Long, MD‡

*Department of Emergency Medicine, Vidant Medical Center, Greenville, North Carolina, †Department of Emergency Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas, and ‡Department of Emergency Medicine, Brooke Army Medical Center, Fort Sam Houston, Texas

Reprint Address: Brit Long, MD, Department of Emergency Medicine, Brooke Army Medical Center, 3841 Roger Brooke Dr., Fort Sam Houston, TX 78234

☐ **Abstract—Background: Evaluation and treatment of the acutely ill patient is typically complicated by multiple comorbidities and incomplete medical histories. This is exemplified by patients with sepsis, whose care is complicated by variable presentations, shifting definitions, and a variety of potential sources. Many practitioners fail to consider and recognize less-common sources of infection in a timely manner. Additionally, multiple noninfectious conditions can present with the fever and tachycardia typical of the septic patient. The errors of anchoring and premature closure may lead to delay in, or failure of, diagnosis of these conditions. Objective: This review addresses the evaluation of the acutely ill-appearing patient without an apparent source, focusing on occult sources of infection and conditions that mimic sepsis. Discussion: Musculoskeletal, cardiac, neuraxial, and abdominal sources of sepsis should be considered in the acutely ill patient. Indwelling devices should be carefully examined for signs of infection. Consideration for sepsis mimics, such as neuroleptic malignant syndrome, malignant hyperthermia, medication toxicity, and thyroid storm, in patients who fail to respond to standard therapies for sepsis, may lead the physician to potentially reversible life-threatening diagnoses and management. Conclusion: In the seemingly septic patient who does not respond to antimicrobials and fluids, the differential should be broadened to include acutely life-threatening conditions that can mimic sepsis. A review of the patient's medical history, medications, and recent exposures can assist in identifying the source of the patient's elevated body temperature and tachycardia. Consideration of potential sources and other mimics of sepsis is needed in the emergency department. - Published by Elsevier Inc.**

☐ **Keywords—sepsis; syndrome; occult; mimic**

INTRODUCTION

Although care of the undifferentiated acutely ill patient is a staple of emergency medicine, evaluation and treatment of these patients is typically complicated by multiple comorbidities and incomplete medical histories. Further muddying the waters are rapidly shifting definitions of disease states that seek to incorporate better understanding of pathophysiology and improve sensitivity and specificity for diagnosis. This is exemplified by sepsis, a syndrome of organ dysfunction resulting from dysregulated host response to an infectious agent. The burden of sepsis on the health care system is heavy; in the United States alone, care of septic patients is estimated to result in more than $20 billion in annual expenditures (1). The cost in human life is similarly high; mortality is estimated to be > 10% in sepsis and > 40% in septic shock (2). Sepsis continues to be one of the most common reasons for admission to the intensive

Received: 20 February 2018; Final submission received: 1 September 2018;
Accepted: 20 September 2018

care unit (ICU) and the most common cause of death in the ICU worldwide. Since the release of the first formal definition of sepsis nearly three decades ago, the definition has been hotly debated (3). This is further complicated by government agencies such as the Centers for Medicare and Medicaid Services attempting to concretely define this process in an attempt to improve patient outcomes. Though emergency clinicians see sepsis regularly, several studies have shown that the diagnosis of sepsis is delayed in the emergency department (ED), with resulting increase in patient morbidity and mortality (4–6). In the United States, urinary tract and lower respiratory tract infections are the most common causes of sepsis (6). Although screening for these conditions can be done rapidly by obtaining a chest x-ray and urinalysis, these simple tests do not always readily yield the cause of the patient's illness. This is due to many practitioners failing to consider and recognize less-common sources of infection in a timely manner. Additionally, multiple noninfectious conditions can present with the fever and tachycardia typical of the septic patient. The errors of anchoring and premature closure may lead to delay in, or failure of, diagnosis in these conditions. The following discussion addresses the evaluation of the acutely ill-appearing patient without an apparent source, focusing on sources of infection beyond the urinary and respiratory tracts. Sepsis mimics, their diagnosis, and treatment are also discussed.

DISCUSSION

Pathophysiology of Sepsis

Sepsis is a complex, multisystemic, and poorly understood process. Describing sepsis, Sir William Osler wrote: "Except on few occasions, the patient appears to die from the body's response to infection rather than from [the infection itself]" (7). Two centuries of research and observation after that statement have shown this to be the likely case. At its core, sepsis seems to be an overzealous immune response to infection, an unregulated and self-sustaining exaggeration of the normal immune mechanisms set in place to fight infection and repair damaged tissues. What causes an otherwise normal host response to infection to become uncontrolled is yet unclear and is likely multifactorial. It is theorized that sepsis may be due to a pathologic imbalance of the pro-inflammatory and anti-inflammatory mediators of the immune response, leading to cellular injury and multiorgan dysfunction (8). Patient genetic susceptibility as well as direct effects of the invading microorganism or its toxic byproducts may also play a role (8).

Recognizing Sepsis

Approximately one- to two-thirds of septic patients enter the health care system through the ED (9). With hospital overcrowding increasing wait times as well as length of ED stay, optimizing management of sepsis in the ED has become a priority. Additionally, because sepsis is a time-critical disease process, ED management of septic patients has the potential to improve patient outcomes (10–15). Timely and effective treatment of sepsis necessarily depends on recognition of sepsis. In fact, each hour of delay in administration of appropriate antimicrobials, as well as adequate fluid resuscitation, results in a 7.6% increase in patient mortality (10). Unfortunately, a cursory physical examination may not readily identify a source of infection in a patient in whom sepsis is suspected. The diagnosis of sepsis is further made difficult by the current lack of a gold-standard diagnostic biomarker (16). Finally, recognition of sepsis is hampered by the remarkable variability in its presentation and shifting definitions of the disease process itself (17).

There is no gold standard or clearly outlined clinical criteria to define sepsis. The history of defining sepsis as a disease mirrors the increasing recognition of its pathophysiology as a multisystemic process resulting in end-organ dysfunction. In a joint consensus statement in 1992 by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine, the spectrum of sepsis to septic shock was defined by the presence of elements of the patient's systemic inflammatory response syndrome (SIRS) (Table 1) (3). This was based on the then-prevailing theory that sepsis is secondary solely to the patient's immune response to infection. This was the first published definition of SIRS, sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome. It was, however, limited by its lack of specific clinical or laboratory criteria to define end-organ dysfunction. Multiple guidelines since have revised these definitions, all with variations on the same theme of organ dysfunction, as defined by abnormal vital signs or laboratory values. Most recently in 2016, the Sepsis-3 consensus statement by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine defined sepsis as the presence of a suspected or documented infection in addition to two or more of the quick Sequential Organ Failure Assessment (qSOFA) criteria (Table 2) (2). Septic shock was defined clinically as sepsis requiring vasoactive agents to maintain mean arterial pressure $\geq$ 65 mm Hg despite adequate fluid resuscitation and a lactate $>$ 2 mmol/L. Importantly, this eliminated the category of severe sepsis entirely, reflected in the most recent Surviving Sepsis Campaign guidelines released in early 2017 (15). However, even these definitions fail to achieve clinical certainty. In one

Table 1. Systemic Inflammatory Response Syndrome (SIRS) and the Definition of Sepsis*

SIRS	Two or more of the following: Temperature > 38°C or < 36°C Heart rate > 90 beats/min Respiratory rate >20 breaths/min or $PaCO_2$ < 32 mm Hg White blood cell count > 12,000 cu/mm < 4000 cu/mm > 10% bands
Sepsis	The presence of two SIRS criteria in the setting of known or suspected infection
Severe sepsis	Sepsis associated with end-organ dysfunction
Septic shock	Sepsis with a systolic blood pressure < 90 mm Hg or > 40 mm Hg decrease in baseline systolic blood pressure

ACCP = American College of Chest Physicians; SCCM = Society of Critical Care Medicine.
* Adapted from the 1992 ACCP/SCCM consensus statement (3).

study the SIRS criteria were demonstrated to have 72% sensitivity and 61% specificity for predicting organ dysfunction (18). For predicting mortality, the presence of two or more SIRs criteria was only 77% sensitive and 57% specific (18). By comparison, the qSOFA score displayed sensitivities of 30% and 50% and specificities of 96% and 91% for predicting organ dysfunction and mortality, respectively (18). Another large meta-analysis comparing the sensitivities of qSOFA and SIRS for the diagnosis of sepsis showed a risk ratio of 1.32 in favor of SIRS criteria, whereas qSOFA was found to be a better predictor of in-hospital mortality (19). In the setting of such ambiguity and in the face of such high stakes, recognition of sepsis depends on maintaining high clinical suspicion for this disease syndrome in the acutely ill patient.

Current guidelines for the management of sepsis recommend the continuous administration of crystalloid fluids as long as hemodynamic factors continue to improve (15). If the administration of fluids fails to achieve a mean arterial pressure of ≥ 65 mm Hg, the use of vasoactive agents is recommended, with norepinephrine being the vasopressor of choice in septic patients (15). Prompt and aggressive source control is of utmost importance. This can be achieved through the administration of antimicrobials and, in some cases, through surgical intervention. In the septic patient, early broad-spectrum antimicrobial therapy is indicated. The choice of antimicrobial should take into account the pathogen profile of the suspected anatomic site of infection, local pathogen prevalence and resistance patterns, and

Table 2. Quick Sequential Organ Failure Assessment Criteria (qSOFA) (2)

qSOFA	Altered mental status Systolic blood pressure < 100 mm Hg Respiratory rate ≥ 22 breaths/min

the presence of immunodeficiencies in the patient. If available, input from clinical pharmacists can assist in optimizing the initial antimicrobial regimen in the ED. Pharmacist input in the treatment of septic patients has been shown to decrease time to antimicrobial administration, lead to more appropriate medication stewardship, and decrease patient mortality (20–22). Cultures should be collected prior to the initiation of antimicrobials if doing so does not significantly delay the administration of antimicrobials (15). This is particularly important as positive blood cultures are currently the only confirmatory laboratory test to support the clinical diagnosis of sepsis, though several other biomarkers such as lactate, C-reactive protein, and pro-calcitonin have shown promise as potential tools for diagnosis and prognostication (16). Blood cultures are also important as they allow for the appropriate narrowing of the spectrum of antimicrobials started in the ED, typically on the floor or the intensive care unit.

Considering Other Sources of Sepsis

Sources of infection beyond the urinary and lower respiratory tracts are common and may be less readily evident (23). A high clinical suspicion for sepsis and focused physical examination are important in these undifferentiated patients, and a source may be revealed through additional imaging and laboratory testing. Though by no means comprehensive, the following is a discussion of potential sources of sepsis in the acutely ill patient in the ED.

Musculoskeletal. Patients with poor vascular circulation, diabetes, recent surgery, and immunocompromise are at the greatest risk for serious musculoskeletal infection. Cellulitis due to *Staphylococcus aureus* or *Streptococcus pyogenes* is the most common cause of sepsis secondary to skin and soft tissue infection (24). Laboratory values in musculoskeletal causes of sepsis are generally nonspecific, and in the altered or obtunded patient, physical examination becomes even more important. This includes turning the patient to evaluate the back, palpating the large joints, and carefully examining the feet and genitourinary regions. Skin changes such as discoloration or erythema may be the only clue to a musculoskeletal infection (24). Many patients, especially those with limited mobility or those in long-term care facilities, will have decubitus ulcers, which may become a source for osteomyelitis or systemic infection. Crepitus or pain out of proportion to examination is concerning for necrotizing fasciitis or myositis. A genitourinary examination may reveal a life-threatening infection such as Fournier gangrene. Consider toxic shock syndrome in the ill-appearing patient with a generalized macular rash (25).

An erythematous, hot swollen joint, especially the hip or knee, should raise suspicion for a septic joint (26,27). Aspiration is required for diagnosis of septic arthritis (27). Magnetic resonance imaging (MRI) or surgical pathology may be necessary for definitive diagnosis of many musculoskeletal causes of sepsis; this should not preclude early, aggressive antimicrobial coverage in the ED.

Cardiac. Whereas the subtle aspects of a cardiac examination are difficult in the chaos of the ED, the presence of a new murmur in the acutely ill patient should raise suspicion for endocarditis. Intravenous drug use is a risk factor for endocarditis, and in light of the current opioid crisis in the United States, endocarditis should be considered in septic patients without an obvious cause of sepsis (28). Diagnosis and appropriate management of endocarditis in intravenous drug users presents an opportunity for significant morbidity reduction in an otherwise young and healthy patient group. In addition to intravenous drug use, risk factors for endocarditis include the presence of a prosthetic valve, intravascular devices, and immunocompromise (28). The presentation of endocarditis is remarkably variable and dependent upon the stage of the disease. The most common symptom is fever. Other physical examination findings consistent with endocarditis include stigmata of peripheral thromboembolism such as Osler nodes, Janeway lesions, Roth spots, or splinter hemorrhages. Patients may present initially with complications of endocarditis, including cerebrovascular ischemia or hemorrhage, septic emboli, and metastatic infection. Diagnosis of endocarditis in the ED is possible if the vegetation is large enough to be visible on bedside ultrasound, though this is not sensitive (28–30). Transesophageal echocardiography, which is typically not available in EDs, is the most sensitive modality for the detection of valve vegetations (30). If endocarditis is a possibility, obtaining multiple blood cultures is recommended (30).

Meningitis and encephalitis. The classic triad of meningitis is altered mental status, nuchal rigidity, and fever, though the majority of patients only have one or two of these symptoms (31). The most common causes of bacterial meningitis in adults in the United States are *Streptococcus pneumoniae,* group B streptococci, and *Neisseria meningitidis* (31,32). *Listeria monocytogenes* is more common in children, adults > 50 years of age, and immunocompromised individuals (33). Meningitis and encephalitis may also be caused by viruses such as herpes, enteroviruses, and cytomegalovirus. Lumbar puncture is needed to make a diagnosis of meningitis, but therapy should not be delayed for this procedure. Computed tomography (CT) of the head without contrast should be performed prior to lumbar puncture in patients with a history of immunocompromise or central nervous system disease, new-onset seizure, papilledema, focal neurologic deficit, or abnormal mental status (34,35). Administration of antimicrobials prior to lumbar puncture has little effect on the chemistry and cytology findings in cerebrospinal fluid but may result in a falsely negative Gram stain or culture (36,37). Time to sterilization of cerebrospinal fluid is highly variable and dependent on the pathogen; this should not affect the decision to start empiric antimicrobials in the patient in whom meningitis or encephalitis is suspected (36). Empiric therapy includes ceftriaxone to cover streptococcal species and *Neisseria*, vancomycin to cover ceftriaxone-resistant streptococci, and ampicillin to cover for *Listeria* if the patient is > 50 years or immunocompromised (31). Intravenous dexamethasone should be given shortly prior to administration of antimicrobials if suspicion for bacterial meningitis is high (31). If there is concern for herpes infection, acyclovir should be added (31,32).

Spinal infections. Back pain is a common chief complaint in the ED (38). Despite the myriad of relatively benign musculoskeletal causes of back pain, spinal infection should be considered in all patients presenting with back pain. Vertebral osteomyelitis, discitis, and epidural abscesses are potential sources of sepsis from a spinal infection. The presence of fever is inconsistent in these patients and is seen in approximately half of cases (39,40). Neurologic abnormalities may or may not be present. Risk factors for spinal infection include immunosuppression, recent invasive procedures, spinal implants, and intravenous drug use (38). Eliciting these risk factors in the history of a patient with back pain may be pivotal for diagnosis. This is particularly important as these patients present with great variability in physical examination and laboratory findings. MRI is the imaging study of choice in cases of suspected spinal infection, although CT myelography may be useful if MRI is unavailable (38).

Urinary tract pathology. If a patient is more ill-appearing than is explained by a simple urinary tract infection, imaging to evaluate for a perinephric abscess, infected nephrolithiasis, or emphysematous pyelonephritis should be considered (41,42). Although most simple cases of sepsis secondary to urinary tract pathology can be managed medically, emergent urological or surgical intervention is warranted in these cases. Bedside ultrasound showing nephrolithiasis, hydronephrosis, or a perinephric fluid collection can be quickly done in the ED and may change management. CT imaging may take longer to obtain but will also help evaluate for other causes of pyuria, including appendicitis (43,44).

Abdominal sepsis. Abdominal sepsis is relatively common, but diagnosis is sometimes hampered by the patient's mental status or body habitus. Conscious patients may be able to localize their discomfort, but in the obtunded patient, an especially thorough abdominal examination is vital. Absence of bowel sounds, abdominal distention, and rigidity should raise concern for an intra-abdominal source of infection (44–46). In the obtunded or unconscious patient who is unable to verbalize pain, grimacing, guarding, or reflex tachycardia to palpation can be used to localize pain. Causes of intra-abdominal infection include abscesses (perinephric, ovarian abscess), spontaneous bacterial peritonitis, cholecystitis or cholangitis, ruptured hollow viscus, or infection of the gastrointestinal tract (appendicitis, colitis, diverticulitis) (45). Pelvic examination may assist in the diagnosis of tubo-ovarian abscesses and pelvic inflammatory disease and may identify the infectious source in toxic shock syndrome (46). Although occult intra-abdominal infections may initially respond to empiric antimicrobial treatment, recognition of these infections is vital, as aggressive source control through surgical or vascular interventional means is typically necessary for treatment (44,45,47).

Indwelling devices. Infections are a well-recognized and common complication of indwelling devices such as central venous catheters, ports, and dialysis access. Physical examination of any ill patient with invasive devices should include examination of the device site, taking particular note of erythema or purulent drainage. Signs of exit-site infection, however, are not sensitive for the presence of line-associated bacteremia. One study suggested that only 4.6% of catheter-associated bacteremia cases were associated with purulent drainage at the exit site (48). In the absence of clear physical examination findings for line-associated bacteremia, clinical suspicion is required for diagnosis of line infection in patients with indwelling devices. If possible, the device should be promptly removed and cultured (49,50).

Broadening the Differential

Although a reflex diagnosis of sepsis is tempting for the tachycardic, ill-appearing patient with an elevated temperature, it is important to consider life-threatening conditions that mimic sepsis. *Fever* and *hyperthermia* are distinct clinical entities. Although both words describe a state of elevated body temperature, the two processes are physiologically different. Fever results from the normal thermoregulatory system operating at a higher set point, typically in response to an infection (51). Hyperthermia, on the other hand, results from a defect in the thermoregulatory system itself, leading to pathologically elevated body temperature (52,53). This distinction is important because hyperthermia does not respond to antipyretics like fever, and suspicion for hyperthermia rather than fever may reveal a potentially reversible pathology (51,53). If a seemingly septic patient does not appear to have an obvious source or is not improving with antimicrobials and fluids, it is important to broaden the differential to conditions that mimic its presentation (Table 3).

Sepsis Mimics, Presentation, and Management

Neuroleptic malignant syndrome (NMS). NMS is a clinical syndrome of altered mental status, autonomic instability, hyperthermia, and classic "lead pipe" rigidity

Table 3. Sepsis Mimics, Presentation, and Management

Condition	Presentation	Management
Sepsis	Fever or hypothermia, tachycardia, leukocytosis or leukopenia, tachypnea	Fluids, antibiotics, source control
Neuroleptic malignant syndrome	Altered mental status, dysautonomia (hyperthermia, tachycardia), rigidity	Supportive care, dantrolene sodium, bromocriptine
Serotonin syndrome	Altered mental status, hyperthermia, tachycardia, hyperreflexia/clonus	Supportive care; consider cyproheptadine
Malignant hyperthermia	Hyperthermia, tachycardia, hypercarbia, muscle rigidity in the setting of volatile anesthetic or depolarizing muscle relaxants	Dantrolene sodium, cooling measures, treatment of hyperkalemia
Salicylate toxicity	Hyperthermia, tachycardia, hyperpnea, gastrointestinal irritation, tinnitus, triple acid-base disturbance	Sodium bicarbonate infusion; severe cases may require dialysis
Anticholinergic toxicity	Tachycardia, agitation, dilatated nonreactive pupils, urinary retention, anhidrotic hyperthermia	Supportive care; consider physostigmine
Sympathomimetic toxicity	Tachycardia, agitation, hyperthermia, hypertension, dilatated reactive pupils	Benzodiazepines
Thyroid storm	Tachycardia, hyperthermia, agitation, lid-lag, ophthalmopathy, hand tremor	Beta-blockers, thioamides, iodine preparation, steroids
Nonexertional heat stroke	Fever, tachycardia, neurologic manifestations	Evaporative and convective cooling

associated with the use of certain medications. NMS may be caused by medications that act as dopaminergic antagonists or, less commonly, withdrawal from medications with dopaminergic effects, such as those used in the treatment of Parkinson's disease (54,55). Although most of the medications implicated with NMS are neuroleptics, it is important to remember that antiemetics, central nervous system stimulants, and other medications can precipitate NMS as well. Haloperidol and fluphenazine are the medications most commonly associated with NMS (54). Risk factors include higher doses of neuroleptic agents, recent or rapid dose escalation, a switch from one agent to another, and parenteral administration. Although NMS typically develops in the first 2 weeks of therapy, this syndrome can occur after a single dose or after years of treatment with the agent (56). A review of the patient's medication list is needed. Management is prompt discontinuation of the offending agent as well as aggressive support of the cardiopulmonary system, maintenance of normothermia and euvolemia, and prevention of complications including deep venous thrombosis, acute renal failure, and cardiac dysrhythmias (54–56). In severe cases of muscle rigidity, intravenous dantrolene sodium or oral bromocriptine mesylate may assist (56).

Serotonin syndrome (SS). SS is a clinical syndrome of altered mental status, neuromuscular abnormalities, and autonomic hyperactivity caused by excess serotonin, typically due to therapeutic medication or interactions between medications (57). The neuromuscular abnormalities include hyperreflexia, clonus, and muscle rigidity, which may lead to muscle breakdown and resultant rhabdomyolysis (58,59). Common medications that may lead to SS include linezolid, fentanyl, and any selective serotonin reuptake inhibitor (SSRIs) (59). SSRIs are the first-line treatment for a large spectrum of psychiatric disorders and are among the most commonly prescribed medications in the United States. Incidence of SS has risen in recent years due to increased use of SSRIs (60). SS is a clinical diagnosis, and there is no laboratory test to confirm the diagnosis (57). The symptoms of SS are highly variable and range from mild to acutely life-threatening. The Hunter criteria for serotonin syndrome (Table 4) outline the symptoms needed to make a diagnosis of SS (61). Initial management includes aggressive supportive therapy to normalize vital signs, benzodiazepines for agitation, and discontinuing all serotonergic agents. If supportive management is insufficient or ineffective, use of cyproheptadine (under the guidance of a toxicologist) should be considered (57). If neuromuscular paralysis becomes necessary to control neuromuscular rigidity, nondepolarizing agents should be used, as succinylcholine may exacerbate the hyperkalemia associated with the rhabdomyolysis.

Table 4. Hunter Criteria for Serotonin Syndrome (61)

Serotonergic agent plus one of the following:
Spontaneous clonus
Inducible clonus and agitation or diaphoresis
Ocular clonus and agitation or diaphoresis
Tremor and hyperreflexia
Hypertonia, temperature > 38°C, and ocular or inducible clonus

Hunter Criteria for Serotonin Syndrome

Malignant hyperthermia (MH). MH is an autosomal dominant genetic disorder that results in a hypermetabolic response to volatile anesthetics and depolarizing muscle relaxants such as succinylcholine (62). It is caused by the release of excessive calcium from the sarcoplasmic reticulum in response to these medications, leading to uncoupling of oxidative phosphorylation and a pathologic rise in metabolic rate (63). MH is characterized by hyperthermia, tachycardia, tachypnea, hypercarbia, increased oxygen consumption, and muscle rigidity, which may lead to rhabdomyolysis. In the ED, this is most likely to present after an intubation using succinylcholine. This diagnosis should be considered if an intubated patient is deteriorating post intubation. In the inpatient setting, MH should be considered in patients who recently received volatile anesthetics or succinylcholine (63). Dantrolene sodium is the antidote to MH and should be loaded at a dose of 2.5 mg/kg intravenously followed by bolus doses of 1 mg/kg until symptoms abate (64). Treatment of hyperkalemia caused by rhabdomyolysis may also be required. Cooling measures should be instituted to prevent end-organ effects of hyperthermia. Patients and families should be counseled after recovery to prevent future reactions in the patient as well as the family; genetic testing is available (62,64).

Salicylate overdose. Salicylate toxicity can easily be confused for sepsis. Salicylate toxicity is most commonly caused by aspirin, but salicylates are ingredients in common household items such as oil of wintergreen and certain wart removers and keratolytics (65). Patients with salicylate toxicity often display tachycardia, tachypnea, and elevated temperature, much like patients with infection. This is due to interference with aerobic metabolism, which also leads to lactic acidosis (65). The classic triad of salicylate toxicity is hyperpnea (increased depth and rate of breathing), tinnitus, and gastrointestinal irritation as manifested by abdominal pain, vomiting, and diarrhea (66). Tinnitus may be difficult to elicit if the patient is altered and may be described by patients as hearing loss rather than "ringing in the ears." Patients with salicylate toxicity can display the classic "triple acid-base disorder" on laboratory testing, which will show a

respiratory alkalosis (from hyperventilation), a compensatory non-anion-gap metabolic acidosis, and an anion-gap metabolic acidosis (from lactic acid accumulation) (65). Prompt recognition of salicylate toxicity is important for the initiation of appropriate management through systemic alkalinization with sodium bicarbonate (67).

Anticholinergic overdose. Substances with anticholinergic properties are ubiquitous in medicine and nature and include antihistamines, tricyclic antidepressants, tainted recreational drugs, and jimson weed. Like sepsis, anticholinergic toxicity may present with high temperature, agitation or altered mental status, and tachycardia (68). Clues to anticholinergic toxicity include dilatated nonreactive pupils, urinary retention, and anhidrotic hyperthermia (whereas the septic patient may be diaphoretic) (68). Management of anticholinergic toxicity is supportive and includes benzodiazepines for agitation or seizures (68). An antidote is available in the form of physostigmine, an acetylcholinesterase inhibitor. Indications for, and the use of, physostigmine are controversial, and the decision to use this medication should be made with the aid of a toxicologist (68,69).

Sympathomimetic intoxication or overdose. Overstimulation of the sympathetic system leads to hyperthermia, tachycardia, altered mental status, and dilatated but reactive pupils (52). Sympathomimetic substances can cause hyperthermia through multiple mechanisms, including directly through alpha-receptor agonism or indirectly through heat production from agitation (70). Illicit recreational drugs resulting in sympathomimetic toxicity include cocaine, 3,4-methylenedioxymethamphetamine, phencyclidine, and amphetamines and their derivatives. Alcohol withdrawal, a fairly common presentation to the ED, can present similarly to intoxication with sympathomimetics (52). History is key to these diagnoses. Benzodiazepines are the cornerstone of management of sympathomimetic intoxication or overdose, as well as alcohol withdrawal, and should be titrated to level of psychomotor agitation (70).

Thyroid storm. Thyroid storm is a rare condition characterized by severe manifestations of thyrotoxicosis. It can be caused by overdose of therapeutic thyroid hormone or may present in patients with underlying thyrotoxicosis. In patients with underlying thyrotoxicosis, thyroid storm may be seemingly unprovoked, or may be precipitated by an acute event such as trauma, infection, or childbirth (71–73). Presenting symptoms include tachycardia, hyperthermia, diarrhea, and agitation. Cardiovascular collapse and liver failure may also occur (71). Laboratory abnormalities may include a severely low or undetectable thyroid-stimulating hormone. Physical examination may reveal findings such as altered mental status, widened pulse pressure, ophthalmopathy, hand tremor, enlarged thyroid, and lid lag. Acute management of thyroid storm includes immediate treatment with a beta-blocker, a thioamide, an iodine preparation (at least one hour after the thioamide), and glucocorticoids (71–73). Antimicrobials are recommended to cover infectious etiologies, which may trigger thyroid storm (73).

Heat stroke. Nonexertional heat stroke typically affects older individuals with underlying chronic medical conditions that impair thermoregulation, prevent removal from a hot environment, or decrease access to adequate hydration (74). Exertional heat stroke more often occurs in young and healthy individuals in the setting of excessive exertion that overwhelms the body's thermoregulatory mechanisms (74). The diagnosis of nonexertional heat stroke is a diagnosis of exclusion made clinically based upon an elevated core body temperature (generally >40°C), central nervous system dysfunction as manifested by encephalopathy, and exposure to severe environmental heat (74). Liver function testing often reveals elevated liver enzymes. Early and aggressive evaporative and convective cooling are the treatments of choice and result in decreased morbidity and mortality (75,76). Common methods for cooling in the ED include ice water immersion, evaporative cooling, and lavage with cooled fluids (75,76). Less commonly, dantrolene may be used for refractory hyperthermia, but data on its efficacy are mixed and limited (77,78).

CONCLUSIONS

In the acutely ill patient without a urinary or lower respiratory tract source, other sources should be considered, including the musculoskeletal system, heart, nervous system, and abdomen as potential sources of sepsis. A focused physical examination, abdominal CT scan, and lumbar puncture may help determine the etiology of infection and tailor treatment. In the patient with suspected sepsis, early and aggressive treatment with antimicrobials is paramount and has a significant effect on patient outcomes. In the seemingly septic patient who does not respond to antimicrobials and fluids, other acutely life-threatening conditions that can mimic sepsis should be considered. A review of the patient's medical history, medications, and recent exposures can assist in identifying the source of the patient's elevated body temperature and tachycardia. Consideration of potential sources and other mimics of sepsis is needed in the ED.

Acknowledgments—MB, BL, and AK conceived the idea for this manuscript and contributed substantially to the writing and editing of the review. This manuscript did not utilize any grants, and

it has not been presented in abstract form. This clinical review has not been published, it is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. This review does not reflect the views or opinions of the U.S. government, Department of Defense, U.S. Army, U.S. Air Force, or SAUSHEC EM Residency Program.

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ARTICLE SUMMARY

1. Why is this topic important?

Sepsis is a common presentation to the emergency department (ED) and is the source of significant burden on the health care system in terms of expenditure and patient morbidity and mortality. Early recognition and appropriate aggressive management of sepsis leads to significant reduction in patient morbidity and mortality.

2. What does this review attempt to show?

This review addresses the evaluation of the acutely ill-appearing patient without an apparent source, focusing on occult sources of infection and conditions that mimic sepsis.

3. What are the key findings?

Pulmonary and urinary sources of sepsis are the most common, but other sources may be present. Musculoskeletal, cardiac, neuraxial, abdominal, and indwelling foreign body sources of sepsis should be considered in the acutely ill patient. In the seemingly septic patient who does not respond to antimicrobials and fluids, the differential should be broadened to include acutely life-threatening conditions that can mimic sepsis. A review of the patient's medical history, medications, and recent exposures can assist in identifying the source of the patient's elevated body temperature and tachycardia. This is important, as many conditions that mimic sepsis cause significant mortality and are reversible if recognized in a timely manner.

4. How is patient care impacted?

Consideration of potential occult infectious sources and sepsis is needed in the ED, as recognition of these entities leads to early appropriate management and improvement in patient outcomes.