Chapter 10
Organ Dysfunction in Sepsis: Brain, Neuromuscular, Cardiovascular, and Gastrointestinal

Brian J. Anderson and Mark E. Mikkelsen

Introduction

Sepsis-related organ dysfunction is common, complex, and associated with significant morbidity and mortality. Its presence defines sepsis, in addition to sepsis-related hypotension and sepsis-related hypoperfusion [1], and it has utility as a risk stratification tool to identify those at increased risk of death. Organ failure manifests in myriad ways in sepsis, mediated by a complex interplay between preexisting organ function and acute inflammation and endothelial and coagulation dysfunction incited by the infectious insult. Given the pathophysiology of sepsis-associated organ dysfunction, each organ in the body is known to manifest tissue injury in response to sepsis that is clinically apparent to various degrees (Table 10.1).

Using readily available diagnostic criteria to define organ dysfunction, a number of scoring systems have been validated to define sepsis and predict outcomes [1–3]. Given the prevalence and frequent need for life support in the setting of sepsis-related respiratory and renal failure, lung injury and kidney injury are covered in separate chapters. In this chapter, we focus on non-pulmonary, non-renal sepsis-associated organ dysfunction. We begin by examining neurologic complications of sepsis, followed by examination of cardiovascular and gastrointestinal organ dysfunction.

B.J. Anderson, MD, MSCE
Pulmonary, Allergy and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Gibson 05002, 3400 Spruce Street, Philadelphia, PA 19104, USA
e-mail: brian.anderson@uphs.upenn.edu

M.E. Mikkelsen, MD, MSCE (✉)
Pulmonary, Allergy and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Gates 05042, 3400 Spruce Street, Philadelphia, PA 19104, USA
e-mail: mark.mikkelsen@uphs.upenn.edu

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Table 10.1 Clinically apparent organ dysfunction related to sepsis and criteria established to define sepsis [1–3]

Organ system	Clinical manifestation	Diagnostic criteria
Neurologic	Altered mental status Consciousness level Delirium	Glasgow Coma Scale Richmond Agitation-Sedation Scale (RASS) Sedation-Agitation Scale (SAS) Confusion Assessment Method for the ICU (CAM-ICU)
Neuromuscular	Myopathy Neuropathy Neuromyopathy Functional impairment	Medical Research Council (MRC) score Electrophysiology testing Barthel Index Functional Status Score for the ICU
Cardiovascular	Cardiomyopathy Arrythmia Myocardial ischemia Myocardial injury Hypotension	Echocardiogram Electrocardiogram Cardiac biomarkers Systolic blood pressure Mean arterial pressure
Respiratory	Tachypnea Hypoxemia	Use of mechanical ventilation Respiratory rate PaO_2:FiO_2
Gastrointestinal	Hepatocellular injury Biliary Intestinal	Alanine aminotransferase Aspartate aminotransferase Bilirubin Ileus
Renal	Acute kidney injury	Serum creatinine Urine output
Hematologic	Thrombocytopenia Coagulopathy Disseminated intravascular coagulopathy	Platelet count Protime Activated partial thromboplastin time Fibrinogen
Skin	Reduced capillary refill Mottling Livedo reticularis	Physical examination

Brain Dysfunction

Introduction

One of the initial signs of sepsis is often a change in mental status, one of many clinical manifestations that define its presence. In the literature, this clinical manifestation is known as sepsis-associated encephalopathy or septic encephalopathy, in addition to the more general terms of coma or delirium. Acute brain dysfunction, defined as coma and/or delirium during the critical illness state, is common and is associated with short- and long-term morbidity and mortality.

Diagnosis

Sepsis-associated encephalopathy is defined variably in the literature, ranging from objective measures such as an abnormal Glasgow Coma Score (GCS) to subjective measures such as an abnormal mental status according to a health provider [4–9]. Many studies now use coma and delirium as outcomes to describe brain dysfunction in critical illness because they utilize reliable and valid measurements to define these states. However, as GCS is included in many well-accepted illness severity scores, it remains an important measure of neurologic function that is routinely used in clinical practice.

At the bedside, an objective evaluation of consciousness is a vital initial step in the neurologic examination. Two of the more commonly used scales to assess consciousness are the Richmond Agitation-Sedation Scale (RASS) [10] and the Riker Sedation-Agitation Scale (SAS) [11], both of which can be used to screen for eligibility for delirium assessment. The RASS is a 10-point scale ranging from −5 to +4 (Fig. 10.1). A score of 0 corresponds to an alert and calm state, increasingly negative values correspond to deeper degrees of sedation, and increasingly positive values correspond to an increasingly agitated state [10]. The RASS has been validated against a variety of neurologic measures including neuropsychiatric evaluation, GCS, and electroencephalography [10]. In addition, the RASS has excellent inter-rater reliability that is superior to GCS [10]. Most studies define coma as a RASS of −4 or −5 and define deep sedation as a RASS of −3, −4, or −5 [12–40].

The most frequently cited method for diagnosing delirium in critically ill patients is the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Fig. 10.2) [12–37, 39–44]. The CAM-ICU is a well-validated screen for delirium with high sensitivity and specificity when compared to expert evaluation using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, has excellent inter-rater reliability, and can be administered to the nonverbal mechanically ventilated patient [43, 44]. Other strategies to identify delirium include the Intensive Care Delirium Screening Checklist (ICDSC) [38, 45–49], the Neelon and Champagne Confusion Scale [50], and the DSM criteria [45, 51, 52]. Strategies to measure delirium severity appear promising [53], but require further investigation before implementation in the clinical setting.

Ancillary neurologic testing, including EEG and brain imaging, frequently reveals nonspecific findings. Recent evidence suggests that certain malignant EEG patterns (e.g., triphasic spikes) correlate with abnormal brain MRI findings in sepsis (e.g., ischemic lesions, leukoencephalopathy) [54]. While these strategies have the potential to enhance our understanding of the neuropathology of sepsis-associated brain dysfunction [55–57], the clinical utility of these diagnostic studies remains uncertain.

From: Monitoring Sedation Status Over Time in ICU Patients: Reliability and Validity of the Richmond Agitation-Sedation Scale (RASS) JAMA. 2003;289(22):2983-2991. doi:10.1001/jama.289.22.2983

Table 1. The Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert and calm		
−1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)	Verbal stimulation
−2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	
−3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Physical stimulation
−5	Unarousable	No response to voice or physical stimulation	

Procedure for RASS Assessment

1. Observe patient
   - Patient is alert, restless, or agitated. — Score 0 to +4
2. If not alert, state patient's name and say to open eyes and look at speaker.
   - Patient awakens with sustained eye opening and eye contact. — Score −1
   - Patient awakens with eye opening and eye contact, but not sustained. — Score −2
   - Patient has any movement in response to voice but no eye contact. — Score −3
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   - Patient has any movement to physical stimulation. — Score −4
   - Patient has no response to any stimulation. — Score −5

Adapted with permission.[29]

Fig. 10.1 Consciousness assessment: Richmond Agitation-Sedation Scale as an example. From: Monitoring Sedation Status Over Time in ICU Patients: Reliability and Validity of the Richmond Agitation-Sedation Scale (RASS) JAMA. 2003; 289(22):2983–2991 doi:10.1001/jama.289.22.2983

Epidemiology

Acute brain dysfunction occurs in the majority of critically ill septic patients. Early studies of sepsis-associated encephalopathy reported an incidence as high as 62 % [4–8]. The incidence of coma and delirium among patients with sepsis is difficult to know with certainty because most studies have enrolled critically ill patients with a variety of diagnoses, and the rates may vary by disease process. Although few studies have evaluated coma as a distinct outcome from delirium, an incidence of coma between 56 and 92 % [14, 15, 23, 38] with a median duration of approximately 2–3 days has been reported [12–14, 23]. However, many studies exclude patients

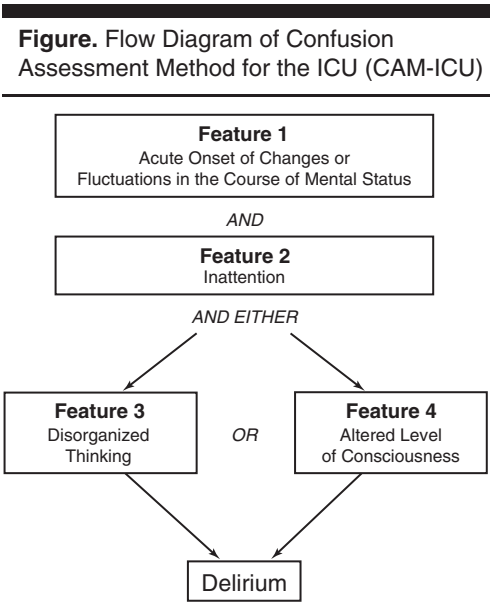

Fig. 10.2 Delirium assessment according to the Confusion Assessment Method for the ICU (CAM-ICU). From: Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703–10

with persistent coma, accounting for roughly 2–18 % of patients, so the true burden of coma may be underestimated [13, 20–22, 33–36, 40, 41, 46]. As many as 75–90 % of critically ill patients suffer delirium during their illness [12–21, 33–38, 41, 42, 45–47, 50–52]. Delirium occurs early in the ICU course, with an onset usually within the first 1–4 days [20, 41, 45, 51, 52], and lasts for an average of approximately 2–5 days [12–14, 17, 18, 20–22, 33, 35, 41, 51, 52] representing approximately 50 % of all ICU days in one study [21].

Risk Factors

Studies evaluating risk factors for delirium have not exclusively enrolled patients with sepsis but provide some important findings. Observational studies in a variety of critically ill populations have reported that age [40], severity of illness [24, 40, 41, 46, 50], dementia or preexisting cognitive impairment [16, 41, 50], hypertension [45, 46], current smoking [45, 50], alcoholism [46, 50], and the use of restraints [58] are all risk factors for delirium. Sedative medications have also been identified as risk factors for delirium. While studies have reported conflicting results demonstrating a relationship between opiates and delirium [33–35, 38, 40, 41, 45, 50], in part due to the association between pain and delirium, benzodiazepines have more consistently been identified as a risk factor [13, 24, 33–35, 38, 40, 41, 45, 46, 50]. Of interest, a genetic predisposition to delirium may exist, as apolipoprotein E epsilon 4 genotype has been associated with increased risk and/or duration of delirium [36, 59–64].

Although the pathophysiology of sepsis-associated delirium remains unclear, inflammation, microglial activation, and disruption of the blood-brain barrier are frequently implicated [55–57]. Based on the inflammatory hypothesis, a number of studies have investigated statins as an intervention that may mitigate the risk of delirium development or severity. While the effect of prehospital statin use remains unclear in the surgical patient population [65–68], recent evidence suggests that continuing statins in prehospital statin users may reduce the risk of delirium, and this relationship may be of greatest benefit early in the course of critical illness in patients with sepsis [32, 42].

Prognosis

Acute brain dysfunction during sepsis is associated with worse outcomes. Early studies of sepsis-associated encephalopathy demonstrated an association with a longer duration of mechanical ventilation [7], longer ICU and hospital length of stay [7], and higher mortality [4–9]. Early deep sedation (RASS < 2) has also been shown to be associated with longer duration of mechanical ventilation and mortality [37]. Delirium, more specifically, is associated with myriad sequelae including longer duration of mechanical ventilation [13, 34, 39], longer ICU and hospital length of stay [19, 21, 24, 34, 39, 46, 51, 52], and mortality [13, 20, 24, 39, 46]. Furthermore, there appears to be a dose-response relationship, with longer duration of delirium (i.e., higher dose) being associated with future functional disability [12] and both short- and long-term mortality [13, 21, 22, 39].

Patients who experience delirium are also at higher risk of long-term cognitive impairment (LTCI) [13, 14, 17, 18]. LTCI has been reported in as many as 78 % of critical illness survivors at 1 year depending on the type of cognitive test used [14, 15, 17, 69, 70]. In the largest study to date, which enrolled patients with shock or respiratory failure, 34 % of patients had cognitive impairment at 1 year similar in severity to patients with moderate traumatic brain injury [14]. Radiographic studies in critical illness survivors have revealed an association between delirium and volume loss in specific brain regions, as well as disruption of the white matter tract integrity, providing further evidence for a link between delirium and LTCI [71, 72].

Prevention and Treatment

Several clinical trials in a variety of critically ill populations have evaluated interventions aimed at preventing or treating coma and/or delirium. Interventions have included pharmacological and non-pharmacological interventions, as well as different sedation regimens.

The most successful strategies to date have prioritized daily sedation interruption, sedation protocols, and early mobilization. Daily sedation interruption has been

shown to reduce the duration of mechanical ventilation, the number of diagnostic tests ordered to assess changes in mental status [73], and to reduce duration of coma [30], but an effect on the incidence or duration of delirium has not been demonstrated consistently [30, 47]. Implementation of a protocol for de-escalation of excess sedation was associated with reduced odds of developing delirium in one before and after study in a trauma-surgical ICU [31]. Finally, interruption of sedation, paired with early mobilization, has been shown to reduce the duration of delirium [27].

Pharmacological interventions have included the use of antipsychotics, anticholinergics, and different sedation regimens. Antipsychotics may reduce the duration of delirium [48], but additional studies are still ongoing [26]. In the absence of demonstrative data to suggest the benefit of antipsychotic use to prevent or reduce the duration of delirium, and given potential harm [74–76], current guidelines do not recommend their routine use until additional data is available [77]. Rivastigmine, a cholinesterase inhibitor, was associated with longer duration of delirium and higher mortality in one study [25]. Several randomized clinical trials have suggested that dexmedetomidine may be the preferred sedative in treatment of coma and/or delirium [23, 28, 29, 78]. Sedation with dexmedetomidine is associated with lower rates of coma and more coma/delirium-free days when compared to lorazepam [23, 78] and with lower rates of delirium when compared to midazolam [29]. Ultimately, further research is needed to identify preventive and treatment options aimed at reducing rates and duration of acute brain dysfunction in order to potentially improve outcomes.

Neuromuscular Dysfunction

Introduction

Neuromuscular dysfunction in sepsis has been defined by a variety of terms including ICU-acquired weakness, ICU-acquired paresis, critical illness polyneuropathy, critical illness myopathy, or critical illness neuromyopathy. Its development is associated with functional disability that frequently endures and an increased risk of long-term mortality [79].

Diagnosis

Neuromuscular dysfunction in critical illness has been variably defined with some studies using clinical parameters such as muscle strength testing, others using electrophysiological testing, and some using a combination of the two. In the literature, the terms used to describe neuromuscular dysfunction are often used interchangeably prompting the proposal for uniform nomenclature and diagnostic criteria [80].

Table 10.2 Strength testing for ICUAW[a]

Muscle strength	Score
No movement is observed	0
Fasciculation or trace movement observed	1
Movement if the resistance of gravity is removed	2
Movement against gravity	3
Movement against some resistance	4
Movement against full resistance	5

Adapted from Medical Research Council (MRC) Scale for Muscle Strength [81]

[a]Testing for ICUAW involves bilateral evaluation using the above scale of six muscles: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion

For the purposes of this review, we refer to this complication as ICU-acquired weakness (ICUAW). ICUAW describes clinically detectable weakness in the setting of critical illness with no other identifiable causes [80]. Critical illness polyneuropathy (CIP) refers to patients with ICUAW and evidence of axonal polyneuropathy on electrophysiological testing [80]. Critical illness myopathy (CIM) describes patients with ICUAW and either electrophysiological or histological myopathy [80]. Critical illness neuromyopathy (CINM) refers to patients who have ICUAW and evidence of both neuropathy and myopathy based on electrophysiological and/or histological testing [80].

The most commonly published method for identifying clinical muscle weakness is use of the Medical Research Council (MRC) muscle strength scale, which rates the strength of 12 muscles on a scale from 0 to 5 (Table 10.2) [81]. Most studies define ICUAW as a MRC sum score of <48 [82–89]. While the MRC scale has been shown to have good inter-rater reliability [82, 83, 86, 88, 90], it requires an interactive patient and is often not feasible to use early in critical illness given the frequency of coma and/or delirium [82]. A less commonly used measure of strength is the Function Disability Score [91, 92]. Some more recent studies have evaluated the use of ultrasonography, handgrip strength [83, 90, 93, 94], or portable dynamometry [94] as diagnostic tools or measures of clinical strength but additional studies are necessary.

Epidemiology

The true incidence of neuromuscular dysfunction in sepsis is uncertain because most studies enrolled patients with a variety of ICU diagnoses, evaluated patients at different times across studies, and focused on the most severely ill (e.g., prolonged ICU length of stay). In studies that enrolled septic patients, the incidence of abnormal electrophysiological testing ranged from 50 to 76 % [95–97], supporting that neuromuscular dysfunction is common after sepsis.

Additional estimates of the incidence of neuromuscular dysfunction come from studies enrolling all intensive care unit patients regardless of diagnosis or duration of illness. In these studies, ICUAW was diagnosed in 11–18 % based on MRC criteria [89, 98] and 21–57 % based on abnormal electrophysiological testing alone [99, 100]. Among patients admitted with acute respiratory distress syndrome, the incidence of ICUAW appears higher, estimated at 54 % [101]. The rate of neuromuscular dysfunction is higher in critically ill patients who remain in the ICU for at least 3–7 days, with an incidence of ICUAW based on MRC score of approximately 25 % [83, 84]. In this population, the combined incidence of CIP, CIM, or CINM ranges from 33 to 57 % [91, 102, 103], and the incidence of abnormal electrophysiological testing is 32–79 % [104–107]. Additional studies evaluating patients who required at least 10–14 days of mechanical ventilation demonstrated an incidence of ICUAW of 24 % by MRC criteria [98] and an incidence of neuromuscular dysfunction diagnosed by electrophysiological testing alone of 63–75 % [108, 109].

Risk Factors

A multitude of risk factors have been suggested to be associated with the development of neuromuscular dysfunction in critical illness. Risk factors include age [85], gender [84, 98], severity of illness [98], number of organ failures [84, 99], duration of mechanical ventilation [84], renal replacement therapy [98], gram-negative bacteremia [98], sepsis [107], hyperglycemia [98], aminoglycosides [98], and corticosteroid use [84, 110, 111].

Prognosis

Patients with neuromuscular dysfunction in critical illness have longer ICU and hospital lengths of stay [83, 84, 101, 107, 108], longer duration of mechanical ventilation [83, 84, 91, 99, 101, 107, 108, 112, 113], higher ICU readmission rates [83, 114], and higher mortality [79, 83, 96, 105, 108]. In addition, muscle weakness in long-term ventilated patients is associated with pharyngeal dysfunction and symptomatic aspiration [87]. Although patients with ICUAW can improve over time [84, 85], additional evidence demonstrates that critical illness results in prolonged neuromuscular dysfunction and decreased long-term physical function. Survivors of the acute respiratory distress syndrome, which is frequently the result of sepsis, have reduced exercise capacity [15, 85, 115, 116] and report subjective muscle weakness up to 2 years after their illness [85, 115, 116]. In addition, approximately one third of critically ill patients report a disability with their activities of daily living (ADL) 1 year out from critical illness [12]. Finally, studies evaluating quality of life in ICU survivors show low physical function domain scores lasting for several years [117].

Treatment and Prevention

Several studies have evaluated treatments and/or preventive strategies for neuromuscular dysfunction in critically ill patients, although these studies did not specifically enroll patients with ICUAW, CIP, CIM, or CINM. Early mobilization results in improved neuromuscular outcomes including an increased proportion of patients achieving functional independence at the time of hospital discharge [27], shorter time for patients to reach specific milestones such as getting out of bed or walking [27, 118], shorter ICU length of stay [118], shorter duration of mechanical ventilation [27], and a trend toward lower rates of ICUAW [27]. Intensive insulin therapy is associated with a reduced incidence of neuromuscular dysfunction diagnosed based on electrophysiological testing [119–121]; however, additional studies have reported higher risks of adverse events and mortality with intensive insulin therapy [122–124]. Given recent evidence showing that early mobilization promotes euglycemia, the preferred approach at present is to pair sedative interruption, spontaneous breathing trials, and early mobilization with a less intensive insulin therapy protocol [125, 126]. Transcutaneous neuromuscular electrical stimulation may lead to improvement in muscle strength and reduce the incidence of ICUAW, but confirmatory trials are warranted before this technology can be recommended [127]. Recent evidence also suggests that post-discharge rehabilitation after sepsis may reduce long-term mortality, but further investigation is needed [128].

Cardiovascular Dysfunction

Introduction

Cardiovascular dysfunction in sepsis includes myocardial dysfunction, arrhythmias, and reduced systemic vascular resistance that typifies sepsis and frequently requires the use of vasoactive agents to support adequate perfusion pressures. In this chapter, we focus on myocardial dysfunction and arrhythmias.

Myocardial Dysfunction

Myocardial dysfunction can include left ventricular (LV) systolic or diastolic dysfunction as well as right ventricular (RV) systolic dysfunction and is most commonly diagnosed by echocardiography [129–141]. Some reports in the literature have used direct hemodynamic measurements [134, 142–149] to evaluate cardiac function in sepsis, but this is challenging as sepsis is often characterized by a high-output state, and the use of invasive hemodynamic monitoring has declined in recent years. By echocardiogram, approximately 29–67% of patients with sepsis or septic

shock have left ventricular (LV) systolic dysfunction (ejection fraction less than 45–55 %) [129–134], and approximately 15 % have severe LV systolic dysfunction (ejection fraction <30 %) [140]. Using direct hemodynamics or radionucleotide studies, as many as 56 % of septic ICU patients have LV systolic dysfunction [142, 143, 147]. LV diastolic dysfunction is also common [135, 139, 150], occurring in as many as 57 % of patients with sepsis [130]. Few studies have specifically evaluated right ventricular (RV) systolic dysfunction in sepsis, but it has been reported in as many as 32–52 % of patients [129, 142, 145]. Biventricular systolic impairment has been reported to occur in as many as 32 % of patients [142].

The presence of LV or RV systolic dysfunction in sepsis may be associated with higher rates of mortality, although results have been inconsistent [129–131, 147–149, 151, 152] across studies as the relationship may be modified by age and preexisting comorbid conditions [129–131, 147–149, 151, 152]. LV diastolic dysfunction in sepsis, however, has been shown to be associated with mortality in several studies [129, 130, 135, 141].

More recently, cardiac biomarkers have been evaluated as measures of myocardial dysfunction and/or subclinical myocardial ischemia [130–132, 135–138, 153–160]. Brain natriuretic peptide (BNP) and the N-terminal fragment of its prohormone (NT-proBNP), markers of left ventricular filling pressure and myocardial wall stretch, have been evaluated as markers of sepsis-associated myocardial dysfunction. BNP is elevated in approximately 71 % of patients with sepsis [130] but is not specific and may signify either LV systolic or diastolic dysfunction [131, 135, 159, 160]. Elevated BNP levels may be associated with mortality in septic patients, although the data are not conclusive [130, 131, 135, 159]. NT-proBNP has also been shown to be elevated in a wide range of 28–98 % of septic patients [130, 153, 161] and similarly may also be associated with mortality [130, 161]. Both troponin-I and troponin-T, markers of myocardial ischemia, are elevated in patients with sepsis. Elevations in troponin-I have been reported in 41–85 % of patients with sepsis [136–138, 154–158], while troponin-T has been reported to be elevated in 36–67 % of patients with sepsis [130, 138]. Both troponin-I and troponin-T have been proposed as markers of myocardial dysfunction [131, 136, 137] but are not specific and may signify LV systolic or diastolic dysfunction [131, 136, 137]. Elevated troponin in sepsis may be associated with longer ICU length of stay [137, 156] and increased mortality [130, 131, 136, 137, 155–157], although the clinical utility of these measures remains controversial.

Arrhythmias

The incidence of new-onset arrhythmias in critically patients is approximately 12 % [162]. The majority of new-onset arrhythmias are supraventricular tachycardias, most commonly atrial fibrillation [162]. New-onset ventricular arrhythmias are rare with an incidence of approximately 2 % [162]. Additional studies specifically in patients with sepsis report new-onset atrial fibrillation develops in approximately

6–8 % of patients [8, 162–169]. Sepsis appears to be a risk factor for atrial fibrillation and other tachyarrhythmias in both medical and surgical critically ill patients [167, 168, 170–174]. Atrial fibrillation during sepsis occurs within the first 3 days in the majority of patients [168, 169].

Risk factors for the development of arrhythmias in critical illness include age [162, 165, 166, 168, 169], history of paroxysmal atrial fibrillation [165, 169], history of coronary bypass [166], higher severity of illness [165], higher organ failure score [162, 168], lower left ventricular ejection fraction [165], need for mechanical ventilation [166], use of vasopressors [162], and presence of at least one episode of shock [163]. In addition, a recent clinical trial comparing low versus high blood pressure targets in septic shock demonstrated an increased incidence of new-onset atrial fibrillation in the high blood pressure target group presumably due to higher doses of vasopressors [175].

Several studies of noncardiac ICU patients (not exclusive to sepsis) demonstrate that patients with new-onset atrial fibrillation have longer ICU length of stay [163, 164, 168, 172, 173], a greater need for mechanical ventilation [163], and higher mortality rates [163–165, 171–173]. Additional studies evaluating new-onset atrial fibrillation specifically in patients with sepsis demonstrate an increased risk of inhospital stroke and inhospital mortality [167].

To our knowledge, no randomized controlled trials have been performed evaluating treatment of arrhythmias during sepsis nor have studies examined the optimal duration of therapy after developing new-onset atrial fibrillation related to sepsis. One open-label randomized trial of esmolol in patients with septic shock requiring vasopressor therapy with persistent tachycardia but not necessarily with an arrhythmia demonstrated an improvement in heart rate and mortality, but further studies are needed to confirm these findings [176].

Gastrointestinal Dysfunction

Introduction

Gastrointestinal dysfunction associated with sepsis includes liver dysfunction, ischemic hepatitis, and gastrointestinal hemorrhage. In addition, a common manifestation of sepsis that defines sepsis is the development of an ileus.

Hepatobiliary Dysfunction

Hepatobiliary dysfunction is generally identified by lab abnormalities including hyperbilirubinemia, elevated transaminases, and coagulopathy. See Chap. 10 for a detailed discussion of coagulopathy and hematologic dysfunction (e.g., thrombocytopenia) associated with sepsis.

The incidence of cholestasis is approximately 11 % in patients with sepsis [177], with studies in patients with bacteremia or endocarditis with or without sepsis reporting an incidence of hyperbilirubinemia ranging from 20 % when using a cutoff of serum bilirubin level ≥ 2 mg/dL up to 53 % when using a cutoff of serum bilirubin level ≥ 1.2 mg/dL [178–182]. Several other studies enrolling critically ill patients with a wide variety of ICU diagnoses report an incidence of hyperbilirubinemia ranging from 8 to 31 % when defined as a total bilirubin level ≥ 2 mg/dL [183–189]. Finally, in a large cohort of critically ill patients requiring mechanical ventilation, the incidence of hepatic failure was 6.3 % when defined as a total bilirubin ≥ 2 mg/dL in addition to elevated aminotransferase or lactate dehydrogenase levels [190].

Ischemic hepatitis can also complicate critical illness. To our knowledge, no study has evaluated the incidence of ischemic hepatitis specifically in patients with sepsis. However, in a study of 984 critically ill patients, the incidence of ischemic hepatitis defined as a ≥ 20-fold elevation of aminotransferase levels was 12 % [191]. In this study as well as other series of ischemic hepatitis, sepsis was identified as the inciting factor in 13–32 % of the cases [191–195]. Clinically relevant sequelae resulting from ischemic hepatitis include vascular changes consistent with hepatopulmonary syndrome [196], as well as an increased risk for both hypoglycemia and death [191, 197]. Patients with ischemic hepatitis who develop hyperbilirubinemia concomitantly appear to be at even higher risk for adverse outcomes, including nosocomial infections and death [194]. Fulminant hepatic failure is a rare complication of sepsis [198].

Risk factors for hepatobiliary dysfunction in critical illness include age [177, 179, 183, 189], male gender [188], severity of illness [177], degree of organ failure [177, 199], sepsis [184, 185, 199], presence of shock [183–185, 189], major surgery [184], use of positive end-expiratory pressure (PEEP) ventilation [184], gram-negative infection [177, 179, 184], number of blood transfusions [183, 185], and use of total parenteral nutrition [199].

Critical illness associated with hepatobiliary dysfunction is associated with a multitude of poor outcomes including longer ICU and hospital length of stay [177, 183, 186, 189], increased risk for acute respiratory distress syndrome [188], longer duration of mechanical ventilation [183], increased risk of gastrointestinal bleeding [183], and increased mortality [177, 181, 183, 185–190, 200]. Importantly, given the role of biliary transport in drug clearance and the frequency with which renal and hepatic dysfunction coexist in sepsis, impaired drug (e.g., antibiotic) clearance resulting in toxicity likely contributes to the adverse outcomes associated with multisystem organ failure. No specific therapies are currently available for treatment of hepatobiliary dysfunction outside of supportive care.

Gastrointestinal Hemorrhage

Gastrointestinal (GI) bleeding, usually the result of what has been termed stress ulcers, is another feared gastrointestinal complication of critical illness. Several studies have evaluated the incidence of GI bleeding in general critically ill patients,

and estimates range from 8 to 20 % [201–206] down to 0.2–1.5 % [207, 208] depending on the population studied, the definition used, and the frequency of prophylaxis. Risk factors for the development of GI hemorrhage include age [207], respiratory failure requiring mechanical ventilation [201, 204, 206, 208, 209], shock [202, 209], sepsis [207, 209], postsurgical infection [202, 210], renal failure [206, 209], and thrombocytopenia or coagulopathy [201, 204, 206, 208, 211]. The source of hemorrhage is most commonly ulceration of the stomach followed by the duodenum, with esophageal being the least common [202, 206, 208, 210, 211]. GI bleeding in critically ill patients is associated with a higher need for mechanical ventilation [201], longer duration of mechanical ventilation [201], longer ICU length of stay [207], and mortality [201, 206]. Although there have been no randomized controlled trials of stress ulcer prophylaxis specifically in patients with sepsis, a significant number of patients enrolled in the stress ulcer prophylaxis trials had a diagnosis of sepsis. As a result, current recommendations include stress ulcer prophylaxis, using proton pump inhibitors or H2-receptor antagonists, for patients with sepsis or septic shock who have bleeding risk factors [125].

Conclusion

In summary, sepsis-associated organ dysfunction is common and its development is associated with significant morbidity and mortality. In sepsis survivors, the consequences of sepsis-related organ dysfunction frequently endure, which highlights the importance of evaluation and identification of impairment and the timely use of interventions and rehabilitation to restore function.

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