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Sepsis

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1. EPIDEMIOLOGY AND CLINICAL RELEVANCE

1.1. Definitions

Sepsis is the clinical syndrome denoting systemic inflammatory response to an infection. There is some confusion over the use of the terms "bacteremia" and "septicemia." Most studies in the United States used the term bacteremia to denote a positive blood culture with evidence of infection. Septicemia was used to denote a state of microbial invasion from a portal of entry into the bloodstream that causes signs of illness. Sepsis syndrome was initially described by Bone et al. to identify a population of patients at risk for adult respiratory distress syndrome (ARDS) and death *(1)*.

In 1991, the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) developed a classification system for patients with severe infection and its sequelae to help standardize research protocols and allow comparisons with results of clinical trials. Use of the terms septicemia and septic syndrome was discouraged because they were ambiguous and often used inappropriately to imply bacteremia *(2)*. Standardized terms were developed and defined. Bacteremia is defined as the presence of viable bacteria in the blood. Infection is defined as the inflammatory response to the microorganisms of the invasion of normally sterile host tissues by those organisms. The systemic inflammatory response syndrome (SIRS) is used to denote the physiological response to inflammation/infection and the criteria are given in Table 1, which also defines four stages of increasing severity of sepsis. Sepsis is defined as SIRS plus evidence of infection (e.g., positive microbial culture).

There is evidence of a clinical progression of the SIRS from sepsis to severe sepsis and to septic shock showing that the ACCP classification is a hierarchical continuum of increased inflammatory response to infection. For example, Rangel–Frausto and co-workers *(3)* showed that 44–71% of patients in any category had progressed from a previous state of biologic response syndrome and the rest either progressed through more than two stages within a 24-h period or skipped a stage. Also, bacteremia rates, end-organ failure rates, and mortality increased with each subsequent stage of SIR.

Sepsis studies use standard guidelines to decrease recruitment time and increase the ability to generalize the study findings to the practice community *(4)*. Most of the sepsis studies in the elderly were done before 1991, so that bacteremia was used as for the

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Table 1
Definitions for Sepsis and Organ Failure[a]

Systemic inflammatory response syndrome (SIRS)	Four stages of sepsis
Two or more of the following conditions: 1. Temperature >38°C or <36°C 2. Heart rate >90 beats p min 3. Respiratory rate >20 beats p min $PaCO_2$ or <32 mmHg 4. WBC >12,000/mm^3, <4,000/mm^3, or >10% band forms	**Severe sepsis**: sepsis associated with organ dysfunction, hypoperfusion, hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. **Sepsis-induced hypotension:** a systolic blood pressure <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes for hypotension. **Septic Shock**: sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured. **Multiple organ dysfunction syndrome (MODS)**: presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

[a]Adapted from Ref. *2*; $PaCO_2$ = arterial partial pressure of carbon dioxide; WBC = white blood cell.

early phase of sepsis and septicemia denoted a severe infection. This chapter preserves these terms as their originals and also implies them as parts of sepsis.

1.2. Epidemiology

In the United States, sepsis was diagnosed in approximately 2.5 million patients in the period 1979–1987, and accounted for $5–10 billion in annual health care expenditures *(5,6)*. Overall, the incidence of sepsis is 2–2.6 cases per 100 admissions and is higher in the elderly and patients with multiple comorbidities *(7,8,9)*.

Sepsis has a mortality sevenfold higher than other general medical conditions *(10)*. It affects up to 25% of all intensive care unit patients and is the most common cause of death in the noncoronary intensive care unit *(11)*. Sepsis was ranked third among infectious diseases as a cause of death, following respiratory tract infections and HIV/AIDS. The overall mortality rate of sepsis varies between 18% and 33%, increasing to 40%–80% in patients with septic shock *(12)*.

The mortality of bacteremia in the elderly varies from 15–40% (*see* Table 2). A prospective study by Knaus *(9)* found that the 28-d mortality of sepsis increased with age from 26–33% in the persons under 65 yr, compared with 35–42% in the persons aged 65 and older. The higher mortality is observed mostly in older subjects with nonfatal underlying illnesses *(15)*. This point emphasizes that old age alone is not a poor indicator of ultimate outcome.

From 1980–1992, the death rate from sepsis increased 83% from 4.32 per 100,000 population to 7.7 per 100,000 population. The recent incidence and mortality of sepsis in the elderly are not available from the national databases. However, the death certificate data from 1980 and 1992 showed that there was a 25% increase in the rate of infectious disease deaths, and the persons aged 65 yr and older had the highest death rate *(13)*. Two possible explanations for this increase could be increasing awareness of physicians and the real increasing risk of sepsis. The mortality rate from the death certificate data could be overestimated because there were comorbidities independent of the occurrence of sepsis in about 50% of all septic patients, and severe underlying diseases could be found in up to 95% *(10,14)*. The severity of the sepsis and the degree of related organ dysfunction makes comparison between the studies difficult, so it is not surprising that some studies show that mortality rate of sepsis in the elderly is unchanged *(10,15,16)*.

2. CLINICAL MANIFESTATIONS

2.1. Pathophysiology

Sepsis results from infection with a variety of microbes, especially Gram-negative and Gram-positive bacteria and fungi; clinical studies have documented that clinical symptoms are essentially identical with all organisms *(17)*. The process of sepsis begins with the proliferation of microorganisms at a nidus of infection. The organisms can invade the bloodstream directly or release inflammatory mediators into the bloodstream. These mediators are composed of both structural components of the organisms such as teichoic acid and endotoxin, and synthetic products such as exotoxins, which cause a systemic proinflammatory reaction by stimulating the release of endogenous mediators such as tumor necrosis factor (TNF-α)-alpha; interleukins (IL)-1,2,4,6,8; platelet-activating factor; eicosanoids; α-interferon, granulocyte–macrophage colony-stimulating factor; endothelial-derived releasing factor; endothelin-1; and complement. Normally, the body regulates itself by counteracting the proinflammatory stage by production of such factors as interleukin-10 and -11, soluble TNF-α receptors, and IL-1 receptor antagonists. If the equilibrium is lost, however, these mediators can cause systemic damage, including endothelial damage, microvascular dysfunction, and impaired tissue oxygenation and organ injury *(18)*.

Aging has a profound effect on immune function. Immune senescence is characterized by a dysregulation of the immune system, especially in the balance of Th1 and Th2 helper cells that potentially make elderly persons more susceptible to bacterial and virus infections than younger adults. There is, however, no consistent correlation of cytokine production with the severity of the sepsis. The phagocytes (neutrophils, monocytes, and macrophages) have subtle abnormalities that can be detected only by quite sophisticated testing, and thus these minor defects most likely have little impact on

Table 2
Factors Contributing to the Severity of Sepsis in Elderly Patients[a]

Aging changes in various organ systems	Effect of sepsis on various organ systems	Clinical outcome and manifestations
Neurological		
Atherosclerotic plaques, aneurysms, thrombi, and compromised cerebral perfusion Neuronal organelles subtle changes with unclear clinical signifigance Higher incidence of dementia, stroke, Parkinsons disease	Direct bacterial invasion Endotoxin effects on the brain Inadequate or altered cerebral perfusion Altered plasma or CNS levels of amino acids Altered brain metabolism	Septic encephalopathy Polyneuropathy Susceptible to delirium Altered mental status, simple fatigue, or unexplained fall as initial presentations
Cardiovascular		
Hypertrophy, fibrosis, and atherosclerosis Diastolic dysfunction Diminished response to adrenergic stimulation Loss of chronotropic reserve compensation	Redistribution of intravascular fluid volume and increase capillary pressure Depressed LV preload by decreased venous return Depressed ventricular contractility by myocardial depressant substances Early: vasodilatation and decrease systemic vascular resistance Late: contracted plasma volume	Hypotension Less tachycardia in sepsis Drop in CO and increased risk of pulmonary edema Difficult fluid management and may lead to more invasive monitoring, which can increase in iatrogenic complications
Pulmonary		
Decreased VC , no change in TLC Increased RV and FRC Decreased chest wall compliance and respiratory muscle strength Decreased PaO_2 and increased ventilation–perfusion mismatch both at rest and during exercise Decreased ventilatory responses to hypoxia or hypercapnia	Depressed respiratory muscle contractile performance Endothelial injury in pulmonary vessel Interstitial and alveolar edema and hemorrhage	Acute lung injury ARDS 25–42% of patients with sepsis Less hypoxia but more tachypnea Decreased ventilatory reserve in response to higher oxygen demand causing rapid cardiopulmonary derangement Increased frequency of mechanical ventilation Difficult to wean off ventilator Increase nosocomial pneumonia

Renal		
Atrophy of cortex and medulla and increase in connective tissue and fibrosis Decrease in GFR Impaired ability to dilute and concentrate urine Incontinence predisposes to UTI	Ischemic acute tubular necrosis Rhabdomyolysis Veno-occlusive disease	Increased risk of drug-induced nephrotoxicity, e.g., gentamicin, β-lactam, sulfa, amphotericin B Acute renal failure and increased mortality Electrolyte imbalance especially Na, K, Ca, Mg, and P Indwelling catheterization may mask symptoms and increase risk of nosocomial infection
Gastrointestinal tract		
Esophagus: achalasia, diverticula, decrease peristalsis, increase reflux Stomach: atrophic gastritis, gastric achlorhydria Intestine: mucosal atrophy, diverticulosis, polyps, diarrhea and constipation	Increased intestinal permeability and predispose to develop MODS Impaired gut barrier function, allowing translocation of bacteria and endotoxin into the systemic circulation and extending the septic response	Impaired gastrointestinal motility Increase aspiration Gut ischemia, ulcer, bleeding Gastric achlorhydria increase susceptibility to intestinal infections
Hepatobiliary tract		
Deficiency in the inducible mixed oxidase microsomal enzymes Cholelithiasis	Adrenergic receptor dysfunction Early: increased glycogenolysis and gluconeogenesis	Elevation of liver enzymes Hyperbilirubinemia Drug-induced hepatoxicity
Pancreas		
No change in exocrine function	Late: decreased gluconeogenesis Increased glucose-independent fat oxidation Decreased albumin, prealbumin, transferrin	Hyperglycemia Hypoglycemia in cirrhosis patients Prolonged effect of liver-excreted drugs, e.g., benzodiazepines Acalculous cholecystitis
Hematologic		
Immune dysregulation Subtle abnormalities of the phagocytes (neutrophils, monocytes, and macrophages) Anemia of chronic disease	Demarginalization of neutrophils by catecholamines Cytokine-induced release of immature neutrophils from bone marrow Shortened red blood cell survival Increased platelet destruction	Leukopenia may be a poor prognostic sign Most have leukocytosis Anemia Thrombocytopenia DIC

[a] Refs. *82–92*

Abbreviations: CNS = central nervous systems, LV = left ventricular, CO = cardiac output, VC = vital capacity, TLC = total lung capacity, RV= residual volume, FRC = functional residual capacity, PaO^2 = partial arterial oxygen pressure, ARDS = adult respiratory distress syndrome, GFR = glomerular filtration rate, UTI = urinary tract infection, MODS = multiple organ dysfunction syndrome, Na = sodium, K = potassium, Ca = calcium, Mg = magnesium, P = phosphorus, DIC = disseminated intravascular coagulation.

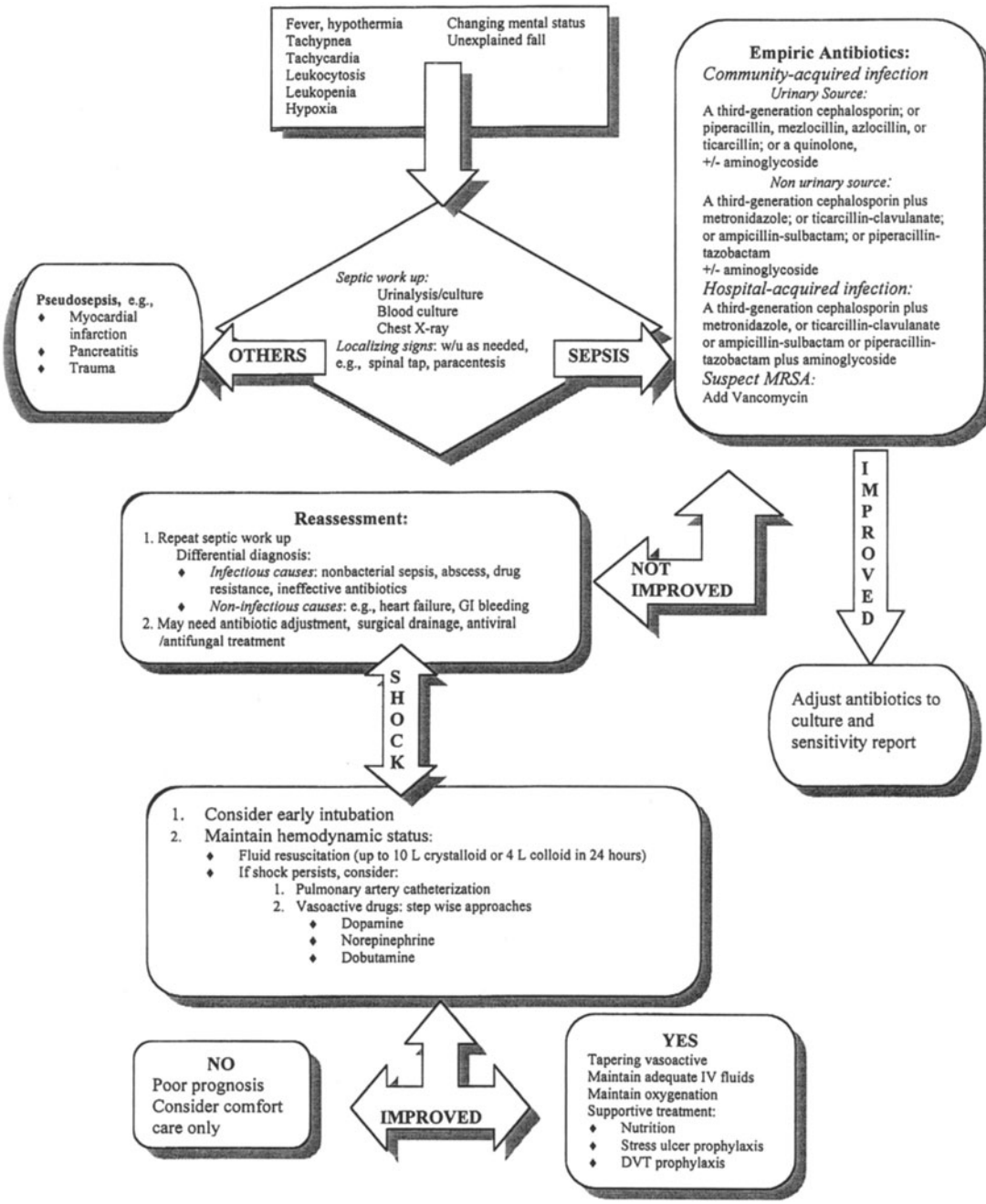

Fig. 1. Management of sepsis in the elderly: MRSA = methicillin-resistant *Staphylococcus aureus*. GI = gastrointestinal; L = liters; W/U = workup; DVT = deep vein thrombosis; IV = intravenous

age-related severity of sepsis. For example, after in vitro lipopolysaccharide (LPS)-induced activation of leukocytes of elderly persons, there were higher amounts of IL-1, IL-6, IL-8, and TNF-α than in younger persons *(20)*. Furthermore, a small prospective

study of the influence of age on circulating adhesion molecules in critically ill patients showed that elderly patients had higher levels of the soluble adhesion molecules, but the clinical significance of this finding is unclear *(19)*.

The foregoing age-related changes in immune function probably play only a small role in the severity of sepsis. A major contributing factor to the higher frequency and mortality of sepsis in older patients, however, is the large number of anatomic and physiologic changes that occur with age (*see* Table 1). These include changes in neurological, cardiovascular, pulmonary, and renal systems.

Infections may not only result from many of the coexisting diseases of aging but also may exacerbate other illnesses. Thus, it is not unusual to see a patient with congestive heart failure and a recent stroke develop an aspiration pneumonia, then sepsis, and further cardiac decompensation.

2.2. *Symptoms and Signs*

An overview of the manifestations of sepsis in the elderly is given in Fig. 1. There are no pathognomonic symptoms or signs of bacteremia in the elderly. The triad of tachycardia, rigors, and hypotension, as the classical manifestations of sepsis, are also rare in most studies. In a prospective study, Chassagne and colleagues *(21)* compared the presentations of bacteremia in young and elderly patients and noted that elderly patients had fewer symptoms and signs than younger infected patients. Elderly persons may have atypical presentation of bacteremia, e.g., lower body temperatures (even hypothermia), change in functional capabilities, simple fatigue, unexplained recurrent falls (up to 30% of a geriatric unit admission), and altered mental status (observed in 30-50% of cases) *(22–26)*. The atypical presentation in elderly patients may delay diagnosis, and septic shock may be the first clue that the patient is infected. A clinical indication of a source of infection can be identified in up to 75% of bacteremic elderly patients *(21)*. A summary of several studies on the clinical presentation of bacteremia in the elderly is shown in Table 3. Many of these studies have emphasized the occurrence of altered mental status, abdominal symptoms, and that fever is not a universal finding.

Fever, increased erythrocyte sedimentation rate, and a clinical indication of the source of infection, were found at least 70% of bacteremic elderly patients *(21)*. The febrile response in the elderly is different from the younger persons. Lower body temperatures with infection are more common in elderly persons and are correlated with higher mortality *(16,24,26,28-30)*. Kreger and colleagues *(31)* noted that transient hypothermia at the onset of bacteremia was not associated with increased fatality, but failure to mount a febrile response >99.6°F (37.6°C) within 24 h was. Body temperatures are normally maintained over a relatively narrow range, and older persons have basal temperatures that are about 0.3–0.5°C lower than in younger persons *(32)*. A retrospective study of infections in nursing home residents by Castle and co-workers found that 47% had temperature less than 101°F (38.3°C) *(33)*. Many of these patients had an adequate change in temperature from baseline (a change in temperature of more than 2.4°F) but failed to achieve a significant temperature (>101°F) because of a low baseline value *(33)*. Possible mechanisms for lower body temperature have not been completely elucidated but may be due to both a reduced capacity for thermogenesis and increased heat loss following infection *(34); see* also Chapter 3.

Table 3
Clinical Presentation of Bacteremia and Sepsis in Older Persons

Clinical/Reference	Madden 1981 *(41)* Septicemia in the elderly	Windsor 1983 *(23)* Bacteremia in a geriatric unit	Rudman 1988 *(40)* Nursing home Bacteremia	Meyers 1989 *(40)* Bloodstream infection in the elderly	Whitelaw 1992 *(44)* CA[a] Bacteremia in the elderly
Study method and population	Retrospective 44 patients[b] Geriatric unit	Retrospective 50 patients Geriatric unit	Retrospective 42 episodes Nursing home	Retrospective 100 episodes Hospital	Prospective 121 patients Hospital
Fever	88%	60%	95%	T>101°F = 65% T99–101°F = 25%	47%
Altered mental status	16%	36%	43% lethargy 2% delirium 1% seizure	52%	21%
Nausea and vomiting	40%	NA[c]	25%	NA	30%
Rigors	28%	NA	25%	34%	35%
Abdominal pain	28%	Included vomiting and diarrhea 14%	17%	NA	NA

Source	NA High ratio of common bile duct stone (15%)	GU 50% Pneumonia 22% Joint 10% Cellulitis 8% Biliary 8% Endocarditis 4% Pressure sore 4% Unknown 20%	GU 60% Pneumonia 7% Skin/soft tissue 7% Surgical wound 5% Bone/joint 2% Unknoan 22%	GU 27% Pneumonia 12% Intra-abdominal 16% Intravascular devices 9% Skin/soft tissue 6% Indeterminate 21% Endocarditis 3% Graft 3% Multiple 3%	GU 32% Pneumonia 18% Unknown 26%
Mortality	33%	24%	21%	40%	38%

[a]CA = community acquired; GU = genitourinary

[b]Total of 4; data given 26 patients with Gram-negative bacteremia.

[c]NA = Not available.

There are other differences in the presentation of sepsis between elderly and younger persons. The incidence of tachycardia and hypoxemia was significantly lower and the incidence of increased respiration, elevated plasma lactate, and altered mentation significantly higher in the patients >75 yr of age with Gram-negative sepsis as compared with patients <75 yr old *(35)*. Leukocytosis (greater than 10,000/mm^3) is seen about 70% *(21,23,29,40)*. Leukopenia is rare (less than 10%) and the incidence does not differ from younger persons *(21)*.

Elderly patients are prone to have associated clinical problems that can mislead the physician into making an incorrect diagnosis. For example, the history from a patient with dementia may be unreliable. As with other diseases of the elderly, physicians must coordinate the complexities of multiple, interacting diseases often present in the elderly. Particular expertise is required to discriminate important and relevant clinical problems in an initial evaluation.

2.3. Source and Microbial Causes

The genitourinary tract is the most common source of bacteremia in older persons, accounting for 20–50% of cases. Other sources include the respiratory tract, the gastrointestinal tract, and endovascular devices. Esposito noted that 10–20% of bacteremias were due to biliary tract infection and should be considered as a feature unique to aged patients presenting with community-acquired bacteremia *(36)*.

Because the urinary tract is the most frequently identified site of infection in older persons, it is not surprising that Gram-negative bacteria account for most cases of bacteremia in this age group. *Escherichia coli* is the most common Gram-negative organism, accounting for between 14% and 44% of isolates *(15,16,21–23,29)*. *Klebsiella*, *Providencia*, and *Proteus* are also commonly isolated.

The bacterial etiology of sepsis appears to be changing with rising number of cases of Gram-positive bacteremia. This has been related to changing demographics, new antibiotics, immunosuppressive agents, and invasive technology in the treatment of inflammatory, infectious, and neoplastic diseases *(37)*. Patients from long-term facilities in particular have a higher incidence of Gram-positive bacteremia *(39)*, and *Staphylococcus aureus* is the most frequently recovered organism *(23,39)*. *Streptococcus pneumoniae* is more common than *S. aureus* in community-dwelling elders who were admitted from the emergency room *(38)*. Other Gram-positive organisms frequently found include *Enterococcus* spp, and viridans group streptococci (23,40–42).

When polymicrobial sepsis occurs in the elderly, the most likely sources are the urinary and respiratory tracts, frequently associated with indwelling catheters and aspiration, respectively *(38)*. There are no published studies on the epidemiology of the sepsis in the elderly related to emerging pathogens such as *Legionella*, human immunodeficiency virus, and *Haemophilus influenzae*.

Elderly patients also have an increased risk of nosocomial infection and sepsis. The daily bacteremia rates of hospitalized patients were 0.59% in patients over age 60 and 0.40% in younger patients (a relative risk of 1.49) *(43)*. *E. coli* was the most common isolate in older persons with hospital-acquired bacteremia, most of which were associated with a urinary or abdominal focus. Staphylococci species, especially *S. aureus*, were the second most common isolates, mainly associated with intravenous access or surgical wound infection *(16,29)*.

3. DIAGNOSTIC TESTS

Microbiologic studies should be performed promptly when sepsis is suspected and before starting antibiotics (*see* Fig.1). All patients should have blood cultures obtained from two different sites as well as cultures and smears (e.g., Gram stain) of relevant body fluids (sputum, urine, cerebrospinal/peritoneal/pleural fluid) and exudates (abscesses, transcutaneous drain, loculated fluids). Other diagnostic tests may be required and obtained later if the diagnosis remains unclear.

Approximately half the patients with severe sepsis have positive blood cultures at the time of diagnosis *(2)*. Broad-spectrum antibiotics are frequently initiated pending culture and sensitivity, but physicians seem to be reluctant to change the antibiotic regimen when culture results return *(45)*.

The yield from sputum examination is lower in the elderly when compared with the younger patients due to inadequate cough or cooperation in the patients with impaired cognition. Adequate specimens have fewer than 10 squamous epithelial cells and more than 25 polymorphonuclear cells per low-power (100×) field. Only one third of sputum specimens from the elderly patients meet these cytologic criteria *(46)*.

The most common source of sepsis in older persons is the urinary tract. Urinary tract infections are discussed more completely in Chapter 10.

Chest X-rays are usually obtained in the initial evaluation of most septic patients. Elderly patients may have an underlying illness, especially heart failure, malignancy, or chronic lung disease that may make radiologic interpretation more difficult. Older persons are also more prone to have dehydration, which, theoretically could blunt the initial radiographic appearance, but this has not been confirmed in animal and human studies *(47,48)*.

Patients with sepsis and acute respiratory distress syndrome (ARDS) may have a normal chest radiograph despite abnormal blood gases early in the disease, but the majority will develop radiograph abnormalities within 24 h. The rate of progression to ARDS is variable. There is no relationship between the amount of infiltration and gas exchange or survival at any time point, but a worsening or persistently opacified chest radiograph suggests a poor prognosis. If there are new findings after 5 d, a superimposed process, e.g., nosocomial pneumonia, fluid overload, atelectasis, barotrauma, or sepsis, should be suspected. Effects of advancing age on ARDS is unknown.

In the elderly septic patient with an acute abdomen, flat and erect plain radiographs are an appropriate first diagnostic step because of their low cost, portability, rapidity, and high yield. They can identify free air collections in the intraperitoneal or retroperitoneal space and also radio-opaque stones in the hepatobiliary tract as well as genitourinary tract. To search for an occult source of infection, ultrasonography and computed tomographic (CT) scan have higher yields. The CT scan is superior to the ultrasonogram for detection of an intraabdominal abscess, which carries a mortality of 30% for surgically treated abdominal abscess, and 80–90% for cases without surgical drainage *(49)*. (*See also* Chapter 9.)

Currently, the diagnosis of sepsis requires combination of clinical signs of systemic inflammation and evidence of infection. Elderly persons with sepsis may present with minimal or subtle findings of infection, however, and diagnosis can be delayed. Because many of the inflammatory cells and mediators have been identi-

fied, future studies and clinical management will likely focus on using these mediators as both diagnostic and prognostic markers for sepsis. Because of the relative ease with which they can be obtained, peripheral blood markers are likely to become clinically useful diagnostic and prognostic markers. In a recent study in febrile patients with community-acquired infection, a high serum ratio of IL-10 to TNF-α was associated with poor outcome, but age, sex, and duration of fever were not *(50)*.

4. TREATMENT

The two most important aspects of the initial management in the patient suspected of sepsis are prompt initiation of antibiotics and fluid and hemodynamic resuscitation. Pseudosepsis or conditions that mimic sepsis, e.g., myocardial infarction, adrenal insufficiency, gastrointestional hemorrhage, pulmonary emboli, and acute pancreatitis, should be excluded to avoid unnecessary use of antibiotics *(51)* (*see* Fig.1). Older patients still benefit from having their management occur in an intensive care unit (ICU). For example, a retrospective study by Lundberg and colleagues *(52)* showed that the mortality of septic shock was higher (70%) in patients treated on a hospital ward as compared with patients treated in an ICU (39%), despite the fact that the ICU patients were older and more ill.

Even though older patients have higher mortality rates than their younger counterparts, factors other than age, such as the presence of multiorgan system failure, are more important in predicting outcome *(53)*. For example, a prospective study by Deulofeu and colleagues *(54)* noted that age alone did not influence the outcome of bacteremia, and the main prognostic factors were shock, impaired functional status, immunodeficiency, acquisition of infection in the hospital, and absence of fever on admission. Therefore, treatment in elderly patients is generally similar as in younger patients. Because of the age-related decline in the general physiological reserve and more comorbid conditions, care has to be even more individually adjusted.

4.1. Antimicrobial Therapy

The outcome of sepsis is improved with early diagnosis and initiation of antibiotics. Inadequate and delayed antibiotic treatment can lead to higher mortality rate *(55,56)*. Empiric antibiotic therapy is based on the site of infection and the usual resident flora of the involved organ. Because a large variety of pathogens is possible, broad-spectrum coverage is mandatory (*see* Fig.1). A third-generation cephalosporin, imipenem/cilastin, ticarcillin/clavulanate, or antibiotic combinations such as a penicillin or cephalosporin with an aminoglycoside, aztreonam, or parenteral quinolone are probably equally efficacious in most patients *(34)*. Empiric therapy with vancomycin and an aminoglycoside is effective against most aerobic pathogens including methicillin-resistant staphylococci species and resistant Gram-negative organisms. However, this regimen is potentially nephrotoxic, especially in older patients with already compromised renal function, and fails to treat anaerobic infections. Sepsis caused by anaerobic organisms is particularly common in intraabdominal sepsis and aspiration pneumonia. When the culture and sensitivity results are available, the initial regimen should be changed based on the laboratory results and the patient's response to initial therapy.

Once culture and sensitivity data become available, monotherapy may be considered if organisms are susceptible; multiple antibiotics do not necessarily cure patients

more quickly or effectively. A retrospective study showed that patients older than age 70 with Gram-negative bacteremia given multiple antibiotics had a signficantly higher mortality rate (30%) than those given one antibiotic (13%), but this may have been owing to a selection bias with sicker patients receiving more antibiotics *(15)*. Double-drug therapy is generally perceived to be more effective in the treatment of serious *Pseudomonas aeruginosa* infections, febrile neutropenic patients, and possibly the treatment of intraabdominal infections *(57)*. Further principles of antibiotic therapy in the elderly are discussed in Chapter 4.

4.2. Hemodynamic Support

The goals of hemodynamic support in sepsis are to restore and maintain an adequate tissue perfusion pressure (mean arterial pressure greater than 60 mmHg), decrease heart rate, maintain adequate renal perfusion (urine output greater than 0.5 mL/kg/h), and improve mental status. In its early stage, sepsis causes tachycardia and peripheral vasodilatation, as well as myocardial depression and ventricular dilatation despite normal or increased cardiac output. Stroke work and ejection fraction are decreased. These outcomes lead to a reduction in the effective intravascular volume and circulatory instability. If volume resuscitation is not adequate, multiple organ failure and death can result despite control of the infection. Aggressive volume resuscitation is the best initial treatment. Hypotension can be usually reversed with fluid administration up to 10 L of crystalloid or 4 L of colloid in the first 24 h *(58)*. However, aggressive fluid replacement must be carefully monitored in elderly patients, especially those with coexisting cardiac and/or renal disease (see next paragraph). No conclusive data have shown which type of resuscitation fluid has the best impact on outcome.

Pulmonary artery catheters may be helpful to determine the optimum ventricular filling pressures and cardiac output in such settings as ARDS, cardiac and/or renal dysfunction, or hypotension unresponsive to fluid administration. The characteristic hemodynamic changes in sepsis are high cardiac output and low systemic vascular resistance. Elderly patients frequently have poor cardiac compliance, which can be compromised by pulmonary edema after aggressive fluid resuscitation. Even though pulmonary artery catheter placement in patients with sepsis/septic shock has not been proven to improve the clinical outcome and may even increase in mortality and cost *(59)*, it is generally agreed that it is appropriate in patients with septic shock who have not responded to initial fluid resuscitation and low-dose inotropic/vasoconstrictor therapy or have significant underlying comorbidities affecting hemodynamic status.

Sepsis causes a hypermetabolic state with increased oxygen consumption resulting in tissue hypoxia. Studies in adults up to age 80 suggest that a mean arterial pressure of 70–80 mmHg and/or cardiac index of 2.8 L/min/m^2 is required to maintain adequate tissue oxygenation. An older practice was to deliver therapy to induce supranormal hemodynamic variables (cardiac index more than 4.5 L/min/m^2, oxygen delivery greater than 600 mL/min/m^2, and systemic vascular resistance index of 1100 to 1300 dyne·s/cm^3·m^2), but more recent randomized trials have not found this to be effective in lowering mortality *(60,61)*.

If fluid resuscitation alone can not restore mean arterial pressure to adequate level, a vasoactive agent should be given (*see* Fig.1). Dopamine is the most commonly used first-line agent. It is usually given in a low dose (<2 µg/kg/min; activates dopaminergic

vasodilatory receptors) for renal or gastrointestinal protection, although this not been demonstrated to be beneficial in critically ill patients because the increase in blood flow to the renal and splanchnic regions may be due to increase in cardiac output alone *(62)*. In higher doses (5–10 μg/kg/min), dopamine activates β adrenergic receptors; at doses above 10 μg/kg/min, especially over 20 μg/kg/min, alpha adrenergic (vasoconstricting) receptors are activated. Older patients with coronary artery disease may not be able to tolerate this β_1-adrenergic receptor-mediated cardiac stimulation due to increased myocardial oxygen demand and decreased coronary artery blood flow. In patients with severe shock that requires the higher doses of dopamine (>10μg/kg/min), norepinephrine should be added or therapy switched to this agent. Norepinephrine is a potent α adrenergic agonist with moderate β_1 and minimal β_2 adrenergic activity. It increases the systemic vascular resistance, which may reverse the vasodilatation effects of sepsis. Because of this effect, some clinicians use norepinephrine early in the treatment of septic shock *(63)*. Dobutamine is a selective β_1 adrenergic agent without α agonist activity and should be used to support the myocardium and maintain an adequate oxygen supply to the tissues if shock is persistent *(64)*. Dopexamine, a new agent that combines β adrenergic and dopaminergic effects, may be a useful alternative to increase splanchnic blood flow. Epinephrine is usually used as a last resort because of its tachyarrhythmic effect and decrease in splanchnic perfusion.

Experimental treatments for septic shock include phosphodiesterase inhibitors, calcium agonists, and nitric oxide inhibitors. No definitive recommendations can be made regarding the use of these agents due to inconclusive published data *(65)*.

Sepsis can increase the ventilatory load by increasing oxygen demand from poor tissue extraction and increasing catabolism. It also compromises the ventilatory supply by impairing gas exchange and respiratory muscle function. Because elderly patients have less cardiopulmonary reserve, intubation should be considered if there is an early sign of respiratory failure or poor tissue perfusion. Adequate oxygenation should be monitored carefully to maintain saturation of oxygen at >95%.

In seriously ill patients, old age alone is not an appropriate criterion to make a decision to withhold life-sustaining treatment. Unfortunately, physicians typically underestimate older patients' preferences for life-extending care. A recent study showed that although there was an age-associated decrease in the desire of older persons for life-extending care (from 61% of those under age 50 yr to 27% of those over age 80 yr), physicians thought that octagenerians wanted life-extending care in only 14% of the cases. Moreover, for patients who wanted life-extending care, in 79% of the cases of octagenerians, the treating physician thought that the patient did not want this therapy. Probably because of these views, the rate of decision to withhold ventilator support increased 15% with each decade of age over 50 yr *(66)*.

Although anemia can decrease oxygen delivery, there is little improvement in oxygen consumption following blood transfusion in patients with sepsis *(67)*.

Nutritional support can increase lymphocyte counts and serum albumin, which are used as surrogate markers of immune competency *(68)*. The route of feeding must be individualized, but the enteral route is preferred to maintain gut function and avoid complications from catheter-induced infection. Gastric tube feeding may decrease the risk of bleeding from a stress ulcer but may increase the risk of aspiration pneumonia *(69)*.

Sepsis can lead to stress ulcers with higher risk in the patients with mechanical ventilation. Appropriate cytoprotective agents are indicated to prevent stress ulcers, such as using a continuous parenteral histamine 2 blocker drug, unless the patient develops side effects of nephritis, thrombocytopenia, and confusion *(70)*. Sucralfate might be a better choice as a cytoprotective agent because of the lower incidence of late-onset pneumonia *(71)*.

5. PREVENTION AND IMMUNOTHERAPIES

Indwelling catheters should be removed as soon as clinically feasible. Elderly persons are more prone to aspiration pneumonia, which is the leading cause of death due to hospital-acquired infections. Selective decontamination of the digestive tract is not recommended by the Centers for Disease Control and Prevention *(72)*. Simple procedures such as elevation of the head, using sucralfate, and early detection in at-risk patients (chronic lung disease, changing mental status, nasogastric tube, reintubation) are preferred. Old age probably does not increase the risk of intravenous catheter-associated infection, but these occur more frequently in the elderly due to the age-associated increased use of these devices. Appropriate skin care, e.g., using chlorhexidine antiseptic, and probable antibiotic-coated intravascular devices, may decrease the incidence. Hand washing after examining each patient is a simple preventive method that is commonly ignored.

Sepsis is characterized by an imbalance in proinflammatory and anti-inflammatory cytokines. TNF-α and IL-1 are the principal mediators causing most manifestations of sepsis and shock. In animal studies, anti-TNF α antibody and IL-1 receptor antagonists can protect septic animals from death *(73,74)*. Clinical trials, however, have had mixed results. Two multicenter phase II/III trials in patients with sepsis were held evaluating a monoclonal antibody to TNF-α (antiBAY x1351). The North American Sepsis Trial I (NORASEPT 1) showed that septic patients without shock had no benefit from treatment with this monoclonal antibody and in septic patients with shock, the 3-d mortality rate was decreased but not the 28-d mortality. In the International Sepsis Trial (INTERSEPT), the circulating TNF-α levels and the development of organ failure were decreased with the use of the monoclonal antibody, but there was no reduction in the 28-d mortality. Recently, a double-blind, randomized control phase III trial, NORASEPT II, that was conducted in 105 hospitals with 1879 patients, did not find any survival benefit from TNF α blockade *(75–77)*.

Studies on endotoxin blockade have also yielded disappointing results. Clinical studies of two antibodies to the lipid A fraction of lipopolysaccharide and the core region of endotoxin yielded conflicting results. Although the first study showed some clinical benefit in patients not in shock *(78)*, a second randomized large controlled clinical study of a monoclonal antibody to endotoxin found no improvement in survival, although a modest benefit in resolution of organ dysfunction was shown *(79)*.

Despite some early enthusiasm for the use of corticosteroids in patients with septic shock, a meta-analysis has shown that corticosteroids are not beneficial *(80)*. A study on the use of ibuprofen showed that it decreased fever but not survival *(81)*.

A variety of other agents, e.g., interferon-γ, N-acetylcysteine, antithrombin III, naloxone, pentoxifylline, and hemofiltration, have been tested in patients with sepsis, but the results are disappointing. The immune response to infection is quite compli-

cated so that it is unlikely that a single agent will prove beneficial. It is clear that the mortality of sepsis is not improved dramatically despite more intensive therapy. The greater frequency of underlying comorbid conditions in study subjects that included more elderly with chronic illness, immunosuppressive patients, and new innovative and invasive treatment may have contributed to the lack of improvement in survival. There are no published studies focusing on older patients. Whether septic elderly patients would respond differently from younger remains to be answered.

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