

PART I

Clinical Syndromes – General

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1. Fever of Unkown Origin

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OVERVIEW

Fever of unknown origin (FUO) describes prolonged undiagnosed fevers. In 1961, Petersdorf introduced a standard definition of FUO; his criteria included fevers of temperature >101°F that lasted ≥3 weeks that remained undiagnosed after 1 week of intensive, in-hospital diagnostic testing. This classical definition of FUO still applies today but with one modification. Because of advanced imaging techniques available on an outpatient basis, the intensive diagnostic workup may be conducted in the outpatient setting. The causes of FUO include a wide variety of infectious and noninfectious disorders capable of eliciting fever. By definition, acute febrile disorders are not included in the definition and, even if diagnosed, should not be termed FUOs. Prolonged, difficult-to-diagnose fevers may be due to infection, malignancy, rheumatic diseases, or a variety of other miscellaneous causes.

CAUSES OF FEVER OF UNKNOWN ORIGIN

The types of disorders that are associated with prolonged fevers have remained relatively constant over time, but the relative proportion of different disease categories has changed over the years. In Petersdorf’s initial description, infectious diseases constituted the largest single category of disorders causing FUO. Decades later, in reevaluating the distribution of FUO causes, Petersdorf noted that malignancies had exceeded infectious diseases as the most important singular cause of FUO. Recently, in some series, the distribution has changed again, which reflects the demographics of the population being studied. For example, a recent study of FUOs indicates a majority of patients had unexplained fevers due to noninfectious, inflammatory conditions (ie, predominantly rheumatic disorders). Therefore, the relative distribution of disorders presenting as FUO depends on a variety of factors, including the patient’s age, geographical location, and underlying host immune defects. Some authors have even further broken down FUOs into those occurring in specific subpopulations (ie, HIV, returning travelers, nosocomial FUOs, etc). Although the differential diagnosis in each subcategory reflects

a preponderance of diseases that are specific to age, region, or host defense defects, the overall causes of FUOs in each subpopulation remain essentially the same (Table 1.1).

DIAGNOSTIC APPROACH

Because the appropriateness of any therapy is based on a correct diagnosis, the main focus of the proper approach to the FUO patient is diagnostic rather than therapeutic. The diagnostic workup of the FUO patient should take into account the frequency of distribution of disorders, noninfectious as well as infectious, that relates to the patient’s age, geography, and host defense status. The diagnostic workup should further be refined and focused based on the presence of signs, symptoms, and laboratory abnormalities, which can either eliminate diagnostic categories or suggest a particular diagnosis. Nonspecific laboratory tests are often overlooked as potential clues in the FUO workup. Nonspecific laboratory tests are, by definition, nonspecific but, particularly when taken together, should suggest a particular diagnosis and prompt specific diagnostic testing. Importantly, the diagnostic workup should not be shot-gun, including diagnostic testing for every conceivable cause of FUO. Diagnostic testing should be focused and appropriate to the patient’s age and geographical location and based particularly on the findings/absence of findings on physical examination and pertinent aspects of the patient’s history.

NONSPECIFIC LABORATORY TEST CLUES

Nonspecific laboratory clues are also important in further focusing the diagnostic workup. There are certain radiologic/laboratory investigations that are generally useful when no particular cause of FUO is apparent from the initial diagnostic history, physical, and workup. In addition to basic laboratory tests, computer tomography/magnetic resonance imaging (CT/MRI) scans of the chest, abdomen, and pelvis are high-yield diagnostic tests. Gallium or indium scanning also may localize otherwise

Table 1.1 Diseases Causing Classical Fever of Unknown Origin

Type of Disorder	Common	Uncommon	Rare
Malignancy	Lymphoma Hypernephromas	Preleukemias Hepatomas Myeloproliferative disorder (MPDs) Pancreatic carcinoma Metastases to liver	Atrial myxomas CNS tumors Multiple myeloma Colon carcinoma
Infections	Miliary TB Extrapulmonary TB (Renal TB, TB meningitis) Intraabdominal/pelvic abscesses SBE Typhoid fever malaria	CMV Toxoplasma gondii Salmonella enteric fevers Intra/perinephric abscess Splenic abscess Cat scratch fever EBV	Periapical dental abscesses Chronic sinusitis Subacute vertebral osteomyelitis Listerial Yersinia Brucellosis Relapsing fever Rat bite fever Chronic Q fever HIV Leptospirosis Histoplasmosis Coccidioidomycosis LGV Whipple's disease Relapsing mastoiditis Leishmaniasis (Kala-azar)
Rheumatologic	Still's disease (adult JRA) Polymyalgia rheumatica/temporal arteritis	PAN Rheumatoid arthritis (elderly)	SLE Takayasu's arteritis Kikuchi's disease Felty's syndrome Pseudogout (CPPD) Behçet's disease FMF
Miscellaneous causes	Drug fever Cirrhosis	Granulomatous hepatitis Regional enteritis Subacute thyroiditis	Fabray's disease Hyperthyroidism Pheochromocytomas Addison's disease Cyclic neutropenia Pulmonary emboli (multiple, Hypothalamic dysfunction Factitious fever Pseudolymphomas Hyper IgD syndrome

Abbreviations: CNS = central nervous system; TB = tuberculosis; SBE = subacute bacterial endocarditis; CMV = cytomegalovirus; HIV = human immunodeficiency virus; EBV = Epstein-Barr virus; LGV = lymphogranuloma venereum; JRA = juvenile rheumatoid arthritis; PAN = polyarteritis nodosa; SLE = systemic lupus erythematosus; FMF = familial Mediterranean fever.
Adapted from: Cunha BA. Fever of unknown origin (FUO). In: Gorbach SL, Bartlett JB, Blacklow NR, eds. *Infectious Diseases in Medicine and Surgery*. 3rd ed. Philadelphia, PA: WB Saunders, 2004:1568–1577.
Adapted from: Cunha BA. Overview. In: Cunha BA, ed. *Fever of Unknown Origin*. New York, NY: Informa Healthcare; 2007.

unsuspected areas of inflammation, infection, or malignancy. Other nonspecific tests are helpful in suggesting or eliminating particular diagnostic categories as well as refining the diagnostic workup, for example, serum ferritin levels, serum protein electrophoresis (SPEP), febrile agglutinins. The SPEP is useful and important, not only for detecting monoclonal gammopathies but also in the differential diagnosis of FUO in demonstrating a polyclonal gammopathy. Polyclonal gammopathy in SPEP

in a patient with a heart murmur, signs of endocarditis, and negative blood cultures should suggest the possibility of atrial myxoma rather than culture-negative endocarditis. Perhaps the most underutilized laboratory test in the FUO workup is serum ferritin determinations. Highly elevated serum ferritin levels most frequently suggest a neoplasm/myeloproliferative disorder. However, elevated serum ferritins levels are also present in flares of systemic lupus erythematosus (SLE) or

Table 1.2 FUO: Initial Laboratory Tests

For all FUO categories <ul style="list-style-type: none">• CBC• ESR• LFTs• Chest x-ray• UA• Routine blood cultures• Imaging studies-chest (if abnormal CXR) abdominal/pelvic CT/MRI
CBC^a <ul style="list-style-type: none">• Leukocytosis → neoplastic and infectious disease panels^a• Leukopenia → neoplastic, infectious, and RD panel^a• Anemia → neoplastic, infectious, and RD panel^a• Myelocytes/metamyelocytes → neoplastic panel^a• Lymphocytosis → neoplastic and infectious panels• Lymphopenia → neoplastic, infectious, and RD panel^a• Atypical lymphocytes• Eosinophilia → neoplastic, RD, and infectious panels^a• Basophilia → neoplastic panel^a• Thrombocytosis → neoplastic, infectious disease, and RD panels^a• Thrombocytopenia → neoplastic, infectious disease, and RD panels^a
ESR <ul style="list-style-type: none">• Highly elevated → neoplastic, infectious, and RD panels^a
LFTs <ul style="list-style-type: none">• ↑ SGOT/SGPT → infectious and RD panel^a• ↑ Alk. phosphatases → neoplastic and RD panels^a
Chest x-ray <ul style="list-style-type: none">• Any lung parenchymal abnormality/adenopathy/pleural effusion → neoplastic, infectious and RD panels^a
^a See Table 1.3. Abbreviations: CBC = complete blood count; CXR= chest X-ray; CT= Computer tomography; ESR = erythrocyte sedimentation rate; LFTs = liver function tests; MRI= Magnetic Resonance Imaging; UA = urine analysis; RD = rheumatic disease; SGOT/SGPT = serum glutamic-oxaloacetic transaminase/serum glutamic pyruvate transaminase. Adapted from Cunha BA. A focused diagnostic approach. In: Cunha BA, ed. <i>Fever of Unknown Origin</i> . New York, NY: Informa Healthcare; 2007.

adult Still’s disease (juvenile rheumatoid arthritis) or temporal arteritis. Elevated ferritin level also has important exclusionary value as a nonspecific test in FUO patients. For example, the likelihood of a patient having a malignancy is greatly decreased if the patient has a normal serum ferritin level. The diagnostic workup should be focused and guided by findings and laboratory abnormalities as they become apparent after the initial diagnostic workup (Tables 1.2–1.4).

THERAPEUTIC APPROACH

Empiric therapy of FUOs is rarely justified. Fever, per se, should not be treated, as it

eliminates an important sign that may be helpful diagnostically. The only rational antipyretic intervention that may be employed in a patient with FUO is the use of the Naprosyn test (naproxen 375 mg orally every 12 hours for 3 days) for *diagnostic*, not therapeutic, purposes. In FUO patients where the differential diagnosis is between malignancy and infection, the Naprosyn test has important diagnostic implications. The Naprosyn test is positive when the patient’s temperature dramatically decreases during the test period. Little or no decrease in the patient’s temperature indicates an infectious disorder, whereas a prompt/dramatic decrease in the febrile response indicates a malignancy.

Table 1.3 FUO: Laboratory Clues

Leukopenia Miliary TB Brucellosis SLE Lymphomas Pre-leukemias Typhoid fever Kikuchi's disease	Atypical Lymphocytosis EBV CMV Brucellosis Toxoplasmosis Drug fever	ESR (>100 mm/hr) Adult JRA PMR/TA Hypernephroma SBE Drug fever Carcinomas Lymphomas MPDs Abscesses Subacute osteomyelitis LORA Hyper IgD syndrome
Monocytosis TB PAN TA CMV Sarcoidosis Brucellosis SBE SLE Lymphomas Carcinomas Regional enteritis (Crohn's disease) MPDs	Thrombocytosis MPDs TB Carcinomas Lymphomas Sarcoidosis Vasculitis Temporal arteritis Subacute osteomyelitis Hypernephroma	SPEP Polyclonal gammopathy Atrial myxoma Alcoholic cirrhosis Sarcoidosis PAN HIV Takayasu's arteritis ↑ α_1/α_2 globulin Lymphoma SLE ↑ gammaglobulin spike Multiple myeloma Schnitzler's syndrome Hyper Ig D syndrome
Eosinophilia Trichinosis Lymphomas Drug fever Addison's disease PAN Hypersensitivity vasculitis Hypernephroma MPDs	Thrombocytopenia Leukemias Lymphomas MPDs EBV infectious mono Drug fever Vasculitis SLE	Increased Serum Transaminases EBV mononucleosis CMV Q fever Drug fever Leptospirosis Toxoplasmosis Brucellosis Kikuchi's diseases
Basophilia Carcinomas Lymphomas Pre-leukemia (AML) MPDs	Rheumatoid Factor SBE Chronic active hepatitis Malaria Hypersensitivity vasculitis LORA	Abnormal Renal Tests SBE Renal TB PAN Leptospirosis Brucellosis Lymphomas SLE Hypernephroma MPDs
Lymphocytosis TB EBV CMV Toxoplasmosis Non-Hodgkin's lymphoma	Alkaline Phosphatase Hepatoma Miliary TB Lymphomas EBV CMV Adult JRA Subacute thyroiditis TA Hypernephroma PAN Liver metastases Granulomatous hepatitis	
Lymphocytopenia Whipple's disease Miliary TB SLE Lymphomas Multiple myeloma	Serum Ferritin Malignancies SLE TA LORA Adult JRA	

Abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; ESR = erythrocyte sedimentation rate; PAN = periarteritis nodosa; SBE = subacute bacterial endocarditis; SLE = systemic lupus erythematosus; TB = tuberculosis; MPDs = myeloproliferative disorders; LORA = late onset rheumatoid arthritis.
Adapted from Cunha BA. Nonspecific tests in the diagnosis of fever of unknown origin. In: Cunha BA, ed. *Fever of Unknown Origin*. New York, NY: Informa Healthcare; 2007.

The patient's temperature as well as the pulse response has important diagnostic implications, which is another reason antipyretic therapy should be used only under unusual circumstances.

Among the infectious diseases, empiric therapy of presumed culture-negative endocarditis

and presumed miliary TB are two of the few exceptions to blindly treating patients with prolonged undiagnosed fevers. With rheumatic diseases, empiric therapy of polymyalgia rheumatica with low-dose prednisone (ie, 5–10 mg orally per day) is important diagnostically. The main difficulty in FUO is to arrive at a correct diagnosis.

Table 1.4 FUO Infectious Panel/Neoplastic Panel/Rheumatic Panel

FUO Infectious Panel	FUO Neoplastic Panel	FUO Rheumatic Panel
Blood Tests		
<ul style="list-style-type: none">• Special blood cultures (↑ CO₂/6 weeks• Q fever serology• Brucella serology• Bartonella serology• Salmonella serology• Viral serologies<ul style="list-style-type: none">EBVCMVHHV-6	<ul style="list-style-type: none">• Ferritin• SPEP	<ul style="list-style-type: none">• ANA RF• Ds DNA• SPEP• Ferritin• CPK• ACE
Radiologic Tests		
<ul style="list-style-type: none">• CT/MRI abdomen/pelvis^a• Gallium scan• Panorex film of jaws (if all else negative)	<ul style="list-style-type: none">• CT/MRI abdomen/pelvis^a• Gallium scan	<ul style="list-style-type: none">• Head/chest CT/MRI• Low dose steroids (prednisone 10 mg/day if PMR likely)
Other Tests		
<ul style="list-style-type: none">• Naprosyn test• Anergy panel/PPD	<ul style="list-style-type: none">• Naprosyn test• BM biopsy (if myelophthistic anemia/ abnormal RBCs/WBCs)• TTE (if heart murmur with negative blood cultures)	<ul style="list-style-type: none">• Temporal artery biopsy (if ESR >100, without alternate diagnosis)
^a Chest/head CT/MRI (if infectious etiology suspected in head/chest). Abbreviations: EBV = Epstein-Barr virus; CMV = cytomegalovirus; HHV-6 = human herpes virus-6; CPK = creatinine phosphokinase; SPEP = serum protein electrophoresis; ACE = angiotensin converting enzyme. Adapted from Cunha BA. A focused diagnostic approach. In: Cunha BA, ed. <i>Fever of Unknown Origin</i> . New York, NY: Informa Healthcare; 2007.		

Table 1.5 Therapy in Fever of Unknown Origin

Empiric Therapy	Disorder
Infectious diseases	<ul style="list-style-type: none">• Culture negative subacute bacterial endocarditis• Miliary TB
Rheumatic diseases	<ul style="list-style-type: none">• Polymyalgia rheumatica (PMR)• Temporal arteritis (TA)
Specific Therapy	Disorder
Infectious diseases	<ul style="list-style-type: none">• All treatable with effective antibiotics
Rheumatic diseases	<ul style="list-style-type: none">• All treatable with effective therapies
Neoplastic diseases	<ul style="list-style-type: none">• All treatable with effective therapies
Abbreviations: TB = tuberculosis; TA = temporal arteritis; PMR = polymyalgia rheumatica.	

Empiric antimicrobial therapy of a patient with an FUO should be reserved for unusual circumstances, when a therapeutic intervention with an antimicrobial may be of critical importance (eg, culture-negative endocarditis) and may be lifesaving (eg, miliary tuberculosis [TB]). There is a place for specific therapy of FUO once the diagnosis has been determined. Clearly, patients

with treatable malignant disorders should receive appropriate antineoplastic therapies/interventions, those with rheumatic diseases should receive steroids/immunosuppressives as appropriate for the disorder and the severity of the illness, and infectious disorders should be treated if therapy is available against the etiologic agent (Table 1.5).

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2. Sepsis and Septic Shock

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DEFINITIONS

Sepsis is a complex syndrome comprising a constellation of systemic symptoms and signs in response to infection, including inflammatory, pro-coagulant, and immunosuppressive events. Septic shock occurs when there is significant hypotension in the presence of sepsis. The definitions and diagnostic criteria for sepsis and related conditions were developed in 1991 at a consensus conference sponsored jointly by the American College of Chest Physicians and the Society for Critical Care Medicine and reviewed by the 2001 International Sepsis Definitions Conference (sponsored by the Society of Critical Care Medicine, European Society of Critical Care Medicine, American College of Chest Physicians, American Thoracic Society, and the Surgical Infections Society). Apart from expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience, the definitions remained unchanged. The sepsis-related terminology and definitions are presented in Table 2.1; the diagnostic criteria for sepsis presented in Table 2.2 have been updated by the Conference to include a variety of signs of systemic inflammation in response to infection. This international group proposed a classification scheme for sepsis that stratifies patients based on their predisposing conditions, the nature and extent of the insult (infection), the host response, and the degree of concomitant organ dysfunction (acronym PIRO). This concept will have to be further tested and refined before it can be routinely applied in clinical practice.

EPIDEMIOLOGY

The incidences of sepsis, severe sepsis, and septic shock are probably underestimated because most of the available estimates are based on hospital discharge diagnoses. A recent review by Martin et al. found that the incidence of sepsis increased fourfold from 1979 to 2000 to 240 cases per 100 000 population per year (approximately 750 000 cases/year). In-hospital mortality rates in patients with a sepsis-related diagnosis

remain high, with estimates between 18 and 70%, depending on the severity. Approximately 150 000 persons die annually in Europe from severe sepsis and more than 200 000 die annually in the United States. Certain populations such as the elderly, neutropenic patients, and infants (especially low-birth-weight newborns) have higher attack and mortality rates. The incidence of sepsis is higher in men and nonwhite persons, as compared with women and white persons, respectively, for unclear reasons.

PATHOGENESIS

The clinical manifestations of the sepsis syndrome are caused by the body's immune, inflammatory, and coagulation responses to toxins and other components of microorganisms. For example, infusion of endotoxin into humans is sufficient to initiate the cascade of inflammatory mediators seen in sepsis. Endotoxin is the lipoidal acylated glucosamine disaccharide core of the cell wall of many aerobic gram-negative bacteria. This moiety, known as *lipid A*, is highly conserved among the Enterobacteriaceae and, to a lesser extent, among the Pseudomonaceae. Anaerobic gram-negative bacteria, such as *Bacteroides fragilis*, lack *lipid A*, perhaps explaining why sepsis is not commonly seen when infection is caused solely by this anaerobe.

Once a pathogenic microorganism invades a host barrier, these highly conserved microbial cell wall molecules, usually lipids or sugars, are sensed by the local defense cells (eg, tissue macrophages, mast cells, dendritic cells) expressing specific host proteins on their surface, such as CD14 and toll-like receptors (TLRs). The bacterial peptidoglycan of gram-positive bacteria is recognized by TLR2 and the lipopolysaccharide of gram-negative bacteria is recognized by TLR4. The activation of the TLR receptors initiates intracellular signaling pathways that lead to the production of cytokines and immunomodulatory molecules that mediate the inflammatory response and contribute to the clinical manifestations of sepsis.

Table 2.1 Sepsis-Related Terminology and Definitions

Infection	A pathological process caused by invasion of normally sterile host tissue by pathogenic or potentially pathogenic microorganisms
Bacteremia	The presence of viable bacteria in the blood
SIRS	The systemic inflammatory response to a wide range of infectious and noninfectious conditions. Currently used criteria include 2 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; WBC >12 000 cells/mm ³ or ≤4000 cells/mm ³ , or ≤10% immature (band) forms
Sepsis	The clinical syndrome defined by the presence of both infection and a systemic inflammatory response
Severe sepsis	Sepsis complicated by organ dysfunction, hypotension, or signs of hypoperfusion (eg, lactic acidosis, renal failure, altered mental status, and acute respiratory failure)
Septic shock	Sepsis accompanied by acute circulatory failure, characterized by persistent arterial hypotension that, despite adequate fluid resuscitation, requires pressor therapy
MODS	Multiple organ dysfunction syndrome; the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention; primary multiple organ dysfunction syndrome is the direct result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself; secondary multiple organ dysfunction syndrome develops as a consequence of a host response and is identified in the context of SIRS
Abbreviations: SIRS = systemic inflammatory response syndrome; MODS = multiple organ dysfunction syndrome; WBC= white blood cells.	

Tumor necrosis factor- α (TNF- α); interleukin (IL)-1 β , IL-10, IL-12, and other interleukins; interferon- γ ; and several colony-stimulating factors are produced rapidly (minutes to hours) after the interaction of monocytes and macrophages with the microbial molecules. Although the effects of TNF- α appear to be central to the pathophysiology of sepsis, many other immune modulators interact with TNF- α , host defense mechanisms, and bacterial pathogens in complex ways.

The sepsis cascade can be simplified by dividing it into at least five components with feedback loops among them. The process starts with the release of intracellular or extracellular bacterial activators, such as lipid A in gram-negative sepsis and peptidoglycan, teichoic acid, or toxic shock toxin-1 (TSST-1) in gram-positive sepsis. The second event is the activation of macrophages by the bacterial products. This activation leads to the third component of sepsis, which consists of the release of highly active molecules (eg, cytokines) that have many potent biologic effects. The most important and best studied cytokine is TNF- α ; IL-1 β is another cytokine that is released early in the sepsis cascade, with effects similar to those of TNF- α . The release of TNF- α and IL-1 β leads to the fourth component in the sepsis cascade, which includes the release of stress hormones, other cytokines (eg,

IL-2, IL-6, IL-8, IL-10), and other inflammatory mediators of sepsis (eg, nitric oxide released by activated endothelial cells, the lipooxygenase and cyclooxygenase metabolites, platelet activation factor, interferon γ , adhesion molecules in neutrophils and endothelial cells). All of these immune modulators interact in a complex fashion to effect, in the fifth stage, the various observable changes to multiple organ systems (eg, vascular endothelium, myocardial cells, pulmonary alveolar cells, liver cells). The result is the clinical picture of sepsis and the development of multiorgan system failure. Table 2.3 lists some of the important biologic effects of the mediators involved in the sepsis syndrome with the ensuing clinical manifestations.

There are several points to be made based on our understanding of sepsis: (1) it is essential to contain and eliminate the infection source with all possible measures (eg, antibiotics, surgical or needle drainage of pus); (2) after the sepsis cascade has been activated, the clinical outcome of the patient may depend not only on effective antiinfective therapy but also on the ability to control the vigorous inflammatory response that led to the manifestations of sepsis; (3) elevations of many of the cytokines have been correlated with poor outcome among persons with sepsis. Greatly elevated levels of the inflammatory mediator IL-6, in particular,

Table 2.2 Diagnostic Criteria for Sepsis

Infection (documented or suspected) and some of the following parameters must be present:	
General appearance	Altered mental status
Vital signs	Core temperature >38° C (100.4°F) or ≤36°C (96.8°F) Heart rate >90 beats/min or >2 SD above the normal value for age Tachypnea
Laboratory parameters	Hyperglycemia (plasma glucose >110 mg/dL or 7.7 mM/L) in the absence of diabetes White blood cells >12 000 cells/mm ³ or ≤4000 cells/mm ³ or >10% immature (band) forms
Hemodynamic parameters	Arterial hypotension (SBP ≤90 mm Hg, MAP ≤70 mm Hg, or an SBP decrease of >40 mm Hg in adults or >2 SD below normal for age) Mixed venous oxygen saturation >70% ^a Cardiac index >3.5 L/min/m ² BSA Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Organ dysfunction parameters	Arterial hypoxemia (PaO ₂ /FIO ₂ ≤300) Acute oliguria (urine output ≤0.5 mL/kg/h or 45 mmol/L for at least 2 h) Creatinine increase ≥0.5 mg/dL Coagulation abnormalities (INR >1.5 or aPTT >60s) Ileus (absent bowel sounds) Thrombocytopenia (platelet count ≤100 000/mm ³) Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
Tissue perfusion parameters	Hyperlactatemia (>3 mmol/L) Decreased capillary refill or mottling
Abbreviations: SBP = systolic blood pressure; MAP = mean arterial pressure; SD = standard deviation; BSA = body surface area; INR = international normalized ratio; aPTT = activated partial thromboplastin time. ^a Normal values in children and newborns are 75%–80%, therefore this criterion should not be used as a sign of sepsis in this population.	

have been shown in multiple studies to be correlated with decreased likelihood of survival.

The first biologic treatment for sepsis, activated protein C, was approved by the U.S. Food and Drug Administration (FDA) in 2001. More recently, the administration of systemic hydrocortisone has been shown to decrease mortality in adults with relative adrenal insufficiency in one randomized clinical trial. However, in a retrospective cohort study in critically ill pediatric patients with severe sepsis, steroids were not found to improve outcome and their use was associated with increased mortality. In addition, the diagnosis of adrenal insufficiency in patients with sepsis is challenging. For instance, patients with sepsis and low serum albumin levels may have low total serum cortisol levels but normal or increased free serum cortisol levels. Therefore, at this time, corticosteroids in patients with sepsis should be used only with extreme caution, if at all.

Multiple large, well-controlled trials have failed to demonstrate any efficacy of monoclonal antibodies directed against lipid A, other components of the gram-negative bacterial cell wall, and TNF-α. However, a large prospective,

randomized, double-blind, placebo-controlled, multiple-center clinical trial published in 2004 showed that afelimomab (an anti-TNF F(ab')₂ monoclonal antibody fragment) resulted in a significant reduction in TNF and IL-6 levels and a more rapid improvement in organ failure scores compared with placebo with an adjusted reduction in the risk of death of 5.8% (*P* = .041) and a corresponding reduction of relative risk of death of 11.9% at 28 days. Nevertheless, this monoclonal antibody has not been developed further for clinical use, perhaps because of the relatively modest effects on survival (especially when compared to activated protein C).

Etiology

Historically, antibiotic recommendations for therapy of sepsis and septic shock were based primarily on coverage of gram-negative organisms. However, sepsis caused by gram-positive organisms is clinically identical to sepsis caused by gram-negative organisms and, since 1987, gram-positive pathogens have become the predominant pathogens. In most clinical series 30%–50% of the cases are caused