By means of its mannose-containing side chains, THP, secreted by cells of the ascending loop of Henle, binds strongly to *E. coli* expressing type 1 and S fimbriae. Tamm-Horsfall protein is the most abundant protein of renal origin in urine and may function as a urinary antibacterial defense mechanism by binding to mannose-sensitive strains of *E. coli,* preventing them from attaching to epithelial cell receptors (Fig. 72.3). Tamm-Horsfall protein, a kidney-specific glycoprotein, activates complement and dendritic cells but also has immunoregulatory function in UTI via a TLR4-dependent mechanism (see Fig. 72.3).[58] Significantly reduced levels of THP in older adults occur during episodes of UTI and may contribute to susceptibility to infection.

The flushing mechanism of the bladder exerts a major protective effect. When bacteria are introduced into the bladders of humans, there is a tendency for spontaneous clearance. Because flushing alone would probably not completely clear the bacteria, there must be additional protective factors. Certain host factors, including bladder catheterization, increase the susceptibility of uroepithelial cells to attachment by uropathogens, which in turn increases susceptibility to bacteriuria.

In a study of bladder defense mechanisms in dogs, it was demonstrated that there is an active antiadherence mechanism of bladder mucosa. Pretreatment of the bladder with acid increases bacterial adherence 20- to 50-fold independent of the bacterial species used. Histochemical studies revealed that bacterial adherence is increased by the removal of glycosaminoglycan, a surface mucopolysaccharide that seems to be responsible for the natural resistance to adherence. Thus normally small inocula of bacteria are probably unable to adhere, remain suspended in urine, and are removed by voiding. In the presence of a larger bladder inoculum of bacteria, especially with good adhesive qualities, the primary defense of antiadherence may be overcome, colonization can occur, and subsequent bladder infection may result. Following bladder infection, secondary defense mechanisms such as mobilization of leukocytes, phagocytosis, and bacterial destruction remove bacteria. Bacteria stimulate PMNs to secrete IL-8, IL-1β, and tumor necrosis factor and stimulate lymphocytes to elaborate immunoregulatory cytokines, ultimately resulting in immunoglobulin synthesis and modifying epithelial cell responses to bacteria. Epithelial cells participate in PMN recruitment by secreting neutrophil chemoattractants (e.g., IL-8) and by the expression of adhesion molecules involved in PMN transmigration (intercellular adhesion molecule 1).[51]

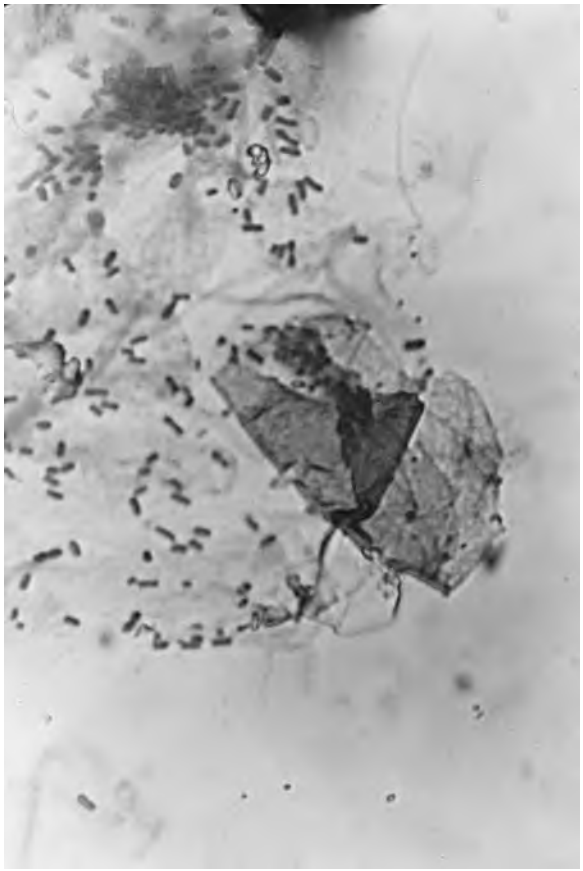


**FIG. 72.3 Light microscopic specimen of urine showing uromodulin (Tamm-Horsfall protein) with large numbers of adherent uropathogenic bacteria.**

As mentioned previously, upon reaching the bladder, UPEC bind to superficial epithelial cells in a type 1 pili–dependent manner. A subset of adherent bacteria are then internalized into epithelial cells, which in turn undertake active expulsion of internalized UPEC. This process is complex and involves exocytosis of UPEC-containing lysosomes, and activation of TLR4 by internalized UPEC. The efficiency and protective role of expulsion of intracellular bacteria in humans is under investigation[59]; however, uropathogens can occupy the cytoplasm of bladder epithelial cells and using this mechanism can replicate and persist, protected from infiltrating neutrophils. The bladder epithelial surface may serve as yet another bacterial reservoir and a source of recurrent UTI, especially since these cells are protected from urinary antibiotics.

## Adherence and Colonization

In women, bacterial adherence and colonization of the vaginal introitus and periurethral region by Enterobacteriaceae are critical in the pathogenesis of UTIs. Periurethral colonization with the same organism almost invariably precedes episodes of significant bacteriuria. Microbiologic studies have demonstrated that the urethra, periurethral region, and vaginal vestibule of women with recurrent UTIs tend to be more commonly colonized with coliform bacteria.[60,61] Stamey has postulated that such colonization is often the prelude to new infection and that women with recurrent UTIs have a biologic predisposition to colonization.[60] In a series of studies, the effects of several factors in vaginal secretions on colonization were examined. A low vaginal pH level was the most important factor reducing colonization with UPEC. *Escherichia coli* was more resistant to low pH levels and less susceptible to the inhibitory effects of vaginal fluid than *P. mirabilis* or *Pseudomonas aeruginosa.* Finally, it was noted by others that *E. coli* adhere more avidly to vaginal epithelial cells of women and young girls with recurrent UTIs. These observations, together with experimental studies using inbred mice, indicate predisposition of some women to UTI because of genetically determined host epithelial cell receptors for UPEC. This is supported by several epidemiologic studies demonstrating that women who are epithelial antigen and receptor nonsecretors have an increased risk of UTI, and their uroepithelial cells bind *E. coli* more avidly than do cells from secretors.[62] The secretor gene, *Se,* encodes a glycosyltransferase that transfers a fucose residue to specific acceptor molecules, resulting in detectable blood group antigens in secretions of people carrying the gene.[63] Lewis gene nonsecretors appear to have an increased susceptibility to urinary infections and express two unique globoseries glycosphingolipids present on vaginal and uroepithelial cells, which preferentially bind UPEC expressing class II *pap*-encoded adhesin.

Other endogenous factors, such as estrogenic hormones, may influence bacterial attachment to uroepithelial cells and affect the risk of UTI.[64] From an acquired or behavioral point of view, both colonization of the vaginal introitus and bacteriuria caused by *E. coli* have been strongly associated with diaphragm and spermicide use, which may contribute to the increased risk of UTI associated with sexual activity. Others have concluded that the decisive predisposing factor is not the colonization of the periurethral area per se, but rather the ability of these organisms to ascend the urethra, including the ability of infecting organisms to adhere to uroepithelial cells and withstand normal host defense mechanisms.

## Humoral and Cellular Immunity

The role of humoral immunity in the host's defense against infection of the urinary tract, although extensively studied, is poorly understood. The defense against acute UTI does not rely on specific immunity defined by antigen-specific lymphocyte activation. During acute pyelonephritis,

there is a systemic antibody response to O antigen and occasionally the K antigen of the infecting strain, and antibodies to type 1 and P fimbriae have been described. Immunoglobulin M (IgM) antibodies dominate in the response to the first upper tract infection but not to subsequent episodes. High levels of IgG antibodies to lipid A correlate with the severity of renal infection and the progression of renal parenchymal destruction. An antibody response consisting of IgG and secretory IgA antibodies can be detected in the urine. In contrast to upper UTI, lower UTI is usually associated with a reduced or undetectable serologic response, reflecting the superficial nature of the infection. Macrophages are well distributed in the submucosa throughout the urinary tract, and uroplakin Ia–expressing cells, analogous to Langerhans cells, have been identified in the urinary mucosa, including renal tubules. Macrophage subsets regulate neutrophil-mediated defense in UTIs. Immunoglobulin A–producing lymphocytes are found in the submucosa of infected rat bladders. Similarly, high numbers of IgA-producing plasma cells have been observed in the bladder submucosa of patients with bacterial cystitis in comparison with healthy controls. Finally, in animal models, antibody-secreting cells and B lymphocytes migrate to kidney and urinary tract submucosa during UTIs. The reduced immunologic response to the infecting organism in cystitis may contribute to reinfection with the same strain. However, in a monkey model, systemic and urinary IgG and IgA were observed to accompany experimental cystitis. Antifimbrial antibodies are absent in the urine in lower tract infection. At least one-third of females with a second UTI have an identical strain isolated, indicating incomplete or inadequate immunity with a single episode of infection.[65]

In spite of the impressive systemic and local urinary antibody production that follows acute pyelonephritis, the protective role of these antibodies is unclear. When bacteria persist in the kidney for several months, antigenic drift may occur. Antibodies against several bacterial structures, including O and K antigens and, more recently, fimbrial antigens, have been found to protect against hematogenous or ascending pyelonephritis in experimental animals. Animal recipients of vaccines based on *Pap A* fimbriae were protected against experimental pyelonephritis caused by homologous and heterologous Gal-Gal–binding uropathogenic *E. coli* strains. Mitigating against an important role for urinary and systemic antibodies are experimental studies with mice exhibiting profound B-cell immunodeficiency and a normal capacity to clear experimental ascending UTI.

Antibodies may be of value in limiting the damage incurred in the kidney or preventing colonization preceding recurrence. Svanborg-Eden and Svennerholm[66] have reported that the urine of patients with pyelonephritis inhibits the adherence of *E. coli* to uroepithelial cells and that this activity is removed by absorption with O antigen. Antibodies have not been shown to protect against bladder infection. Cell-mediated immunity has not been shown to play a major role in host defenses against UTI. Urinary tract mucosa contains few T lymphocytes, although both $CD4^+$ and $CD8^+$ T cells can be found in the submucosa and lamina propria; however, they generally lack γδ T cells.[67] Experimental studies in athymic mice have shown similar resistance to intravesical infections when compared with normal controls. Similarly, clinical experience in human immunodeficiency virus–infected women with severe defects in cell-mediated immunity, including low CD4 lymphocyte counts, does not indicate increased susceptibility to or severity of urinary infection.[68] Nevertheless, a useful role for cell-mediated immunity may still exist in that T-cell–derived proinflammatory cytokines (e.g., interferon-γ) stimulate epithelial cells to produce IL-6 in a similar manner to Th2 lymphocyte responses involving IL-4, IL-5, IL-8, IL-10, and IL-13.[28] Interleukin-8 is an inflammatory cytokine that promotes neutrophil migration across the infected uroepithelial cells. Thus urinary tract T cells producing immunoregulatory cytokines may influence the mucosal epithelial cell response to bacterial adherence and invasion. The IL-6 secreted by renal tubular epithelial cells[28] may contribute to mucosal antibacterial activity by increasing IgA secretion by committed B cells. During pyelonephritis, an acute inflammatory exudate consisting predominantly of PMNs is present. Although the inflammatory reaction is directed at limiting bacterial spread and persistence in the kidney, infiltrating phagocytic cells may contribute to tissue damage[48] and renal scarring, as evidenced by reduced parenchymal kidney destruction in experimental neutropenia. It has been suggested that chronic pyelonephritis and persistent renal damage may develop after successful eradication of bacterial pyelonephritis with antimicrobial therapy. According to these concepts, bacterial remnants or antigen or THP persistence induces a chronic humoral immunologic response resulting in cryptogenic renal scarring. Secretory IgA is one of three glycoproteins that bind type 1 *E. coli* and could affect vaginal colonization.[69]

## Genetic Factors

It is apparent that multiple genetic risk factors exist for UTIs, influencing host defense mechanisms operative at different levels of the urinary tract.[70,71] Investigators have reported the increased incidence of UTI in the immediate female family members of women with recurrent UTIs, supporting a genetic propensity to uncomplicated cystitis and pyelonephritis.[72,73] Overall, genetic determinants of familial susceptibility are not well characterized. Genetic influences relate to uroepithelial cell receptors (secretor status) and to the inflammatory response and antibacterial peptide elaboration. Studies of experimental UTIs in C3H/HeJ female mice have shown diminished resistance in this mouse strain, which is genetically unresponsive to the biologic effects of *E. coli* lipopolysaccharide, although several genes are likely to be operative. Candidate genes include the *ABH* secretor gene and the IL-8 receptor *CXCR1* gene. Knockout mice lacking CXCR1 were unable to clear bacteria from the kidney and developed bacteremia. Lundstedt and colleagues[70] reported familial associated pyelonephritis, but not cystitis, in girls and women with polymorphisms having significantly lower expressions of CXCR1, an IL-8 receptor. In addition, levels of CXCR2 expression on neutrophils of women with recurrent UTI were significantly lower than those of control patients.[74] Similar findings were observed in family members of acute pyelonephritis–prone children. As noted, the innate immune system involves the TLR family of receptors in microbial recognition. This recognition is through bacteria-specific common antigens (e.g., lipopolysaccharide) rather than a specific ligand for TLR4. Studies have identified single nucleotide polymorphisms of the TLR4 molecule affecting innate immune responses to uropathogenic *E. coli*.[75] Selected polymorphisms that reduce TLR4 functions are associated with asymptomatic bacteriuria, whereas genotype variants of interferon regulatory factor 3, a transcription factor, are associated with increased familial incidence of pyelonephritis. Although women with recurrent urinary infections were shown to have lower levels of urinary secretory IgA, the clinical significance is highly questionable. Bates and associates[76] have shown that knockout mice for THP inoculated with type 1 fimbriated *E. coli* have a longer duration of bacteriuria and more intense bladder colonization compared with $THP^{+/+}$ mice.

## Structural Abnormalities

Several abnormalities of the urinary tract interfere with its natural resistance to infection. Obstruction to urine flow is the most important of these. Extrarenal obstruction can result from the following: congenital anomalies of the ureter or urethra, such as valves, stenosis, or bands; calculi; extrinsic ureteral compression from various causes; and benign prostatic hypertrophy. Intrarenal obstruction may be produced by entities such as nephrocalcinosis, uric acid nephropathy, analgesic nephropathy, polycystic kidney disease, hypokalemic nephropathy, and the renal lesions of sickle cell trait or disease. Obstruction inhibits the normal flow of urine, and the resulting stasis is important in increasing susceptibility to infection. Men of any age and pregnant women are the most prone to lesions that result in obstruction to the free flow of urine.

In animals, obstruction of a ureter markedly increases susceptibility to ipsilateral hematogenous infection. Intrarenal obstruction, experimentally produced by scars in various ways, also increases the susceptibility of the kidney to infection. Medullary scars, which produce greater amounts of obstruction than cortical scars, increase the susceptibility of animals to infection more than cortical scars. Calculi may increase susceptibility to UTI by producing obstruction (Fig. 72.4). However, not all stones obstruct, and local irritative phenomena may also be

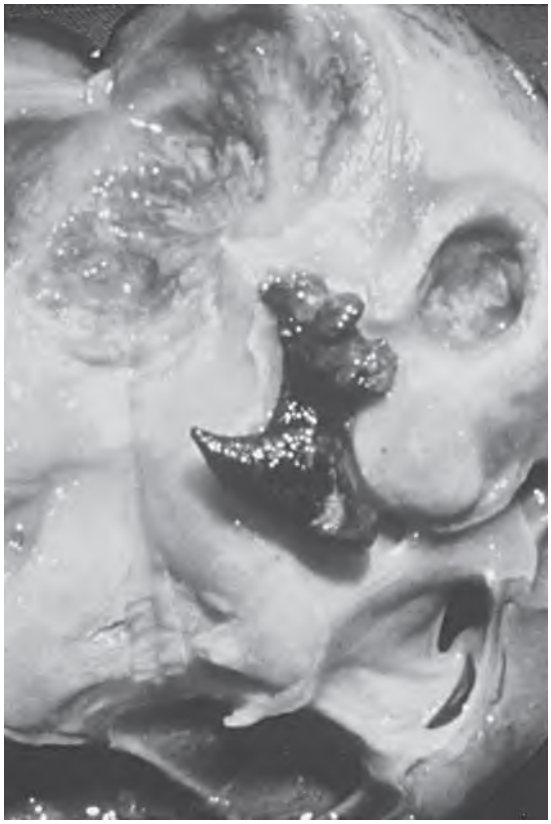


**FIG. 72.4 Staghorn calculus visible in the dilated pelvis of a hydronephrotic kidney.** *(Courtesy Dr. M. Bergeron.)*

important. Furthermore, calculi may develop secondary to infection. It has been observed clinically and experimentally that *Proteus* spp. and other urea-splitting organisms are most likely to produce calculi. Furthermore, bacteria survive deep within the calculi and associated biofilm and are extremely difficult to eradicate, even by artificial means such as by incubating in solutions containing antibiotics or iodine and alcohol. This may account for the well-known difficulties encountered clinically in trying to cure UTI in the presence of stones.

Vesicoureteral reflux and UTI are also intricately related. The significance and management of reflux have undergone considerable review (see "Imaging Studies" later). Reflux caused by a congenital abnormality, bladder overdistention, or unknown causes probably contributes to upper tract infection via the ascending route. On the other hand, clinical observations have demonstrated that infection may, in fact, produce reflux, especially in children. Reflux tends to perpetuate infection by maintaining a residual pool of infected urine in the bladder after voiding. It is probable that severe reflux, especially in young children, plays an important role in the production of upper tract infection and subsequent scarring. Patients with incomplete emptying of the bladder for mechanical reasons (bladder neck obstruction, urethral valves, urethral strictures, prostatic hypertrophy) or neurogenic malfunction (diabetic neuropathy, cord injuries) are prone to frequent UTIs. These patients are subject to bladder overdistention, which may interfere with local defense mechanisms, and, most importantly, frequent instrumentation of the urinary tract.

## EPIDEMIOLOGY AND NATURAL HISTORY OF URINARY TRACT INFECTION[77]

### Infecting Organisms

More than 95% of uncomplicated UTIs are caused by a single bacterial species. There is a difference between the bacterial flora of the urine in patients with an initial episode of UTI compared with the flora from those with frequent recurrences of infection. *Escherichia coli* is the most frequent infecting organism in initial infections.[78,79] In recurrent UTIs, especially with complicated UTI (e.g., obstructive uropathy, congenital anomalies, neurogenic bladder, fistulous communication involving the urinary tract), the relative frequency of infection caused by bacteria such as *Proteus, Pseudomonas, Klebsiella,* and *Enterobacter* spp., by antibiotic-resistant *E. coli,* and by enterococci and staphylococci increases greatly. In the presence of complicated UTI, it is not uncommon to isolate multiple organisms from the urine. Because instrumentation and repeated courses of antimicrobial therapy are common in these patients, antibiotic-resistant isolates might be expected.[1]

The hospital and long-term care facility environments are an important determinant of the nature of the bacterial flora in UTI. *Proteus, Klebsiella, Enterobacter,* and *Pseudomonas* spp., as well as staphylococci and enterococci, are more often isolated from inpatients, compared with a greater preponderance of *E. coli* in an outpatient population.[80] Cross-infections are important in the pathogenesis of hospital-related UTIs, especially with indwelling catheters.[81] *Corynebacterium urealyticum* (formerly known as *Corynebacterium* group D2) has been recognized as an important nosocomial pathogen.[82,83] This gram-positive, urea-splitting, slow-growing bacillus may cause infected mucosal encrustations of the bladder and urinary collecting system, including struvite stones, especially in immunosuppressed patients and in particular in renal transplant recipients. It is highly resistant to antimicrobials, although usually sensitive to vancomycin. It should be considered in the presence of a high urine pH, urologic problems, previous UTI, and recent antibiotic treatment.

In recent years, highly antibiotic-resistant uropathogens such as *Acinetobacter* species and extended-spectrum β-lactamase (ESBL)–producing, AmpC β-lactamase–producing, and carbapenemase-producing Enterobacteriaceae (e.g., New Delhi metallo-β-lactamase 1) have been increasingly reported as causes of health care–related complicated UTIs.[84,85,86,87] There has also been the worldwide spread of antibiotic-resistant uropathogenic clones of *E. coli,* such as CTX-M-15 ESBL *E. coli* O25:H4 sequence type ST131, which has emerged as a significant cause of community-acquired UTI.[88–90]

Anaerobic organisms are rarely pathogens in the urinary tract. Fungi (particularly *Candida* spp.) occur in patients with indwelling catheters who are receiving antimicrobial therapy.[91,92] Coagulase-negative staphylococci are a common cause of UTI in some reports. *Staphylococcus saprophyticus* tends to cause infection in young females who are sexually active, accounting for 5% to 15% of acute cystitis episodes in the United States.[93] Coagulase-positive staphylococci most often invade the kidney from the hematogenous route, resulting in intrarenal or perinephric abscesses. *Actinobaculum schaalii* and other *Actinobaculum* spp. are facultative anaerobic gram-positive bacilli and are often missed in urine cultures because of their slow growth or dismissed as genital flora.[94–96] *Actinobaculum schaalii* is a part of normal skin and vaginal flora. Most cases of urosepsis have occurred in patients older than 65 with renal stones undergoing lithotripsy or other instrumentation. *Actinobaculum schaalii* has been reported as susceptible to ampicillin, cephalosporins, and vancomycin but resistant to fluoroquinolones and TMP-SMX.

Adenoviruses (particularly type 11) have been strongly implicated as causative agents in hemorrhagic cystitis in pediatric patients (especially boys) and in allogeneic hematopoietic stem cell transplant recipients, and in UTI in renal transplant recipients.[97,98] Although various investigators using special media have isolated fastidious organisms from women with lower tract symptoms, the causal role of these organisms is controversial. Similarly, *Gardnerella vaginalis, Ureaplasma urealyticum,* and *Mycoplasma hominis* are possible but unproven causes of UTI.

One group has reported nanobacteria as tiny (0.05- to 0.5-mm) cell wall–possessing bacteria that are associated with renal stones.[99] In vitro, these agents produce carbonate apatite that can fix calcium. These have been found to be self-propagating mineral complexes and not bacteria.[100,101]

### Asymptomatic Bacteriuria Versus Symptomatic Infection

The methodical studies of asymptomatic bacteriuria in different populations (described later) were important in understanding the epidemiology

of UTI. However, except in pregnancy, in those patients undergoing invasive genitourinary tract procedures, it is uncommonly followed by symptomatic infection and is of little consequence. With the exception of these groups, there is rarely a reason for determining the presence of or treating asymptomatic bacteriuria.[2,102] With the exception of these groups and other rare exceptions, the only reason for taking urine cultures or treating infection is for symptomatic infection and for the purpose of relieving symptoms. Screening has not been shown to improve clinical outcome, and asymptomatic bacteriuria does not lead to hypertension, chronic renal failure, or decreased survival. Asymptomatic bacteriuria is used as a marker for poor overall health status in diabetics and in elderly inpatients. In contrast, asymptomatic bacteriuria in pregnancy (4%–7% incidence) is associated with progression to symptomatic pyelonephritis,[103] the most common nonobstetric cause of hospitalization during pregnancy.

## Urinary Tract Infection in Children

The problem of UTI in pediatric patients spans all age groups, beginning with neonates.[104,105] The frequency of UTI in infants is about 1% to 2%. It is more common in boys during the first 3 months and thereafter occurs more often in girls. The highest incidence of febrile UTIs occurs during the first year of life in both males and females, whereas nonfebrile UTIs (i.e., cystitis) are most common in females older than 3 years of age. The significance of fever is that it implies renal parenchymal infection, which is associated with an increased likelihood of underlying urologic abnormalities and renal scarring.[106] Most studies have found that a lack of circumcision predisposes to UTIs in infants and young boys.[107–109] The risk of UTI is increased in those with underlying urinary tract abnormalities, such as vesicoureteral reflux and voiding dysfunction, and this risk may be increased when bladder and bowel dysfunction are also present.[106,110,111]

During the preschool years and thereafter, UTI is much more common in girls than in boys. In preschool boys, it is frequently associated with congenital urologic abnormalities. The annual incidence of UTI in this age group is 4.5% for girls and about 0.5% for boys. Infections during this period are often symptomatic, and it is believed that much of the renal damage that occurs in association with UTI takes place in infancy and the preschool period (Fig. 72.5).[112] However, adult kidneys can also acquire scars due to pyelonephritis, as is seen in children with transplanted kidneys.

About 7% to 8% of girls and 2% of boys have a febrile UTI during the first 8 years of life.[106] Renal scars may be produced by primary renal damage in utero from obstruction, genetic, and developmental factors and can be indistinguishable from those produced by infection in postnatal life.[106] In fact, antenatal ultrasound studies have demonstrated that intrinsic renal disease and not infection is the major cause of chronic renal disease in children.[106] The risk of recurrent infection is 12% to 30% in the first 6 to 12 months after the first UTI and is increased in the presence of urologic abnormalities.[110]

In school-age girls bacteriuria is common, is often asymptomatic, and frequently recurs.[113,113a] For example, the prevalence of bacteriuria among schoolgirls was about 1.2%, and about 5% of the schoolgirls had significant bacteriuria at some time before leaving high school. About one-third of these patients had some symptom referable to the urinary tract when the bacteriuria was first detected. Bacteriuria was rare in schoolboys (prevalence, 0.03%). When many of these girls who had had bacteriuria previously (usually asymptomatic) were married or became pregnant, bacteriuria recurred at a rate far above that expected for the general population. More than 50% developed bacteriuria within 3 months after marriage. Thus the presence of bacteriuria in childhood defines a population at higher risk for the development of bacteriuria in adulthood.

In general, children with UTIs without structural or functional obstruction or severe vesicoureteral reflux have a very good prognosis.[112,114] In the presence of obstruction (e.g., urethral valves), severe injury of renal parenchyma can occur.[105,115] Vesicoureteral reflux is found in 30% to 50% of young children with symptomatic UTI (see Fig. 72.5).[116] Reflux may be primary, which results from delayed development of the vesicoureteral junction or a short intravesical ureter, or it may occur secondary to increased pressure in the bladder due to abnormal bladder function or obstruction. Renal scarring associated with reflux is called *reflux nephropathy* (small scarred kidneys). Acquired reflux nephropathy, which is a result of pyelonephritis, is more common in female children, whereas congenital reflux nephropathy, which results from renal dysplasia, is more common in male children.[117] Children with reflux are more likely to develop pyelonephritis than those without

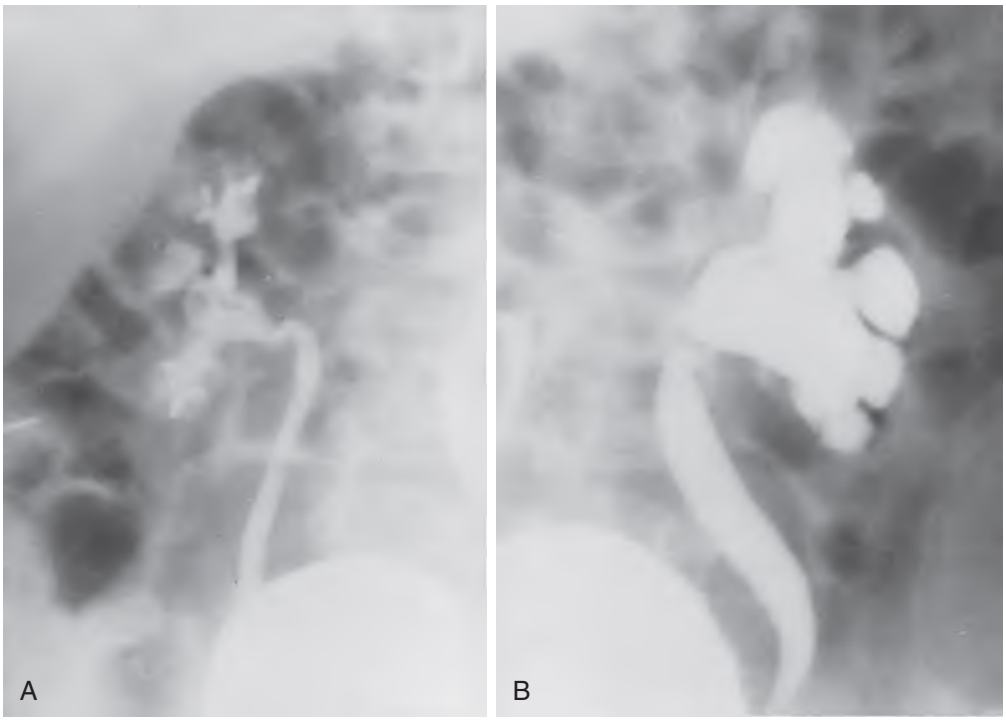



**FIG. 72.5 Vesicoureteral reflux in a young girl with recurrent urinary tract infections.** (A) Right kidney demonstrates grade II reflux. (B) Left kidney shows dilation of the ureter, grade III reflux, and calyceal clubbing. *(Courtesy Dr. T. Slovis.)*

reflux.[118] Reflux in the presence of infection can be associated with the development of scarring.[115,119] Those with reflux are more likely to develop scarring than those without reflux, and those with higher grades of reflux (grade IV or greater) are more likely to develop scarring than those with lower grades.[118] Renal scarring is 27 times more likely in kidneys with grade IV vesicoureteral reflux as compared to kidneys with no reflux.[120] Unlike the previously published studies, the RIVUR study, which included children ages 2 to 71 months, reported significantly more renal scarring in older children (median age of 26 months) as compared to a median age of 11 months in those with no scarring.[120] Complications of renal scarring include hypertension and proteinuria, and end-stage renal failure may occur in some patients. Scarring has also been associated with delay in antibacterial therapy of UTI.[115]

It should be emphasized that the contribution of reflux alone compared with reflux plus infection in the progression of renal scarring has not been clearly delineated. Severe reflux alone may be associated with renal damage and insufficiency. Studies in uninfected animals have demonstrated that reflux alone, and in particular intrarenal reflux, can produce "pyelonephritic" scars. It has also been shown that the immature kidneys of infants are more prone to intrarenal reflux. However, it is probable that reflux is more likely to lead to severe damage and scarring when infection is also present.[119]

Mild to moderate degrees of reflux (and occasionally even severe reflux) are likely to disappear with time, probably in relation to maturation of the vesicoureteral junction (see "Imaging Studies" later).[119] Severity (grade) of reflux is the strongest predictor of lack of resolution of reflux.[121] Progression of scars already present or the development of new ones is uncommon after the age of 5 years.[119] Treatment options are not well defined. In a multisite study of 607 children with vesicoureteral reflux, antimicrobial prophylaxis did reduce the rate of recurrence, but not scarring. Concerns remain about identifying an appropriate subgroup of patients who would benefit from prophylaxis, in order to decrease unnecessary prescription and selective pressure that favors drug-resistant bacteria.[122] Screening of children for asymptomatic bacteriuria and treatment of asymptomatic bacteriuria are not recommended.

## Urinary Tract Infection in Adults

According to the most recently available combined data from the Centers for Disease Control and Prevention's annual National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, in 2007 there were 8.6 million ambulatory visits for UTI in both men and women in the United States.[123] Pyelonephritis is far less common than cystitis, comprising approximately 250,000 cases per year in the United States.[77]

UTIs are much more common in women than in men. Premenopausal women are at especially high risk for acute cystitis; the incidence is 0.5 to 0.7 case per person-year among sexually active women. The strongest risk factors in premenopausal women include sexual intercourse, use of spermicides, and history of previous UTI, as well as diabetes. In this population, risk factors suggesting a genetic component are a history of maternal UTI and age of first UTI. Many of these patients previously had UTIs as children and continue to have infections as adults. Once adulthood is reached, the prevalence of asymptomatic bacteriuria increases in the female but not in the male population. The prevalence of asymptomatic bacteriuria in young nonpregnant women is about 1% to 3%.[124] Each year, about 25% of these bacteriuric women clear their bacteriuria and an equal number become infected, often women who have had urinary infection previously. Up to 60% of the female population (5% in men) will experience at least one symptomatic UTI at some time during their life, and up to 10% of women in the United States have at least one episode of symptomatic infection each year.[78] Worldwide 150 million individuals develop UTIs. The peak incidence of symptomatic infections occurs in young, sexually active women ages 18 to 24 years, with one-third to one-half of women self-reporting at least one UTI by age 32. Recurrent episodes are common.[78,125,126] Frequent sexual intercourse; a new sex partner; diaphragm use, especially with a spermicide; lack of urination after intercourse; and a history of previous infection are risk factors for urinary infection in women.[78,125,127,128] The diaphragm can cause urinary obstruction in some women, but its main effect is probably a change in vaginal flora caused by the spermicide.[125]

About 2% to 5% of healthy women have recurrent UTIs during their lifetime.[129] It seems that there may be a genetic predisposition for recurrent cystitis or pyelonephritis in these women because UTI in female relatives is strongly associated with recurrent UTI.[72,129] Once a woman develops infection, she is more likely to develop subsequent infections than a patient who has had no previous infections. For example, in several studies, after a first episode of cystitis in young women caused by *E. coli,* 24% had a second episode within 6 months. With one or more episodes, the risk of another within 1 year was 70%.[130] Recurrences after the first *E. coli* infection with a different uropathogen (*E. coli* or other) were twice as frequent as recurrences with the same *E. coli* strain.[128] Women with acute pyelonephritis, a much less common infection than cystitis, also tended to have recurrences.[130] It may be a simple matter to cure an individual episode, but recurrence, most often reinfection, is common. The type of infection that recurs (i.e., asymptomatic bacteriuria, cystitis, or pyelonephritis) depends on a complex interaction between genetic factors and virulence characteristics of the uropathogen.[131] It must be stressed that in the nonpregnant adult female with a normal urinary tract, asymptomatic bacteriuria infrequently progresses to symptomatic infection and that cystitis uncommonly progresses to pyelonephritis. *Escherichia coli* causing UTI may be transmitted between sexual partners because the same strains have been found in the urine of men who are sexual partners of women with UTI.[132]

The prevalence of asymptomatic bacteriuria in adult men is low (≤0.1%), as is the occurrence of symptomatic infection, until older age, when it rises.[133] Men with UTI frequently have anatomic abnormalities of the urinary tract and therefore should be considered to have complicated UTI until proven otherwise.[78] In young men, a lack of circumcision increases the risk of UTI caused by uropathogenic strains of *E. coli,* including the development of symptomatic urethritis.[134] Male homosexuality is a risk factor, probably related to rectal insertive intercourse.[135]

It is clear that UTI in adults can lead to progressive renal damage in the presence of obstruction. However, recurrent infection in adults in the absence of obstruction rarely, if ever, leads to renal failure.[124] The United States Renal Data System, which reports causes of renal failure in patients undergoing dialysis, does not even mention infection other than reflux nephropathy, which may or may not have involved infection.[136]

Autopsy studies have shown that it is difficult to implicate infection per se (i.e., in the absence of other renal abnormalities) as an important pathogenic factor in the production of severe renal disease in adults. One exception might be severe papillary necrosis secondary to infection. One group of investigators was unable to find any case of uncomplicated pyelonephritis that progressed to end-stage renal disease among 173 patients admitted to dialysis programs.[137] In prospective studies, hundreds of patients with persistent or recurrent infections in the absence of other underlying renal disease have been followed for years without documenting the progression of renal disease from infection alone.

The role of infection in the progression of clinically or radiographically diagnosed interstitial renal disease has also been examined.[112,124] In general, the studies indicate that infection is rarely, if ever, the major factor leading to further renal decompensation. However, infection may occasionally accelerate the progression of the primary underlying disease process. In summary, except for perhaps rare cases, there is no evidence to indicate that uncomplicated UTI alone produces renal failure in adults.

## Urinary Tract Infection in the Elderly

At least 10% of men and 20% of women older than 65 years have asymptomatic bacteriuria. In contrast to young adults, in whom bacteriuria is 30 times more frequent in women than in men, in those older than 65 years the ratio alters dramatically, with a progressive decrease in the female-to-male ratio.[138,139] In both men and women, the prevalence of asymptomatic bacteriuria rises substantially. Possible

reasons for the high frequency of asymptomatic bacteriuria in older patients include obstructive uropathy from the prostate (with resultant instrumentation) and loss of the bactericidal activity of prostatic secretions in men, poor emptying of the bladder because of prolapse in women, soiling of the perineum from fecal incontinence in demented women, and neuromuscular diseases and increased instrumentation and bladder catheter usage in both genders.[139] The majority of older men with UTI have underlying urologic abnormalities.[133] Urinary incontinence also contributes to UTI in postmenopausal women.[140] There is a high rate of spontaneous cure and reinfection with asymptomatic bacteriuria in women and men.[139] The spectrum of microorganisms is unaltered in the older adult population. Symptomatic infection uncommonly follows asymptomatic bacteriuria, and asymptomatic bacteriuria is much more frequent than symptomatic UTI in this age group.

Asymptomatic bacteriuria in older persons does not seem to have any deleterious effects.[141,142] Furthermore, there is no evidence to suggest that treatment of asymptomatic bacteriuria in older patients has any beneficial effects, including decreasing urinary incontinence.[142,143] Therefore routine treatment of asymptomatic bacteriuria in older patients is not indicated.[142–144] Effective management of symptomatic episodes in older males requires determining whether the site of infection is the kidney, bladder, or prostate.

## Urinary Tract Infection in Other Conditions

There is a higher prevalence of asymptomatic and symptomatic UTI in hospitalized and nursing home patients than in outpatients. The general ill health of these patients and the higher probability of urinary tract instrumentation are probably the major contributors to these differences. A single catheterization causes UTI in only about 1% of ambulatory persons. However, after a single catheterization of hospitalized patients, infection occurs in at least 10%.

Race apparently does not appreciably affect the prevalence of asymptomatic bacteriuria. However, socioeconomic status is important, with pregnant women from lower socioeconomic groups having a higher prevalence of bacteriuria than those from higher socioeconomic groups.[145]

Various underlying diseases have been associated with an increased frequency of UTI. Diabetic women but not men have been found to have a higher prevalence of asymptomatic bacteriuria than nondiabetic patients[146–148]; they also have an increased frequency of symptomatic infection. Diabetics also have a higher incidence of severe infection, including severe pyelonephritis and uncommon complications such as emphysematous pyelonephritis and perinephric abscess. However, studies that followed diabetic women for up to 3 years found no advantage in screening for and treating asymptomatic UTI; it was concluded that diabetes should not be an indication for screening for or treatment of asymptomatic bacteriuria.[102,149]

African-American women with sickle cell trait had been reported to have a higher prevalence of bacteriuria during pregnancy than African-American women without the sickle trait. A more recent report did not find this association.[150] Other conditions stated to be associated with UTI (but without documentation) include chronic potassium deficiency, gout, hypertension, and other conditions causing interstitial renal disease. There is an increased frequency of symptomatic and asymptomatic UTIs in human immunodeficiency virus infection and particularly with low CD4 counts with a higher incidence of nontypical bacterial pathogens.[151,152]

At least 50% of renal transplantation patients develop UTIs in the early postoperative period; up to 14% develop pyelonephritis, and up to 7% develop bacteremia of UTI origin in the first year.[153–155] Antibacterial prophylaxis is often used in the early transplantation period to prevent UTI. Recent studies have emphasized the emergence of enterococci and drug-resistant Enterobacteriaceae as posttransplantation uropathogens.[156] There is a growing perspective that asymptomatic bacteriuria should not be treated because it is not generally associated with development of symptomatic disease or graft dysfunction.[157]

Table 72.3 lists risk factors for UTIs.

**TABLE 72.3 Risk Factors for Urinary Tract Infection (UTI)**

| Age | Female | Male |
|---|---|---|
| All ages | Previous UTI | Lack of circumcision (children and young adults) |
| | Urologic instrumentation or surgery | Urologic instrumentation or surgery |
| | Urethral catheterization | Urethral catheterization |
| | Urinary tract obstruction, including calculi | Urinary tract obstruction, including calculi |
| | Neurogenic bladder | Neurogenic bladder |
| | Renal transplantation | Renal transplantation |
| Adults | UTIs in female relatives | Insertive rectal intercourse |
| | Sexual intercourse | Vaginal *Escherichia coli* colonization in partner |
| | New sex partner | |
| | Lack of urination after intercourse | |
| | Spermicidal contraceptive jellies | |
| | Diaphragm use | |
| | Pregnancy | |
| | Lower socioeconomic group | |
| | Diabetes | |
| | Possibly sickle cell trait in pregnancy | |
| Older age | Functional or mental impairment | Functional or mental impairment |
| | Estrogen deficiency (loss of vaginal lactobacilli) | Prostatic enlargement |
| | Bladder prolapse | Condom catheter drainage |

## Infection in the Obstructed Kidney After Urologic Treatment of Hydronephrosis

Bacteria or *Candida* may reach the renal pelvis through a percutaneous nephrostomy catheter or retrograde from the bladder through a ureteral stent, particularly if the catheter or stent is in place for several weeks. This colonization of the renal pelvis is generally asymptomatic unless the urine flow is obstructed. This can happen when a stent or nephrostomy tube is removed and significant ureteral stricture remains. Infection of the renal pelvis and calyces can develop rapidly, with fever and pain. Pus can fill the renal pelvis and rapidly destroy the kidney. Sometimes pus will exit the renal pelvis along a prior nephrostomy tract and form a perirenal abscess. Emergency drainage of the renal pelvis and systemic antimicrobial therapy are indicated. As a preventive measure, if there is concern about inadequate ureteral drainage after removing a stent or percutaneous nephrostomy catheter, it is useful to treat the organism in the urine just before the procedure. When *Candida* is in the urine, systemic fluconazole may be useful because of its high urinary concentrations.

## Infections in Polycystic Kidneys

Patients with autosomal-dominant polycystic kidney disease are prone to recurrent episodes of infections of their renal cysts, manifesting as fever, leukocytosis, and flank pain. Urine cultures may be negative, but bacteremia is common. *Escherichia coli* is the most common causative organism. Lipid-soluble antibiotics such as fluoroquinolones or TMP-SMX are thought to penetrate best into cysts. Computed tomography (CT) may show intracystic gas or a contrast-enhanced wall. Magnetic resonance imaging (MRI) is useful if renal function permits gadolinium contrast. Distinguishing infection from hemorrhage into a cyst, which is common, can be challenging. Patients not responding to antimicrobial therapy may need ultrasound-guided aspiration of infected cysts.[158]

# CLINICAL MANIFESTATIONS

## Symptoms

Urinary tract infection in children tends to manifest with different symptoms, depending on the age of the child. Symptoms in neonates and children younger than 2 years are nonspecific.[105,107,108,110] Failure to thrive, vomiting, and fever seem to be the major manifestations. When

children older than 2 years (and, more consistently, older than 5 years) develop infection, they are more likely to display localizing symptoms such as frequency, dysuria, and abdominal or flank pain.

The manifestations of UTI in adults are usually easy to recognize. The lower tract symptoms result from bacteria producing irritation of urethral and vesical mucosa, causing frequent and painful urination of small amounts of turbid urine. Patients sometimes complain of suprapubic heaviness or pain. Occasionally, the urine is grossly bloody or shows a bloody tinge at the end of micturition. Fever is generally absent with cystitis and, if present, should suggest upper tract infection. In a male, presence of fever with only symptoms of cystitis may indicate acute prostatitis.

The classic clinical manifestations of pyelonephritis include fever (sometimes with chills), flank pain, and frequently lower tract symptoms (e.g., frequency, urgency, and dysuria). At times the lower tract symptoms antedate the appearance of fever and upper tract symptoms by 1 or 2 days. It should be recognized that the symptoms described, although classic, may vary greatly. In fact, pyelonephritis may show protean clinical manifestations in adults as well as in children. Flank tenderness or discomfort is frequent in upper tract infection in adults and is more intense when there is obstructive disease. Severe pain with radiation into the groin is rare in acute pyelonephritis per se and suggests the presence of a renal calculus. The pain from the kidney is occasionally felt in or near the epigastrium and may radiate to one of the lower quadrants. These manifestations may offer difficulties in differential diagnosis and suggest gallbladder disease or appendicitis. Functionally independent older adults will present with typical symptoms of UTI.[159] Symptoms may not be diagnostic, however, because noninfected older patients often experience frequency, dysuria, hesitancy, and incontinence. In the very old or frail elderly, worsening of cognitive impairment, delirium, or falls may be the only presenting symptom.[159] Older age is an independent risk factor for severe sepsis and septic shock in individuals with acute complicated pyelonephritis.[160] The effect of asymptomatic bacteriuria on the general sense of well-being, appetite, and urinary continence has been studied, but no association could be demonstrated.[138,161–163]

Silent upper tract infection may be accompanied by lower tract symptoms only or no symptoms at all. Patients with UTIs in the presence of an indwelling urinary catheter usually have no lower tract symptoms, but flank pain or fever may occur. Urinary tract infection is the most common source of bacteremia produced by gram-negative bacilli, which may result in the sepsis syndrome. Bacteremia may occur with no urinary symptoms, especially in the presence of an indwelling catheter.

Symptoms of UTI are frequently difficult to elicit in older adults because of the presence of dementia, indwelling urinary catheters, and the atypical symptoms often seen in this population. Therefore a diagnosis of sepsis due to UTI may be made erroneously in the absence of urinary symptoms because of the presence of unrelated fever and asymptomatic bacteriuria, which is often present in this population.

### Alterations in Renal Function

In experimentally produced pyelonephritis, the only consistent abnormality of renal function is the inability to concentrate the urine maximally.[164] The mechanism of the concentrating defect is not clear but seems to be related in experimental animals to inflammation and perhaps to the increased production of prostaglandins. The concentrating defect occurs early in the course of experimental infection and is rapidly reversible with antimicrobial therapy and after the administration of prostaglandin inhibitors. The same phenomenon occurs in humans.

Progressive destruction of the kidney in the presence of obstruction may occur and give rise to clinical manifestations of renal insufficiency. Occasionally, bilateral papillary necrosis can lead to rapidly progressive renal failure. Acute kidney injury in the setting of pyelonephritis may occur secondary to concomitant severe sepsis (acute tubular necrosis).

Pyelonephritis in childhood, even with no evidence of compromised renal function in adolescence, has been shown to be a risk factor for renal disease in adulthood.[165] Among adult women hospitalized with pyelonephritis, renal scars could be demonstrated with sensitive imaging techniques; however, no correlation with hypertension or chronic renal disease was seen.[166]

## DIAGNOSIS

### Presumptive Diagnosis of Urinary Tract Infection

Using the preferred definition of pyuria, which is at least 10 leukocytes/$mm^3$ of midstream urine by counting chamber, the vast majority of patients with symptomatic or asymptomatic bacteriuria have pyuria. In fact, with symptomatic infection, most have hundreds of leukocytes per cubic millimeter. A less reliable method uses a urine specimen that is centrifuged for 5 minutes at 2000 rpm and then the sediment is examined under high power. With this method, 5 to 10 leukocytes/high-power field in the sediment is the upper limit of normal. It should be emphasized that the finding of pyuria is nonspecific, and patients with pyuria may or may not have infection.[167] The absence of pyuria should strongly call into question a diagnosis of UTI.

The dipstick leukocyte esterase test is a rapid screening test for detecting pyuria and has largely replaced microscopic methods. Although the sensitivity and specificity are high for detecting more than 10 white blood cells/$mm^3$ of urine (75%–96% and 94%–98%, respectively), a positive test by no means indicates UTI; in patients with a negative leukocyte esterase test and UTI symptoms, a urine microscopic examination for pyuria or a urine culture should be considered.[168,169]

Microscopic or sometimes gross hematuria is occasionally seen in patients with UTI (i.e., hemorrhagic cystitis). However, red blood cells may be indicative of other disorders, such as calculi, tumor, vasculitis, glomerulonephritis, and renal tuberculosis. White cell casts in the presence of an acute infectious process are strong evidence for pyelonephritis, but the absence of white cell casts does not rule out upper tract infection. White cell casts can also be seen in renal disease in the absence of infection. Proteinuria is a common although not universal finding in UTI. Most patients with UTI excrete less than 2 g of protein/24 h; excretion of 3 g/24 h or more suggests glomerular disease.

Microscopic examination of a urine specimen for bacteria can be useful for the presumptive diagnosis of UTI. The ability to identify bacteria in the urine depends on whether the specimen has been centrifuged and on whether it has been stained with Gram or methylene blue stain (Table 72.4). Smaller numbers of bacteria can be detected microscopically in a stained than in an unstained specimen, and smaller numbers can be detected in centrifuged than in uncentrifuged urine. The presence of at least one bacterium per oil immersion field in a midstream clean-catch, Gram-stained, uncentrifuged urine specimen correlates with $10^5$ bacteria/mL of urine or more. Because this titer is regarded to represent significant bacteriuria, Gram staining of an uncentrifuged specimen is an easy, rapid, and relatively reliable way to detect significant numbers of organisms. The absence of bacteria in several fields in a stained sedimented specimen indicates the probability of fewer than $10^4$ bacteria/mL.

A number of rapid indirect methods have been devised to detect bacteriuria for presumptive diagnosis. Most common are tests (e.g., dipstick) that detect the presence of urine nitrite, which is formed when bacteria reduce the nitrate that is normally present.[168] False-negative test results are common, especially in the detection of low-count bacteriuria ($10^2$–$10^3$/mL) and with certain bacterial species, but false-positive results are unusual. The sensitivity and specificity of screening tests for UTI, such as dipsticks, depends on the likelihood of infection in the group being studied (e.g., acutely symptomatic patients vs. those

**TABLE 72.4 Bacterial Count by Direct Examination of Urine**

| Sample | Unstained (×400) | Stained (×1000) |
|---|---|---|
| Uncentrifuged sample | $\geq 0^6$ | $\geq 10^5$ |
| Centrifuged sample | $\geq 10^5$ | $\geq 10^4$ |

[a]Colony-forming units (CFU)/mL extrapolated from the finding of one bacterium per microscopic field.

who are asymptomatic) and range widely.[170–172] A negative leukocyte esterase test plus a negative nitrite test are strongly predictive of the absence of UTI.

Women with acute onset of symptoms of cystitis and without factors that would make the infection complicated can be diagnosed and safely managed on the basis of history only, without diagnostic testing.[173]

## Diagnosis of Urinary Tract Infection by Culture

### General Considerations

Because the urethra and periurethral areas are difficult to sterilize, even the most carefully collected specimens (including those obtained by catheterization) are frequently contaminated by organisms that are normal colonizers in these sites. By quantitating bacteria in midstream clean-voided urine, it is possible statistically to separate contamination from UTI. Most patients with infection usually have at least $10^5$ bacteria/mL in urine in the bladder, and therefore voided urine usually contains at least $10^5$ bacteria/mL. In patients without infection a properly collected, voided urine sample usually contains less than $10^4$ bacteria/mL. However, it is important to remember that about one-third of young women with cystitis have fewer than $10^5$ bacteria/mL of urine (see "Urinary Tract Infection with Low Numbers of Organisms" later). It is likely that a significant proportion of other patients with symptomatic and asymptomatic infection have fewer than $10^5$ bacteria/mL of urine. The Infectious Diseases Society of America consensus culture definition of cystitis for use in antibiotic treatment studies is $10^3$ colony-forming units (CFU)/mL or more of a uropathogen (sensitivity 90% and specificity 90%) and, for pyelonephritis, $10^4$ CFU/mL or more (sensitivity 90% and specificity 90%).[174] In a subsequent set of practice guidelines, $10^2$ CFU/mL or more of a uropathogen was used.[175] These concentrations of microorganisms can be identified by standard microbiologic techniques in most clinical laboratories. The belief that bladder urine is normally sterile has been increasingly challenged by work that demonstrates the existence of a urinary microbiome.[176,177]

Calibrated loops serve as a simple, inexpensive way to examine the bacteriologic characteristics of urine specimens quantitatively. Platinum loops that deliver 0.01 and 0.001 mL are used to streak urine onto agar plates. After incubation at 37°C for 24 hours, the number of CFU is counted, and the total number of organisms originally present in the specimen is estimated by multiplying the colony count by $10^2$ or $10^3$, respectively. Other methods, such as the dip inoculum method, in which agar-coated glass slides or paddles are dipped into urine and then incubated, have excellent correlations with calibrated-loop techniques.

Acceptable methods for urine collection include (1) midstream clean-catch, (2) "in and out" catheterization, and (3) suprapubic aspiration. The clean-catch method has traditionally been preferred for the routine collection of urine for culture. It avoids the risk of infection inherent in catheterization. The patient must be instructed in the proper technique of obtaining the urine; this is especially important for women. The woman should wash her hands, straddle the commode (facing the back of the commode), wash her vulva from front to back four times with four different sterile gauze pads soaked in green soap or another appropriate cleansing agent, and then rinse with two more sponges soaked in sterile distilled water. She should then spread her labia and void, discarding the first portion of urine and collecting the second. The urine should be processed immediately or, if refrigerated at 4°C, it can be cultured within 24 hours.

Some have challenged the need for cleansing or for using a midstream specimen from women when collecting urine for culture. Similar contamination rates were noted when midstream urine was collected after cleansing versus voiding into a container without cleansing.[178] A more recent study demonstrated similar rates of contamination for midstream clean-catch, midstream, and random samples.[179]

If there are more than $10^5$ bacteria/mL in a clean-catch urine specimen from an asymptomatic woman, there is an 80% probability that this represents true bacteriuria. If two different specimens demonstrate at least $10^5$ of the same bacterium/mL, the probability increases to 95%. Thus two clean-catch specimens should be obtained in an asymptomatic woman to confirm the diagnosis.[144] When the number of bacteria per milliliter is between $10^4$ and $10^5$ in an asymptomatic woman, a confirmatory second specimen will contain $10^5$ or more bacteria/mL in only 5% of cases. Thus in asymptomatic women, 95% of the time $10^4$ to $10^5$ bacteria/mL represents contamination, with occasional infection manifested by fewer than $10^5$ bacteria/mL of urine. In asymptomatic men, in whom contamination is less likely, $10^3$ or more organisms/mL in one culture is suggestive of infection, and $10^5$/mL defines bacteriuria.[144] False-positive cultures are caused by contamination or incubation of urine before processing. False-negative cultures may be caused by the use of antimicrobial agents, soap from the preparation falling into the urine, total obstruction below the infection, infection with a fastidious organism, renal tuberculosis, and diuresis.

These criteria apply only to the Enterobacteriaceae. Gram-positive organisms, fungi, and bacteria with fastidious growth requirements may not reach titers of $10^5$/mL in patients with infection and may be in the $10^4$ to $10^5$/mL range. The organism recovered often helps distinguish contamination from true bacteriuria. Samples with counts of less than $10^4$ organisms/mL often contain saprophytic skin organisms, such as diphtheroids, *Neisseria,* and staphylococci. Pure growth of Enterobacteriaceae is uncommonly found in low-titer specimens but is present in over 90% of urine samples containing more than $10^5$ bacteria/mL. High colony counts containing more than one species of bacteria from the urine of asymptomatic persons often represent contamination but may be more significant in the presence of symptoms. Mixed infection occurs in about 5% of cases.

In patients with symptoms of UTI, one titer of $10^5$ or more bacteria/mL of urine carries a 95% probability of true bacteriuria. With titers below $10^5$/mL but in the presence of frequency, urgency, and dysuria, women have a 33% chance of having bacterial infection (see "Urinary Tract Infection with Low Numbers of Organisms" later). The presence of low numbers of Enterobacteriaceae (i.e., $10^2$–$10^5$/mL) in such women correlates highly with infection. These lower cutoffs do not apply to infection with gram-positive organisms. In women with acute uncomplicated cystitis, enterococci and group B streptococci isolated from midstream urine were often not found in catheterized urine obtained at the same time.[180]

Samples obtained by catheterization from noninfected patients are less likely to become contaminated. According to the guidelines, $10^2$ CFU/mL or more is consistent with bacteriuria.[144] For diagnosis with an indwelling catheter, see Chapter 302.

## Urinary Tract Infection With Low Numbers of Organisms

Most women with an acute onset of frequency, urgency, or dysuria, or all of these, have UTI with $10^5$ or more bacteria/mL of urine (Fig. 72.6). However, up to one-half are found to have fewer than $10^5$ bacteria/mL of urine,[78,181] and the term *urethral syndrome* has been used to refer to this entity. As shown in Fig. 72.6, Stamm and associates have demonstrated

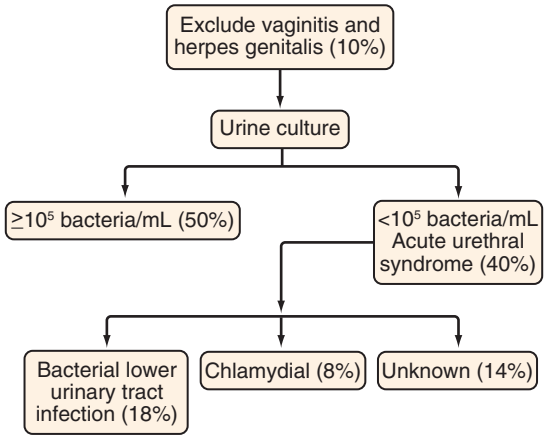



**FIG. 72.6 Relative frequencies of causes of acute onset of frequency or dysuria, or both, in young women.** *(Modified from Stamm WE, Wagner KF, Amsel R, et al. Causes of acute urethral syndrome in women.* N Engl J Med. *1980;303:409–415.)*

that many of these women have UTI but with low numbers of organisms. When suprapubic bladder aspirates are compared with voided midstream urine in acutely dysuric women, $10^2$ or more coliforms/mL in midstream urine have a sensitivity and specificity of 95% and 85%, respectively, for UTI. These women have urinary infections mainly restricted to the lower tract. Furthermore, up to one-third of young women with symptomatic infection localized to the lower urinary tract have fewer than $10^5$/mL bacteria in their urine.

A study of women coming to a university health clinic for any reason demonstrated that stepwise increases in bacterial counts from $10^2$ to $10^5$ CFU/mL are significantly associated with an increased incidence of symptoms and pyuria[182]; it was postulated that low-count bacteriuria represents an early phase of urinary infection. This hypothesis appears to have been supported in a clinical study in which 21 women with low-count bacteriuria ($10^2$–<$10^5$ CFU/mL) had therapy delayed for 2 days, and reculture showed that 10 of 21 (48%) developed concentrations of more than $10^5$ CFU/mL.[182a]

The remaining women with the urethral syndrome, after excluding those with bacteria in the bladder and those with genital herpes infection or vaginitis, can be divided into two groups: (1) those with pyuria from urethritis (e.g., caused by *Chlamydia trachomatis, Neisseria gonorrhoeae,* or *Mycoplasma genitalium* infection); and (2) those without pyuria in whom all bacterial cultures are negative. The pathogenesis of this latter symptom complex is unknown, but various fastidious microorganisms and noninfectious factors (traumatic, psychological, allergic, and chemical) have been suggested as causes. Patients with *C. trachomatis, N. gonorrhoeae,* and *M. genitalium* urethritis respond to antibacterial therapy. Vaginitis is a common cause of dysuria and, accordingly, patients should be questioned regarding vaginal symptoms, particularly if the complaint of burning is external, such as pain felt in the inflamed labia during micturition. If vaginitis is suspected, a pelvic examination should be performed. Dysuria has also been described in 10% of women with initial genital herpes infection.

Although symptoms and the clinical settings cannot reliably distinguish between the causes of dysuria in women, they can be suggestive.[169] Bacterial UTIs tend to have a sudden onset of severe dysuria with frequency and urgency; suprapubic pain and/or hematuria may be present, and there is pyuria. Clinical clues to urethritis (chlamydial, gonococcal, or mycoplasmal) include the following: a patient with a gradual onset of milder dysuria, with or without frequency and urgency, who is sexually active with a recent new sexual partner; hematuria is absent but vaginal discharge or bleeding may be present from chlamydial or gonococcal cervicitis; and/or pyuria is present. With herpes, there are usually lesions in the periurethral area. The diagnosis of urethral chlamydial or gonococcal infection may be confirmed by nucleic acid amplification tests on urine. With vaginitis, the dysuria tends to be mild with gradual onset and is felt externally, frequency and urgency are absent, there is often a vaginal discharge, and pyuria is usually absent in a midstream specimen.

The diagnostic testing for UTI described in the previous sections has changed very little in over 60 years, and new diagnostic techniques are currently under investigation to improve the sensitivity and specificity of diagnosis. Enhanced quantitative urine culture has been reported to detect bacteria in specimens that are reported as sterile by standard culture techniques, including in almost one-half of women with severe symptoms.[183,184] Real-time quantitative polymerase chain reaction and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry have been studied to increase the detection of difficult-to-culture pathogens and decrease the time to positive results; however, neither of these techniques supplies data on antimicrobial susceptibility. More specific markers of infection-associated pyuria—including neutrophil gelatinase-associated lipocalin, a protein from neutrophil granules—are under investigation.[185,186]

Because clinical microbiology laboratories process a high volume of urine cultures and the majority of these cultures are negative, flow cytometry techniques to screen samples for pyuria and bacteriuria and only culture those likely to be positive have been utilized.[187–189] Some of these studies have confirmed the excellent performance of traditional urinalysis, underscoring the value of not submitting urine cultures in patients who do not have pyuria.

### Localization of Site of Infection

Invasive diagnostic techniques to localize the site of infection to the kidney versus the bladder have been utilized to understand the epidemiology and response to therapy of UTI.[190] In clinical practice, localization relies mainly on clinical symptoms and signs. Many studies have looked at the use of both serum and urinary biomarkers to distinguish cystitis from pyelonephritis, especially in infants and very young children, in whom the inability to elicit symptoms increases the diagnostic challenge. A Cochrane Database review did not find evidence to support the routine use of procalcitonin, C-reactive protein, or erythrocyte sedimentation rate to differentiate pyelonephritis from cystitis in children.[191] At present, there is no biomarker that has sufficient evidence to support routine use in clinical practice.

## MANAGEMENT OF URINARY TRACT INFECTION

### General Considerations

The diagnosis of infection in the asymptomatic patient should be made on no fewer than two cultures of clean-voided midstream urine in which the same microorganism is present in titers of $10^5$/mL or greater. If the patient is symptomatic, one specimen suffices.

All symptomatic UTI is usually treated because the relief of symptoms is a clear-cut benefit. However, symptoms of cystitis often subside spontaneously or following symptomatic treatment.[79,192–194] On the other hand, there has been no benefit demonstrated or currently postulated in the treatment of asymptomatic bacteriuria in any group outside of pregnant women; those patients who are to undergo traumatic genitourinary procedures associated with mucosal bleeding, such as transurethral prostatectomy; and those who have recently had renal transplantation. In one study, treatment of asymptomatic bacteriuria in young women with recurrent UTI increased the frequency of symptomatic infection.[195] A rational approach to the treatment of UTI depends on an appreciation of the prognosis of the untreated infection and the long-term results to be expected from therapy. The side effects, cost, and inconvenience of different therapeutic regimens must also be considered. Because there is no demonstrated benefit of treatment of asymptomatic UTI in nonpregnant adult women, therapy of asymptomatic bacteriuria in this group is not recommended.[144]

Although asymptomatic bacteriuria in older adults is associated with degenerative and debilitating diseases and in some old reports with mortality, there is no convincing evidence for a cause-and-effect relationship.[139,141,143,196] There certainly is no evidence that treatment of the bacteriuria alters the patient's course. Asymptomatic bacteriuria serves as a marker for debilitating diseases, which in turn may contribute to mortality. In addition, bacteriuria is common in older adults, and many of these patients become reinfected or relapse after antimicrobial therapy. Furthermore, a higher frequency of side effects from chemotherapy would be expected in an older age group because of preexisting renal, auditory, and other diseases. Considering the large number of patients involved, antimicrobial therapy may lead to an unwarranted financial burden and danger of drug toxicity. Treatment is not indicated for asymptomatic bacteriuria in older patients.[138,144] In contrast, bacteriuria in pregnancy may have serious implications. Treatment of pregnant women with asymptomatic bacteriuria is most likely to be beneficial and is strongly recommended; however, it must be acknowledged that the overall quality of evidence to support this recommendation is not high.[197] A recent study found lower rates of pyelonephritis among pregnant women with untreated asymptomatic bacteriuria than did prior studies on which treatment recommendations have been based; however, these women were still more likely than those without asymptomatic bacteriuria to have a subsequent and recurrent UTI requiring treatment with antibiotics during the pregnancy.[198]

Hospitalized patients with asymptomatic bacteriuria have higher mortality rates than those without bacteriuria.[199] This observation may be related to deaths from bacteremia in patients with indwelling urinary catheters.

Some patients have such frequent symptomatic episodes (either relapses or reinfections) that they are almost chronically incapacitated. In these patients, it may be necessary to give prolonged therapy or prophylaxis to prevent recurrent symptoms.

In an adult male with a UTI, the possibility of complicated UTI is much higher than in a female, and the existence of a correctable obstructive lesion must be considered. At a minimum, a postvoiding ultrasound of the urinary tract should be obtained to evaluate bladder emptying. For management of patients with an indwelling catheter, see Chapter 302.

## Nonantimicrobial Therapy

Although there is a theoretical basis on which to postulate a benefit from hydration and acidification of the urine in the setting of symptomatic UTI, there is no evidence to support the efficacy of these nonpharmacologic interventions, and they should not be recommended. Two recent randomized controlled trials have studied the potential role of nonsteroidal antiinflammatory agents (NSAIDs) in the management of acute uncomplicated cystitis.[200,201] In both studies, NSAIDs were inferior in terms of rapidity of symptom resolution, and women who received NSAIDs had a higher rate of subsequent pyelonephritis. Although the initial use of analgesics clearly results in less antibiotic use, symptom duration is prolonged and the risk of complications (pyelonephritis) may be higher, so this approach should not be routinely recommended at this time. There may be a role for delayed antibiotic treatment in special circumstances such as multiple antibiotic allergies, or recurrent *Clostridioides difficile* (formerly *Clostridium difficile*)–associated diarrhea, since the rate of spontaneous resolution of acute cystitis is substantial. Urinary analgesics such as phenazopyridine hydrochloride (Pyridium) are not recommended because of lack of evidence to support additional benefit in addition to antibiotic therapy. Systemic analgesics are indicated in patients with severe dysuria and those with severe flank pain due to acute pyelonephritis.

## Prevention of Urinary Tract Infection

Prevention is aimed primarily at recurrent symptomatic reinfections in women because this is the group that most often has reinfections. Although elimination of some risk factors such as use of spermicidal contraceptive jellies may decrease the numbers of episodes, many women continue to have symptomatic reinfections. Antimicrobial agents have been the mainstay in approaching reinfections, but with increasing resistance of uropathogens to antimicrobial agents, other approaches have been increasingly evaluated.

The use of vaginal estrogens has been shown to be an effective strategy to prevent recurrent UTIs in postmenopausal women and is recommended in a clinical practice guideline.[202,203] The benefit of topical estrogens is believed to be related to decreasing the vaginal pH and increasing colonization of the vagina with lactobacilli, thereby decreasing colonization with Enterobacteriaceae. There continue to be conflicting data on the use of cranberry products for UTI prevention, with some studies reporting effectiveness in reducing infections and others not. A Cochrane Database review concluded that there was little or no benefit of cranberry juice.[204] However, a meta-analysis published the same year found that there was a protective effect while noting substantial heterogeneity across the included clinical trials.[205] A more recently published meta-analysis also suggested a protective effect; however, again the heterogeneity of both the patient populations studied and cranberry products used must be acknowledged.[206] At present, there are not sufficient data to make a clear recommendation, and further large trials utilizing a standardized cranberry product are needed.

At present, there is also insufficient evidence to support a recommendation for either systemic or intravaginal probiotics as a strategy to prevent recurrent UTI.[207] Vaccines to prevent UTI have been under study for several decades, and several promising candidate vaccines are currently in phase III clinical trials.[208,209]

## Principles of Antimicrobial Therapy

In most cases, many available agents are satisfactory for the treatment of UTI. Given two or more drugs with good activity against the probable infecting microorganism, the agent with the least toxicity, the least likelihood of affecting the normal flora of the vagina and gastrointestinal tract, the narrowest spectrum, and favorable cost should be chosen.

There is no evidence to support any superiority of bactericidal drugs over bacteriostatic agents in UTI. However, there may be theoretical reasons for using bactericidal drugs in the treatment of relapsing UTI.

## Serum, Tissue, and Urine Concentrations of Antimicrobial Agents

A poor correlation exists between the response of bacteriuria and serum levels of antimicrobial agents. In the dosages commonly used for UTI, some oral antimicrobial agents do not achieve serum levels above the minimal inhibitory concentration for most urinary pathogens.

The disappearance of bacteriuria is closely correlated with the sensitivity of the microorganism to the concentration of the antimicrobial agent achieved in the urine.[210] It is probable that the area in which it is most important to reach antibacterial concentrations in pyelonephritis is the intramedullary part of the kidney. Urine concentrations that are inhibitory for sensitive microorganisms are achieved after oral administration of essentially all antimicrobial agents commonly used for UTIs. Although serum levels do not seem to be important in the treatment of UTI, they may be critical in patients with bacteremia and may be important in the cure of patients with renal parenchymal infection who relapse.

In patients with renal insufficiency, dosage modifications are necessary for agents that are excreted primarily by the kidneys and cannot be cleared by any other mechanism. In renal failure, the kidney may not be able to concentrate an antimicrobial agent in the urine, and there may be difficulty in eradicating bacteriuria.[211] This may be an important factor in the failure of therapy for UTI with aminoglycosides.

In addition, high concentrations of magnesium and calcium, as well as a low pH level, can raise the minimal inhibitory concentration of aminoglycosides for gram-negative bacilli to levels above those achievable in the urine of patients with renal failure. In general, the penicillins, cephalosporins, and many fluoroquinolones attain adequate urine concentrations, despite severely impaired renal function. From the point of view of safety, the penicillins and cephalosporins should be considered first-line agents in the treatment of UTIs in patients with renal insufficiency.

## Response to Therapy

If therapy is appropriate, clinical response should occur within 24 hours with treatment of cystitis. With pyelonephritis, response should occur by 48 to 96 hours. Lack of response by 72 hours should be an indication for imaging studies. There are four patterns of response of bacteriuria to antimicrobial therapy—cure, persistence, relapse, and reinfection.

### Bacteriologic Cure

This term is defined as negative urine cultures on chemotherapy and during the follow-up period, usually 1 to 2 weeks. However, it must be understood that many of these patients will develop reinfection at a later time.

### Bacteriologic Persistence

This term has been used in two ways to describe a response to therapy: (1) persistence of significant bacteriuria after 48 hours of treatment, and (2) persistence of the infecting organism in low numbers in urine after 48 hours. Significant bacteriuria usually persists only if the urinary levels of the antimicrobial agent are below the concentration of the drug needed to inhibit the microorganism. This can occur when the infecting strain is resistant to the urinary levels attained (i.e., a resistant organism) or because the urinary levels of the drug are inordinately low (i.e., from not taking the agent, insufficient dosage, poor intestinal absorption, or poor renal excretion, as in renal insufficiency). Persistence of the infecting microorganism in low titers in voided urine may mean persistence in the urinary tract or contamination from the urethra or vagina. Bladder-puncture cultures would be necessary to evaluate the significance of low titers of bacteria obtained when the patient is receiving therapy, but this procedure is rarely indicated. Bacteria may persist in the urinary tract during therapy without excretion of organisms in the urine. Sites of persistence in the urinary tract are the renal parenchyma, calculi, and prostate. Persistence in bladder cells is a theoretical possibility.[212]

### Bacteriologic Relapse

This usually occurs within 1 to 2 weeks after the cessation of chemotherapy and is often associated with renal infection, structural abnormalities of the urinary tract, or chronic bacterial prostatitis. Relapse indicates that the infecting microorganism has persisted in the urinary tract during therapy. However, an apparent relapse can be related to reinfection (new infection) with the same microorganism. In spite of eradication from the urinary tract, the original infecting organism may still be present in the periurethral area, vagina, or intestine and then may cause a new infection. Delayed relapses (more than 1–2 weeks after stopping therapy) are much more likely to be the result of this phenomenon or of chronic bacterial prostatitis than of true relapse. Relapses occurring within 1 week are usually true relapses (i.e., from within the urinary tract).

### Reinfection

After initial sterilization of the urine, reinfection may occur during the administration of chemotherapy (also called *superinfection*) or at any time thereafter. Reinfection is easy to identify when there is a change in bacterial species. However, there may be reinfection with a different strain of the same species (usually *E. coli*) or even the same strain.

## Considerations in Choice of Therapy

With upper tract infection, agents that give antibacterial serum activity, such as fluoroquinolones, TMP-SMX, β-lactam antibiotics, and aminoglycosides, should be used. With lower tract infection, additional agents such as nitrofurantoin (with attention to a requirement for creatinine clearance of at least 60 mL/min) and oral fosfomycin can be used.

Amoxicillin and ampicillin are not recommended as reliable agents for empirical therapy because high levels of resistance have been reported for over 2 decades; many more recent studies of antibiotic resistance among urinary isolates do not even include data for these agents. In female outpatients in the United States, resistance of *E. coli* urinary isolates to TMP-SMX was 30% among those 18 to 64 years of age and 26% percent among those 65 years of age and older; resistance to ciprofloxacin was 12% and 22% in those two age groups, respectively.[213] Nitrofurantoin resistance was less than 5% in both age groups. Studies from other parts of the world show a similar pattern, although the absolute levels of TMP-SMX and fluoroquinolone resistance in some areas of the world are much higher.[214–217] The most concerning resistance problem for the management of UTIs is the increasing incidence of community-acquired infection due to ESBL-producing *E. coli*. While the incidence of community-acquired UTI in the United States is currently low, it is increasing.[218,219]

There is evidence that cell wall–active agents (e.g., penicillins, cephalosporins) are not as effective in eradicating infection in the kidneys, or for that matter anywhere in the urinary tract, as are TMP-SMX, fluoroquinolones, or aminoglycosides.[175,181]

## Classification and Antimicrobial Therapy for Different Groups

Most often when therapy for UTI is initiated, the infecting microorganism and its susceptibilities to antimicrobial agents are not known. Furthermore, it may not be known if there is an abnormality present that would make the UTI complicated (e.g., calculi). Therefore the approach to therapy is usually to follow established clinical practice guidelines when available for choice of initial antimicrobial therapy. In the case of nonresponse, therapy is changed according to culture and sensitivity results.

The guidelines must be periodically revised because of the continuously evolving resistance of uropathogens to antimicrobial agents, development of new agents, and results of studies regarding superiority/inferiority of agents, as well as studies redefining appropriate lengths of therapy.

## Infection in Children

UTI in children younger than 3 months of age is usually caused by *E. coli* or *Enterococcus faecalis*. After obtaining urine (and if indicated, blood) cultures, recommended empirical therapy is usually a β-lactam antibiotic and an aminoglycoside, such as ampicillin and gentamicin, intravenously. Therapy is modified, if necessary, on the basis of culture results. After response, therapy is changed to oral agents such as a β-lactam or TMP-SMX, on the basis of susceptibility studies, for a total period of 7 to 14 days.[110,220–222]

After 3 months of age, IV therapy is used in seriously ill children as for those younger than 3 months; third-generation cephalosporins are a reasonable choice. Oral therapy with a β-lactam such as a second- or third-generation cephalosporin or TMP-SMX (pending cultures for definitive therapy) is recommended for those not seriously ill, administered for 3 days for afebrile cases and 7 to 14 days for febrile cases.[105,110,220–222]

Prophylaxis with an antimicrobial agent following treatment for febrile UTI in infants and young children is controversial. If prophylaxis is given, it should be reserved for children with associated congenital renal anomaly such as high-grade vesicoureteral reflux, particularly with renal scarring.[106] Antireflux procedures (endoscopic or open surgery) are considered in those older than 12 months of age with high grades of reflux and scarring.[223]

Recommendations for imaging in infants and young children have become increasingly stringent over recent years, especially since prenatal ultrasonography is often available and will select out many with significant urologic abnormalities. Postnatal ultrasounds are mainly restricted to those children at highest risk for kidney damage and underlying abnormalities. These children include those who are seriously ill, those with possible obstruction (e.g., poor urine flow, abdominal or bladder masses, elevated creatinine, lack of response to antibiotics), those infected with non–*E. coli* organisms, and those with recurrent UTIs. In practice, many physicians obtain renal ultrasounds for most children after the first UTI to detect obstructive uropathy. $^{99m}$Technetium-labeled dimercaptosuccinic acid ($^{99m}$Tc-DMSA) renal scans are ordered selectively to detect presence of renal scars. Micturating cystourethrograms may be ordered to detect vesicoureteral reflux (see "Imaging Studies" later).[110] When vesicoureteral reflux is found, management is controversial and includes antimicrobial prophylaxis, surgical intervention, or surveillance only.[106,117]

## Acute Uncomplicated Pyelonephritis in Women

All patients with pyelonephritis should have a urine culture with antimicrobial susceptibilities to confirm the appropriateness of therapy chosen. Patients who are severely ill with pyelonephritis should be hospitalized and treated intravenously; because the response to therapy is often rapid, initial admission to an observation unit is often appropriate. The role of blood cultures in patients who require hospitalization continues to be debated and, provided that the urine culture is obtained prior to the receipt of antibiotic therapy, the utility of blood cultures is questionable. However, for those patients ill enough to require hospitalization, we continue to recommend blood cultures. Others can be treated orally if they are reliable, adherent, hemodynamically stable, and able to take oral therapy. If a Gram stain of the urine is available, it will help direct therapy toward gram-negative bacilli, by far the most common causes of pyelonephritis, or gram-positive cocci (usually enterococci), but in the majority of cases the selection of antimicrobial therapy is empirical. If gram-positive cocci in chains are seen on Gram stain, ampicillin or amoxicillin is probably the agent of choice. When staphylococci are implicated on Gram stain, it would be most prudent to use an agent such as vancomycin for inpatients and linezolid or TMP-SMX for outpatients because of the increasing frequency of infection with community-acquired methicillin-resistant staphylococci.

### Oral Therapy

There is good evidence that 7 days of a fluoroquinolone and, with levofloxacin, 5 days of therapy is sufficient for the treatment of uncomplicated pyelonephritis.[224,225] For oral therapy, current international guidelines recommend a 7-day course of ciprofloxacin 500 mg twice daily or 1 g once daily, or a 5-day course of levofloxacin 750 mg once daily if local fluoroquinolone resistance is under 10%.[79] When local resistance is greater than 10% fluoroquinolone, therapy should start

with an initial, additional, single dose of a parenteral antibiotic such as a 2-g dose of ceftriaxone or a dose of an aminoglycoside or ertapenem to provide coverage while awaiting results of the urine culture. With use of any agent other than a fluoroquinolone, 14 days of therapy is generally recommended. A recent retrospective study has suggested that shorter (7 day) courses of TMP-SMX may be effective; however, prospective, randomized control trials are needed before this approach can be recommended.[226] When a fluoroquinolone cannot be used, oral TMP-SMX (160 mg/800 mg twice daily) is reasonable, but an initial injection of ceftriaxone, ertapenem, or an aminoglycoside is recommended pending results of cultures. This is because of the frequency of high levels of resistance of *E. coli* to TMP-SMX in the community. If an oral β-lactam agent must be used, an initial dose of ceftriaxone, ertapenem, or aminoglycoside should also be administered. Routine imaging studies are not required for women with acute uncomplicated pyelonephritis. Follow-up urine cultures are not indicated except in pregnancy.

### Parenteral Therapy

Patients hospitalized for apparent uncomplicated pyelonephritis should receive initial treatment with parenteral antibiotics. Options are a fluoroquinolone, an extended-spectrum cephalosporin such as ceftriaxone or piperacillin-tazobactam with or without an aminoglycoside initially, or a carbapenem. From a stewardship prospective, ceftriaxone is an appropriate choice in most patients. In those with severe sepsis or septic shock, initial therapy with a carbapenem should be considered. Again, from a stewardship perspective, since the microbial etiology of a UTI in this setting should always be eventually confirmed by urine and/or blood cultures, initial broad-spectrum empirical antibiotic therapy in severely ill patients should not be considered problematic. Patients who develop pyelonephritis in a hospital or long-term care facility setting should be assumed to be infected with the resistant flora of that facility, and therapy should be initiated with antibiotics that are likely to be effective. When the susceptibility pattern of the infecting organism is known, therapy can be altered accordingly. Oral treatment can be used to complete the course of antimicrobial therapy once a response has occurred.[79,175,181] Those with bacteremia who respond appropriately do not require a more prolonged course of either parenteral or total antibiotic therapy.

The finding of continuing positive blood cultures or persistent high fever and toxicity past the first 3 to 4 days suggests the need for investigation to exclude complications such as urinary obstruction or intrarenal or perinephric abscess formation. Investigation should include renal ultrasonography, CT or MRI scan, and, according to the findings, a urologic consultation. The availability of sensitive noninvasive studies has resulted in the early diagnosis of intrarenal or perinephric abscess formation that may respond to antibiotic therapy alone.

## Uncomplicated Cystitis in Women

In the woman with classic symptoms of cystitis, urine dipstick or cultures are not necessary for management. However, if obtained, a negative dipstick or microscopic examination for pyuria would raise great suspicion that the diagnosis of cystitis is incorrect. Women with acute uncomplicated cystitis can be treated with short courses of antibiotic therapy. The advantages of short-course therapy include a lower cost, better adherence, fewer side effects, and perhaps less intensive selective pressure for the emergence of resistant organisms in gut, urethral, or vaginal flora.

The international clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women recommend treatment of uncomplicated cystitis with nitrofurantoin (100 mg every 12 hours for 5 days), fosfomycin (a single dose of 3 g with 3–4 oz of water), and if local resistance is under 20% of isolates, TMP-SMX (1 double-strength tablet every 12 hours for 3 days).[79] Clearly one of the challenges in following these recommendations is that local resistance rates are usually not known and data obtained from hospital antibiograms likely overestimate resistance rates. Pivmecillinam (400 mg twice daily for 3–7 days) is also recommended but is not available in the United States. The different durations of administration are based on comparative clinical trials. Fosfomycin, a bacterial cell wall–active antibiotic, is approved by the US Food and Drug Administration for single-dose (3 g oral powder) treatment of uncomplicated lower UTI. Nitrofurantoin, TMP-SMX, or fosfomycin represents an appropriate initial choice of therapy for cystitis because of generally low rates of resistance (variable with TMP-SMX) and low impact on microbiologic flora. It has been reported that the efficacy of single-dose fosfomycin is inferior to 7 days of nitrofurantoin and to other standard short-course regimens, and this agent is the most expensive of the three options.[79] A meta-analysis of 27 trials found no difference in efficacy between fosfomycin and other antibiotics for treatment of cystitis, and it found that fosfomycin was associated with significantly fewer adverse reactions in pregnant women.[227] A potential advantage of fosfomycin is activity against multidrug-resistant pathogens, including ESBL-producing *E. coli,* which may be important in certain epidemiologic settings outside the United States.

The guidelines list fluoroquinolones such as ciprofloxacin, ofloxacin, and levofloxacin given for 3 days as highly efficacious but recommend reserving them for other uses because of "collateral damage"—ecologic adverse effects of antimicrobial therapy.[79] Since these guidelines were published, the US Food and Drug Administration has issued a warning discouraging the use of fluoroquinolones when other agents are available because of safety concerns.

The guidelines also list β-lactam agents other than pivmecillinam, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in 3- to 7-day regimens as appropriate (but not preferred) choices for therapy when other recommended agents cannot be used.[79] Because of inferior efficacy and higher incidence of adverse events, β-lactams should be considered only if nitrofurantoin, fosfomycin, and TMP-SMX cannot be used, with fluoroquinolones reserved as the last resort for therapy.

When acquired in a hospital or long-term care facility, empirical therapy should be based on the usual susceptibility patterns of organisms causing UTI in that facility. Short-course therapy may not be appropriate for women who have a history of previous urinary infection caused by antibiotic-resistant organisms or more than 7 days of symptoms. In these patients, who have an increased likelihood of upper tract infection, 7 to 10 days of therapy are recommended. Some of the risk factors for multidrug-resistant organisms are recent health care facility exposure, recent antimicrobial agent exposure (especially fluoroquinolones and antipseudomonal penicillins), and, in two US-based studies, travel outside the United States in the preceding 3 to 6 months.[79,228]

If symptoms do not respond, or if they recur, a urine culture should be obtained and therapy chosen according to antimicrobial susceptibility testing. A symptomatic response followed by relapse after therapy is discontinued indicates the probability of upper tract infection and the need for a culture and therapy for upper tract infection.

## Complicated Urinary Tract Infection, Including Infection in Men

Because of the relative infrequency of UTI in men and the relatively high proportion of complicated UTI in men who get infected, UTI in men should be managed as a complicated infection.[1,2,229,230] In a male, presence of fever with only symptoms of cystitis may indicate acute prostatitis. In addition to complications related to urinary obstruction from diseases of the prostate in men, chronic bacterial prostatitis may be difficult to cure.

The management of complicated UTI is problematic for a number of reasons.[1,2,229,230] Resistant bacteria (such as ESBL-producing *E. coli;* urease-producing bacteria, including *Proteus, Providencia,* and *Morganella*; *Pseudomonas;* and *Acinetobacter*) and polymicrobial infection are found much more commonly in complicated UTI than in uncomplicated disease. The complication may make persistent or relapsing infection much more likely. For example, in the presence of an infected calculus, relapse from within the calculus is usual after therapy is stopped; the presence of a foreign body, such as a drainage device, makes eradication of infection difficult, probably because of formation of biofilms; and renal insufficiency may result in subinhibitory levels of antibiotic in the urine, as well as more antibiotic side effects.

Asymptomatic bacteriuria is often present in complicated UTI. However, excluding pregnancy, no benefit has been demonstrated in

screening for or treating asymptomatic bacteriuria except in two groups of patients: those with renal transplantation, especially in the early posttransplantation period; and those who will have procedures traumatic to the urethra, in whom elimination of bacteriuria can reduce the occurrence of symptomatic infection.[2,144,152,154] Long-term suppressive antimicrobial therapy has been advocated for struvite stones that cannot be removed in an attempt to prevent stone enlargement.

Urine cultures and antimicrobial susceptibility tests should be obtained in all patients with complicated UTI who require treatment. Imaging by ultrasound, CT scan, and/or MRI is often important to rule out obstructive uropathy and other abnormalities. A urologic consultation is often indicated. With complete urinary obstruction or ureteral obstruction, the patient may be septic, and prompt relief of the obstruction is important. Correction of a complication, if feasible (e.g., removal of a calculus or a catheter), may make cure much easier.

Accurate initial empirical therapy is paramount in the severely ill patient in whom the urinary tract may be the primary source of illness. Fluoroquinolone resistance rates in many communities are high, and there is little evidence that concentration of the drugs in the urinary tract makes them effective in vivo against resistant organisms.[231] *Escherichia coli* and *Klebsiella pneumoniae* have a high rate of carriage of ESBLs, which inactivate extended-spectrum cephalosporins. These species may also be dominant sources of carbapenemase production, but resistance mechanisms are too varied to predict. Current recommendations support the use of in vitro susceptibility rather than mechanism in choosing effective treatment.

Some knowledge of local and individual resistance patterns should be used to guide therapy. Consideration should include the increased risk of drug-resistant pathogens in hospital-acquired cases, in men, and in patients ages 65 years or older, and decisions should incorporate the results of urine cultures obtained within the previous 6 months.[218,228,233,234] The strength of association between intestinal colonization and subsequent disease is still difficult to interpret, but the conjunction of colonization with a strain (e.g., *E. coli* ST131-H30Rx) with high pathogenic potential and subsequent disease suggests that colonization should be taken into consideration.[235] The use of a cephamycin such as cefoxitin, a drug less susceptible to inactivation by ESBLs, has been addressed only in small studies.[236] New β-lactam–β-lactamase combinations (ceftazidime-avibactam and ceftolozane-tazobactam) may be of use against some multidrug-resistant pathogens.[237–240] On an empirical basis in the critically ill patient, carbapenems, aminoglycosides, polymyxins (colistin or polymyxin), or IV fosfomycin (not available in the United States) may be necessary.

Our preference for empirical initial therapy for lower tract infection is a fluoroquinolone pending antimicrobial susceptibility studies, but nitrofurantoin and fosfomycin are reasonable choices. Fosfomycin in particular has maintained activity against many multidrug-resistant bacteria.[87] The duration of therapy should be at least 7 days with a fluoroquinolone or nitrofurantoin. When fosfomycin is used to treat complicated cystitis, there are data to support a regimen of three doses, administered every other day.[228]

With creatinine clearances of less than 50 mL/min, nitrofurantoin and sulfamethoxazole urine levels will likely be subtherapeutic, and nitrofurantoin is contraindicated in renal failure related to resultant peripheral neuropathy. Urine concentrations of TMP used alone should be high enough to allow its use in patients with impaired renal function.[241] With severe renal insufficiency, the β-lactams are the safest agents to use. In general, in the presence of severe renal insufficiency, doses of virtually all antimicrobials must be adjusted. In addition, with renal insufficiency, levels of antimicrobial agent in the urine may be insufficient to inhibit the infecting organism.[241]

When upper tract infection is complicated by abscesses, more prolonged therapy and perhaps drainage are indicated (see "Perinephric Abscess" and "Intrarenal Abscess" later).

Renal infection is a special problem in adults with hereditary polycystic disease. Although parenchymal infections respond well to appropriate antibiotics, cyst infections frequently fail to improve and may require antibiotics that diffuse into these closed sites (e.g., TMP-SMX, fluoroquinolone) or aspiration or surgical drainage. Emphysematous pyelonephritis is most often seen in older female diabetic patients with chronic urinary infections and renal vascular disease (Fig. 72.7). Because of a high mortality rate in spite of appropriate antibiotics and supportive therapy, immediate nephrectomy is frequently indicated for this condition.[242,243] However, advances in percutaneous drainage techniques have allowed some individuals to be successfully managed with antibiotics and drainage alone.[244]

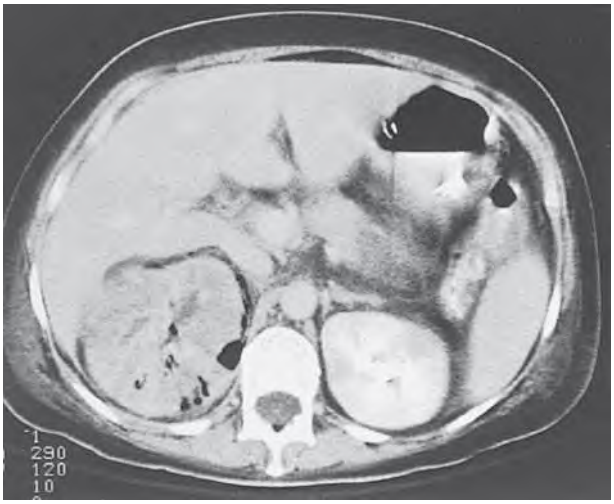



**FIG. 72.7 Emphysematous pyelonephritis in a patient with diabetes.** This computed tomography scan shows an enlarged, inflamed right kidney with air in the parenchyma and subcapsular space. *(Courtesy Dr. M. Bergeron.)*

## Asymptomatic Bacteriuria

Because no benefit has been demonstrated, screening for or treatment of asymptomatic bacteriuria is not recommended for any group of adult patients, including diabetics, except in renal transplantation patients (see "Reinfection of the Urinary Tract and Antimicrobial Prophylaxis" later) and during pregnancy (see "Urinary Tract Infection in Pregnancy" later).[2,138,144,149]

A major exception to not screening for and treating asymptomatic bacteriuria is in those patients who are to undergo traumatic genitourinary procedures associated with mucosal bleeding, such as transurethral prostatectomy and percutaneous lithotomy. There is a high rate of postprocedure bacteremia and sepsis in these patients. To reduce the incidence of bacteremia, a urine culture is obtained several days before the procedure and therapy with a third-generation cephalosporin or another appropriate agent is started 12 hours to just before the procedure. The therapy is usually stopped after the procedure, but some practitioners continue the therapy until any urethral catheter is removed.[2,144,245]

The agents used for management of asymptomatic bacteriuria are those used for uncomplicated bacteriuria, as described earlier in "Uncomplicated Cystitis in Women."

## Relapsing Urinary Tract Infection

If a patient relapses after therapy for UTI, the most likely possibilities are that the patient has (1) renal involvement (pyelonephritis); (2) chronic bacterial prostatitis; or (3) a structural abnormality of the urinary tract (e.g., calculi). Relapses, especially in the absence of structural abnormalities, could be related to renal infection that may require a longer duration of therapy or to chronic bacterial prostatitis, which is difficult to cure even with long-term therapy. Patients who have a symptomatic relapse should have a urine culture and sensitivity study and be treated with a course of antimicrobial therapy for upper tract infection. In the past, it was demonstrated that a 6-week course of therapy with a β-lactam results in a higher cure rate than a 2-week course in patients who relapse after 2 weeks of therapy. These were mainly women who presumably had renal infection.

Structural abnormalities of the urinary tract predispose to relapse. Obstructive lesions can be corrected surgically and should be sought in the evaluation of patients with relapsing infection. Calculi may be a cause of relapse of UTI. The ultimate success of chemotherapy is dependent on the removal of stones. The same is true with drainage devices or other foreign bodies.

Some patients continue to relapse despite surgical correction of urologic abnormalities. In others, surgical correction may not be indicated or feasible or no abnormality may be found. Symptomatic relapses must be treated. In men, chronic bacterial prostatitis should be ruled out.

In carefully selected patients, such as those with frequent symptomatic relapses, prolonged periods of therapy such as 4 weeks or longer should be considered. Some agents that can be used for longer-term therapy are amoxicillin-clavulanic acid, cephalexin, TMP-SMX, TMP, and ciprofloxacin in usual doses, and nitrofurantoin in full dosage for 1 week and then half the usual dosage. Rarely patients may require long-term suppressive therapy to keep them asymptomatic. Nitrofurantoin and TMP-SMX have been used for long-term chronic suppression in many older studies. Fosfomycin would seem to be useful for this purpose, but there have been few long-term studies. For example, one study used 3 g of fosfomycin every 10 days.[246]

## Reinfection of the Urinary Tract and Antimicrobial Prophylaxis

Patients with symptomatic reinfections can generally be divided into two groups: (1) those who have relatively infrequent reinfections, perhaps only once every 2 or 3 years to several times a year (the more common situation); and (2) those who develop frequent reinfections. The latter are usually young and middle-aged sexually active women who have recurrent cystitis. With infrequent reinfections, each episode is approached as a new episode of infection. Women with reinfections associated with lower tract symptoms can be managed with self-administration of standard short-course therapy at the onset of symptoms.[247,248]

In some women, symptomatic reinfections are associated with sexual activity. Voiding immediately after intercourse may help prevent reinfection. However, single-dose prophylactic chemotherapy taken after sexual intercourse (e.g., a single-strength TMP-SMX tablet; 100 mg of nitrofurantoin) is a more effective method of decreasing these episodes.[248–250]

In other patients with frequent symptomatic reinfections, no precipitating event is apparent; in these patients, when symptoms are severe, long-term chemoprophylaxis may be instituted.[248,250] Although these courses seem to decrease the frequency of reinfections and symptoms in most patients, it is impossible to completely prevent reinfection in many patients.

In older studies, long-term chemoprophylaxis was advocated for asymptomatic patients who reinfect frequently and who were thought to be at risk of developing renal parenchymal damage with each reinfection (e.g., young children with severe vesicoureteral reflux and children and adults with obstructive uropathy). This approach is controversial and not generally recommended.[251] In a large study in young children, long-term antimicrobial prophylaxis was not associated with decreased risk of UTI but was associated with an increased risk of resistant infections.[252] Screening for bacteriuria and chemoprophylaxis has been considered for all renal transplantation patients in the postoperative period to prevent symptomatic infection.[2,153–155] Transplantation populations demonstrate an increased frequency of multidrug-resistant pathogens, complicating decisions for therapy.[253] Definitive studies are lacking, but some evidence supports the contention that routine surveillance beyond the second month post–kidney transplantation may not change a primary outcome of acute pyelonephritis during 24 months of follow-up.[254]

Full antimicrobial dosage is not necessary for successful prophylaxis. One 50-mg capsule of nitrofurantoin or one half-tablet of TMP-SMX (40 mg of TMP, 200 mg of sulfamethoxazole) nightly suffices. Fluoroquinolones and other agents have been used with good results.

## Fungal Infections

Most *Candida* UTIs occur in patients with indwelling catheters. Removal of the catheter may result in cure of 30% to 40% of patients with candiduria.[255] Continuous amphotericin B bladder irrigation or oral fluconazole, 200 to 400 mg/day for 7 days, in association with removing (if possible) or replacing the catheter may be effective short term in eliminating candiduria.[91] However, with longer follow-up, oral fluconazole is no more effective than no therapy.[255] There is no demonstrated benefit in the treatment of asymptomatic infection, and therefore therapy is not recommended. Exceptions include only patients who are to undergo procedures involving the urinary tract that result in mucosal bleeding. In these cases, attempts should be made to eliminate or at least suppress the candiduria with oral fluconazole. In the past, asymptomatic candiduria in renal transplant recipients was treated with fluconazole on the basis of a perceived risk of a destructive process in the grafted kidney. However, a large study of posttransplantation patients failed to show excessive morbidity associated with candiduria or any benefit from eradication of candiduria.[256] Infrequently, ascending infection resulting in pyelonephritis occurs, especially in patients with diabetes or obstruction. This obviously requires systemic antifungal therapy and attention to obstruction. Fluconazole-susceptible organisms can be treated with this agent at a dose of 200 to 400 mg daily for 14 days.[257] Pyelonephritis due to azole-resistant *Candida glabrata* and *Candida krusei* should be managed with systemic amphotericin B desoxycholate, with or without oral flucytosine.[257] Symptomatic cystitis is uncommon and is treated with oral fluconazole 200 mg daily for 14 days if the *Candida* species is azole susceptible.[257] *Candida glabrata* and *C. krusei* symptomatic infections are best treated with systemic or amphotericin B irrigation.[257] Azoles other than fluconazole and echinocandins are not recommended for the management of UTIs due to low concentrations of active drug in the urine; for the same reason, lipid formulations of amphotericin B are also not recommended.

## Urinary Tract Infection in Pregnancy

### Physiologic Alterations in the Urinary Tract

During pregnancy, there is dilation of the ureters and renal pelves, with markedly decreased ureteral peristalsis.[145] These changes begin as early as the seventh week of gestation and progress to term. The bladder also decreases in tone so that, late in gestation, it can contain twice its normal contents without causing discomfort. These changes vary from patient to patient. They are more marked on the right side and are more likely to occur during the first pregnancy or when pregnancies occur in rapid succession. The urinary tract tends to revert to normal by the second month after delivery. The urinary tract alterations may be at least partly related to hyperestrogenism. Other possible explanations for the alterations are obstruction of the ureters by the gravid uterus and hypertrophy of muscle bundles at the lower end of the ureter. In addition to host factors, unique gestational bacterial virulence factors are now recognized for a narrow group of genetically related *E. coli*.[258] Each trimester appears to be associated with specific DNA fingerprints and serotypes of *E. coli,* as well as trimester-specific virulence patterns.

### Epidemiology

The incidence of bacteriuria during pregnancy is similar to that seen in nonpregnant women. The prevalence of asymptomatic bacteriuria in pregnancy ranges from 4% to 7%. However, recurrent episodes are more common in pregnant women who had bacteriuria documented at their initial prenatal visit. The prevalence of bacteriuria rises with age, sexual activity, in diabetes mellitus, in women with sickle cell trait, and in women with a past history of UTI; the association of parity and that of socioeconomic status are inconsistent.[259,260] Most women who develop bacteriuria during pregnancy have infection at the first prenatal visit. However, 1% to 1.5% of pregnant women, or about 25% of those with bacteriuria of pregnancy, develop infection in the later trimesters. Acute cystitis and acute pyelonephritis have been shown to complicate 1% to 2% of pregnancies with a microbial spectrum similar to that of asymptomatic bacteriuria in pregnancy and uncomplicated UTI in nonpregnant women. The development of symptomatic pyelonephritis late in pregnancy is usually an expression of asymptomatic bacteriuria that was present earlier in the pregnancy. The marked dilatation of the ureters during the later stages apparently allows bacteria in the bladder to reach the upper tract and to produce symptomatic pyelonephritis.

It has been reported that as many as 40% of the patients with untreated bacteriuria early in pregnancy develop acute symptomatic pyelonephritis later in pregnancy, although, as discussed previously, more recent studies have reported lower rates of pyelonephritis. In contrast, less than 1% of patients whose urine is uninfected early in pregnancy develop acute infection. Screening and treatment for asymptomatic bacteriuria in pregnant patients is recommended by multiple professional organizations, including the US Preventive Services Task Force, the American College of Obstetrics and Gynecology (ACOG), and the Infectious Diseases Society of America. It has also been noted that those whose bacteriuria fails to respond to treatment are at the highest risk of developing symptomatic infection. A lack of cure is probably an indication of upper versus lower tract infection. Untreated asymptomatic bacteriuria has been associated with preterm birth and low birth weight, although the association is inconsistent across studies; the association is most likely due to the increased risk of pyelonephritis.[260]

Postpartum studies of patients with bacteriuria of pregnancy demonstrate a high frequency of bacteriuria, even with treatment during pregnancy. Postpartum intravenous pyelography (IVP) of these patients has shown that 10% to 30% have radiologic changes of chronic pyelonephritis and other abnormalities. These abnormalities are most common in patients in whom renal bacteriuria has been demonstrated or in whom bacteriuria during pregnancy was difficult to eradicate with antimicrobial therapy.[145] However, pyelographic abnormalities should not necessarily be attributed to the infection that occurred during the pregnancy. In fact, these abnormalities probably antedate the pregnancy and, in most cases, are related to childhood infection. Treatment of bacteriuria of pregnancy has little effect on the long-term course of the patient. When patients who had bacteriuria of pregnancy were studied 10 to 14 years later, there were no differences between those who were treated and those who were not.

### Management of Bacteriuria of Pregnancy

All women should be screened at 12 to 16 weeks' gestation or at the first prenatal visit, if later. The goal of therapy is to maintain sterile urine throughout pregnancy and thereby avoid the complications associated with UTI. In the treatment of asymptomatic bacteriuria and cystitis, treatment modalities include single-dose fosfomycin trometamol 3 g or cephalexin 500 mg four times a day for 3 to 5 days. A 7-day course of nitrofurantoin or TMP-SMX for 3 days (when susceptibility tests reveal absence of resistance) can be used; however, ACOG has recently released an opinion bulletin discouraging the use of nitrofurantoin and TPM-SMX during the first trimester due to concern regarding the possibility of previously underappreciated risk of birth defects.[261] Acute pyelonephritis in pregnancy should be managed initially with parenteral antibiotics, such as third-generation cephalosporins for 14 days. In selected patients with mild disease, a trial of oral antibiotic therapy with cefixime can be given for 14 days with close follow-up. If cefixime cannot be used, TMP-SMX can be substituted, if the bacterium is susceptible.

Urine cultures should be obtained 1 to 2 weeks after discontinuing therapy and then at regular intervals (monthly) for the remainder of the pregnancy. Some experts recommend prophylactic antibiotic therapy until delivery; however, a Cochrane Review did not find evidence of additional benefit as compared with close follow-up alone.[262] If relapses or multiple reinfections occur during pregnancy, an imaging evaluation should be considered postpartum. Guidelines from ACOG recommend intrapartum penicillin prophylaxis for all women with group B streptococcus bacteriuria at any point during their pregnancy to prevent early-onset disease in the newborn.

## Perinephric Abscess and Intrarenal Abscess

### Perinephric Abscess

Perinephric abscess is an uncommon complication of UTI.[263] The most common predisposing factors are urinary tract calculi and diabetes mellitus. It usually occurs secondary to obstruction of an infected kidney or calyx or, occasionally, secondary to bacteremia. It may occur insidiously, and up to one-third of cases may not be diagnosed until autopsy. The infecting bacteria are usually gram-negative enteric bacilli and occasionally gram-positive cocci when the infection is of hematogenous origin. Multiple bacterial species are present in about 25% of cases, and occasionally fungi, especially *Candida* spp., can be cultured from the abscess. The abscess is usually confined by the Gerota fascia to the perinephric space but may extend throughout the retroperitoneum to affect adjacent structures.[264]

Patients have a syndrome suggestive of acute pyelonephritis, with fever, abdominal and flank pain (usually unilateral), and often symptoms of lower tract infection. However, presenting symptoms are frequently nonspecific. The patient has often been ill for 2 or more weeks. The diagnosis should be strongly considered in any patient with a febrile illness and unilateral flank pain who does not respond to therapy for acute pyelonephritis. A palpable mass may or may not be present. Pyuria and proteinuria are frequently found, but about 30% of patients have a normal urinalysis and about 40% have sterile urine cultures.[264]

### Intrarenal Abscess

Intrarenal abscess may occur as a consequence of bacteremia, often caused by *S. aureus*. Hematogenous lesions are usually unilateral, single, and located in the cortex. However, these focal suppurative lesions are being recognized with increasing frequency as a complication of classic acute pyelonephritis and are located in the cortex, medulla, or both. The clinical setting is usually that of acute pyelonephritis with high fever, severe flank pain, and tenderness, but with no or slow response to appropriate antimicrobial therapy. In the early stages of abscess formation, contrast-enhanced CT may detect intense parenchymatous inflammation and edema in a lobe of the kidney, termed *acute lobar nephronia* or *acute focal bacterial nephritis* (Fig. 72.8). Although antibiotics may arrest progression at this stage, coalescence of microabscesses (multifocal bacterial nephritis) can lead to intrarenal abscess (Fig. 72.9).

Emphysematous pyelonephritis is an uncommon, severe, life-threatening necrotizing form of acute multifocal bacterial nephritis in which retroperitoneal, extraluminal gas is seen in the renal parenchyma, urinary collecting system, or perirenal space on an abdominal radiograph or CT scan (see Fig. 72.7). The presence of gas suggests a gas-forming, gram-negative facultative anaerobic uropathogen and occasionally *Candida* species. *Escherichia coli* is the most common organism associated with this complication, but *Klebsiella* spp., *P. mirabilis,* and *Citrobacter* spp. may be involved. This condition occurs most commonly in diabetic patients with or without urinary obstruction.[265] Mortality rates have improved significantly in the past 2 decades, and "nephron-sparing" management (percutaneous drainage of localized gas collections as opposed to nephrectomy) is increasingly utilized.[266,267] Emphysematous pyelitis is a distinct clinical entity (class 1 emphysematous pyelonephritis) that occurs as a sequela of infection when gas accumulates in the pelvicalyceal system. Diabetes and urinary tract obstruction are common

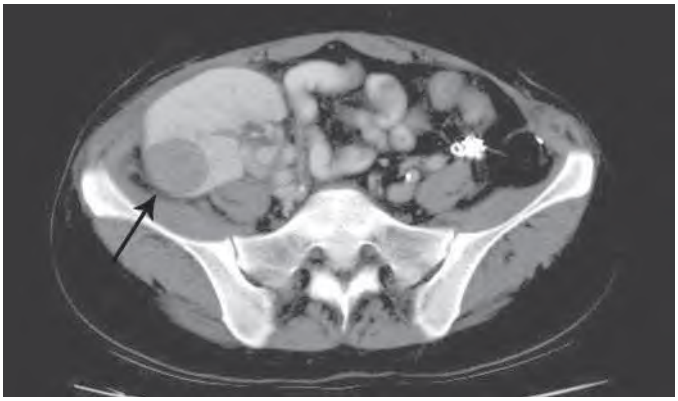


**FIG. 72.8 Computed tomography scan of cadaveric kidney transplant showing acute lobar nephronia or acute focal bacterial nephritis.** Note the bulging renal capsule, reflecting edema of the lobe *(arrow)*.

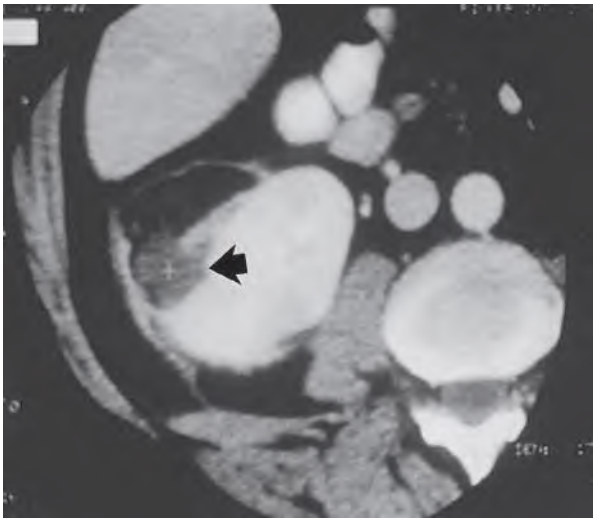


**FIG. 72.9 Intrarenal abscess.** This computed tomography scan shows an intrarenal abscess, evident as a well-delineated hypodense lesion *(arrow),* extending into the intrarenal space. *(Courtesy Dr. M. Bergeron.)*

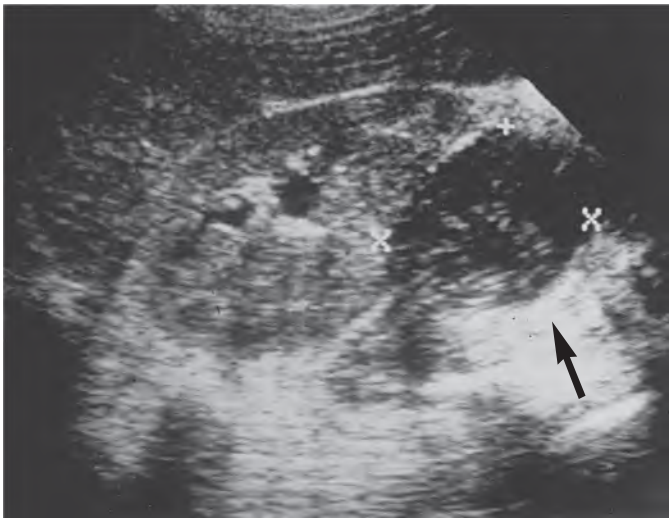


**FIG. 72.10 Perinephric abscess.** Ultrasound examination reveals a perinephric abscess *(arrow). (Courtesy Dr. M. Bergeron.)*

predisposing factors, and *E. coli* and *K. pneumoniae* are commonly implicated pathogens. These patients are generally far less ill and respond well to antibiotics alone in the majority of cases.[267]

Xanthogranulomatous pyelonephritis (XGP) is an uncommon but severe focal or diffuse chronic infection of the renal parenchyma. Destroyed tissue is replaced by granulomatous tissue containing lipid-laden macrophages (foam cells). Predisposing factors include renal calculi, urinary obstruction, lymphatic obstruction, renal ischemia, secondary metabolic alterations in lipid metabolism, an abnormal host immune response, and diabetes mellitus.[268] XGP has a predilection to extend into the retroperitoneal space, leading to internal and external fistulae. The latter complications and mass effect of XGP often mimic those of a genitourinary malignancy.[269]

## Diagnosis and Therapy

Urinalysis is abnormal in 70% of patients with a corticomedullary abscess, whereas it is usually normal in the patient with a hematogenous cortical or perinephric abscess. Confirmation of the diagnosis requires imaging techniques.

The introduction of renal ultrasonography and in particular CT scans added additional sensitivity and specificity, permitting the early diagnosis of intrarenal and perinephric abscesses (Figs. 72.10 and 72.11; see Fig. 72.9).[214,215] The most common CT findings include thickening of the Gerota fascia, renal enlargement, focal parenchymal decreased attenuation, and fluid or gas, or both, in and around the kidney.

In patients with a clinical or radiographic suspicion of perinephric abscess, diagnostic percutaneous needle aspiration can be safely performed by using ultrasonography or CT guidance. When an abscess is confirmed, small catheters can be introduced to provide immediate decompression and continuous and definitive drainage without the need for surgery.[265] Drainage is recommended for abscesses 5 cm or greater in size; drainage or medical management alone are options for abscesses 3 to 5 cm, while abscesses less than 3 cm can often be managed with antibiotics alone.[219,265] Advantages to guided percutaneous drainage compared with open surgical drainage include earlier diagnosis and treatment, the avoidance of general anesthesia and surgery, less expensive therapy, easier nursing care, and greater patient acceptance of closed drainage. Accordingly, it is now recommended that after antimicrobial therapy directed against the most likely pathogens is started, a trial of percutaneous drainage should be the initial mode of therapy for perinephric abscess. Surgical intervention should be undertaken only when percutaneous drainage fails or is contraindicated. Parenteral antimicrobial therapy directed against the infecting organism isolated from blood or urine should be initiated before drainage, but if additional organisms are isolated at the time of drainage, treatment directed against these organisms must be added. Therapy must also be instituted for the underlying disease (e.g., obstructive uropathy).

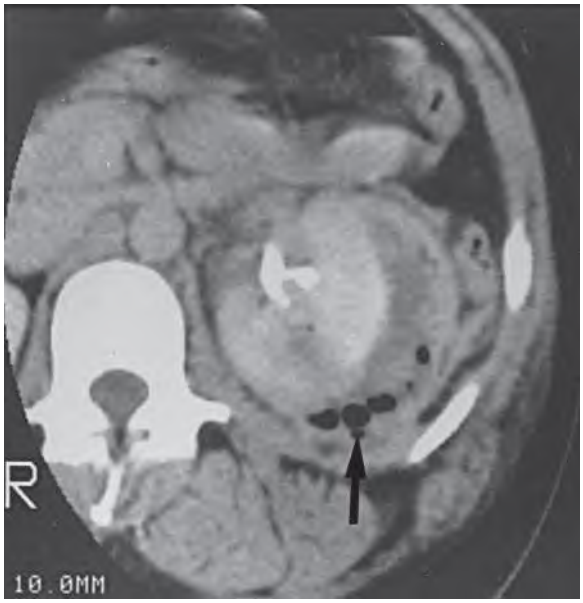



**FIG. 72.11 Left perinephric abscess.** This contrast-enhanced computed tomography scan demonstrates a large left perinephric abscess containing gas *(arrow).*

When antimicrobial therapy with appropriate agents fails with infected renal cysts or abscesses, percutaneous drainage should be tried. Agents that diffuse into these closed sites, such as TMP-SMX and fluoroquinolones, may have an advantage.[270,271] Percutaneous drainage often avoids the previously recommended approach of open surgical drainage or nephrectomy.[272–274]

Successful percutaneous treatment has been reported in 90% of patients with renal or perinephric abscess formation.[274] In the past, delay and missed diagnosis resulted in mortality rates of 20% to 50% in patients with perinephric abscess, with approximately one-third of cases diagnosed only postmortem. Today, with early recognition using modern imaging techniques, together with prompt drainage and antibiotic

therapy, the mortality is extremely low. Most patients with intrarenal abscess respond, although slowly, to antimicrobial therapy, but fever and severe flank pain may persist for days. Open surgical drainage is reserved for nonfunctioning kidneys, multilocular abscesses, and patients who fail initial management with percutaneous drainage.

## Imaging Studies

Imaging procedures play an important role in the diagnosis and management of patients with UTI,[275] both in the control of complicated episodes of acute pyelonephritis and in the investigation of patients of all ages in whom the clinician suspects the presence of underlying structural abnormalities that may be surgically correctable. In adults, uncomplicated acute renal infections do not require imaging. Studies are useful when the diagnosis is in doubt, in severely ill or immunocompromised patients, in those patients with pyelonephritis who fail to improve after 72 hours of appropriate antibiotic therapy, or when complications are suspected. Imaging may also be indicated when certain bacterial species such as *C. urealyticum* are isolated because infection with these organisms may be a clue to the presence of renal stones.

In the past, excretory urography in the form of IVP was the initial and definitive investigatory study, but this has been replaced by ultrasonography and CT (Figs. 72.12 and 72.13). In general, ultrasonography serves as a rapid, noninvasive, and relatively inexpensive means of evaluating the renal collecting system, parenchyma, and surrounding retroperitoneum.[273]

Johnson and associates[276] have confirmed that renal swelling, as demonstrated by ultrasonography, characteristically occurs in almost all women with acute pyelonephritis. Enlargement may be unilateral or bilateral and correlates with protracted pretreatment symptoms, leukocytosis, high fever, focal suppurative complications, and prolonged hospitalization. They also indicated that the frequencies of underlying abnormalities and focal complications are low.

Guidelines from the American College of Radiology recommend contrast-enhanced CT as the study of choice.[265] Computed tomographic imaging is more panoramic and more sensitive than ultrasonography in detecting calculi and underlying urinary tract anatomic abnormalities.[277] The increased sensitivity of contrast-enhanced CT, especially helical CT, is particularly apparent in identifying renal parenchyma abnormalities, especially in the mildest cases of acute pyelonephritis.[277] Ultrasound techniques such as power Doppler and pulse inversion harmonic imaging are now widely used to overcome this lack of sensitivity by demonstrating renal perfusion. Ultrasonography is normal in most uncomplicated cases with acute pyelonephritis. A common CT finding is decreased opacification of the affected renal parenchyma, usually in a patchy, wedge-shaped, or linear pattern. Different patterns may coexist, and abnormalities vary in size. Non–contrast-enhanced CT is often normal but may show focal areas of decreased attenuation. Areas of markedly decreased attenuation should raise a suspicion of abscess formation, and then contrast material should, if possible, be administered. Other CT findings in pyelonephritis include diffuse or focal kidney enlargement, perinephric stranding, and mild collecting system dilatation. In moderate and severe cases of acute pyelonephritis, CT scan abnormalities usually persist for several weeks, well after clinical symptoms and laboratory findings have returned to normal.[277,278] After adequate therapy, most cases eventually demonstrate complete resolution of imaging abnormalities. In recurrent infection associated with chronic reflux, the affected renal lobes develop changes of reflux nephropathy. Recurrent infection results in deformity and dilatation of calyces and focal cortical loss, with upper and lower poles severely affected.

Both CT and ultrasonography are sensitive in diagnosing intrarenal and perirenal suppuration; however, contrast-enhanced CT is preferred if there is a high suspicion for abscess, unless there are contraindications.[265] On contrast-enhanced CT, the hallmark of an abscess is a focal area that fails to enhance, indicating an avascular state. Abscesses are typically sharply demarcated and round or ovoid and contain a low-density center. The abscess wall enhances after contrast injection, resulting in the rind sign caused by the presence of inflamed dilated vessels.[272] When detected, gas within a low-density mass is pathognomonic for abscess formation. In contradistinction to pyelonephritis, intrarenal abscesses reaching 2 to 3 cm are well evaluated by ultrasonography, showing sharp demarcation and the presence of liquefaction. Ultrasonography demonstrates a well-marginated, hypoechoic mass with good through-transmission, an irregular interior wall margin, and scattered echogenic foci within the mass representing debris. Gas formation is highly echogenic. Both these procedures may be used for the guidance of percutaneous needle aspiration.

Neither CT scans nor ultrasonography reliably distinguish an uninfected obstructed renal collection system (hydronephrosis) from pyonephrosis. Suggestive findings on CT scan include an increased thickness of the renal pelvis wall and the presence of increased density within the renal pelvis indicative of pus or debris. The strongest indication of pyonephrosis on CT is the presence of gas within the collecting system, but this is uncommon. Ultrasonography, especially contrast enhanced, may identify echogenic contents or debris (Fig. 72.14).

Gas formation within the renal parenchyma as a consequence of severe infection by facultative anaerobes and occasionally *Candida* spp. is termed *emphysematous pyelonephritis.* Although gas may be seen on plain radiographs, it is often mistaken for bowel gas. Computed tomography is exquisitely sensitive in the detection of gas, which appears as small bubbles or as linear streaks. Gas often collects in a subcapsular

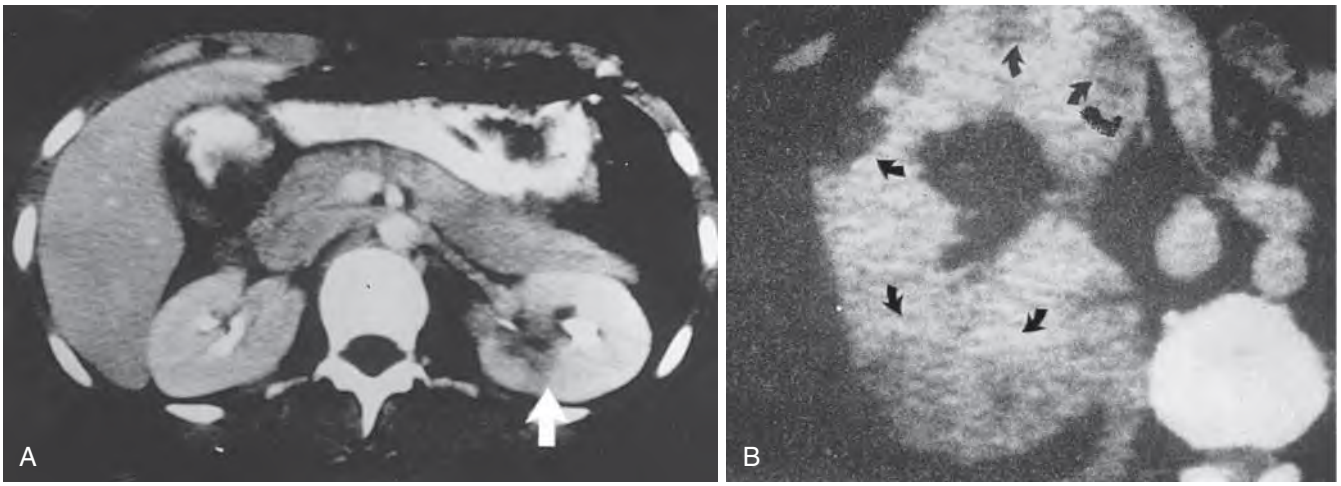



**FIG. 72.12 Computed tomography scan in acute pyelonephritis.** The masslike lesion of pyelonephritis is often well defined because it is less dense than the cortex. (A) It can be irregular with a nonhomogeneous center *(arrow),* as seen in the left kidney. The contralateral kidney is normal. (B) Acute pyelonephritis can also appear as multifocal with diffuse masslike lesions *(arrows). (Courtesy Dr. Huang.)*

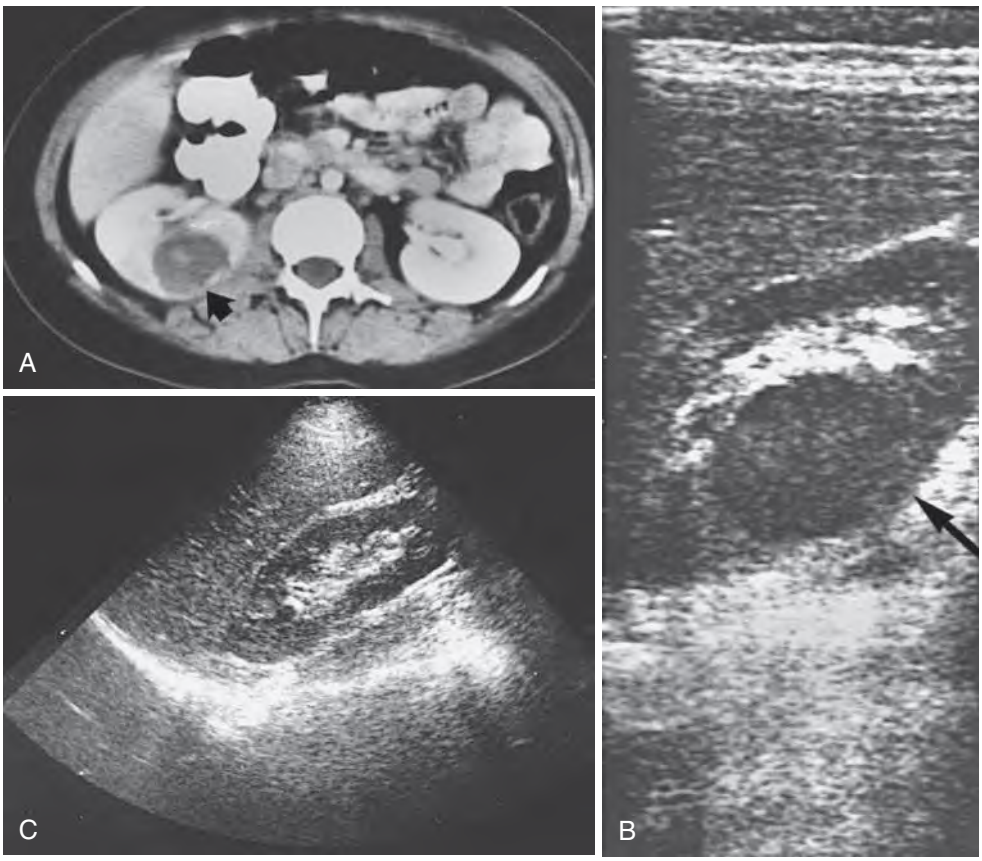



**FIG. 72.13 Acute pyelonephritis with a masslike lesion.** (A) On a computed tomography scan, acute pyelonephritis with a (B) ultrasound examination of the right kidney shows the same masslike lesion *(arrow)*. (C) The mass has resolved on the follow-up ultrasound study performed 2 months later. *(Courtesy Dr. T. Slovis.)*

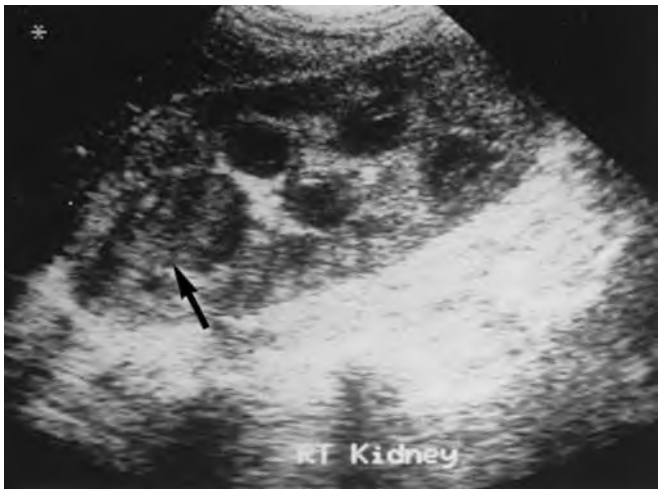



**FIG. 72.14 Ultrasound study demonstrating pyonephrosis (i.e., hydronephrosis) and echogenic content of the collecting system *(arrow).***

location, forming a sharp line around the margin of the kidney, or may be seen within the renal collecting system.

For detecting lesions of the collecting system, CT provides physiologic information similar to that obtained with IVP, with much better parenchymal delineation but less optimal delineation of the collecting system.[275] For cases in which renal calculi may be present, the CT study should also include noncontrast images through the kidney. Helical CT scanning of the abdomen and pelvis without contrast material is now considered the standard approach to confirm or exclude the presence of obstructing ureteral calculi ("stone protocol").[265,279] The accuracy and sensitivity of a non–contrast-enhanced CT scan for renal, ureteral, and bladder stones approach 100%.[280]

All studies requiring the parenteral administration of contrast material are associated with some risk of allergy or contrast-induced renal insufficiency. Predisposing factors for renal insufficiency include myeloma, diabetes mellitus, preexisting renal failure, severe intravascular volume depletion, and the recent administration of large doses of iodinated contrast material. Magnetic resonance imaging offers no advantage over CT in the diagnosis of intrarenal or perinephric abscess but may be considered as an alternative to contrast-enhanced CT in patients with a contraindication to iodinated contrast administration. Previously, the use of gadolinium was thought to be risk free compared with alternative contrast agents, but there is now a recognized risk of systemic fibrosis and, more recently, concern about toxicity related to deposition in brain and bone.[281,282] Radioisotope studies play only a small role in the investigation of the urinary tract. Indium 111–labeled white blood cell studies and renal scintigraphy using $^{99m}$Tc-DMSA scans occasionally prove useful in localizing inflammation or infection to the kidneys in patients with fever of unknown origin, especially patients with spinal cord injuries (Fig. 72.15). Radionuclide scanning may be of value, after ultrasonography or CT scanning has identified a solid renal mass, in suggesting the inflammatory nature of the lesion. However, neither of these radionuclide studies distinguishes pyelonephritis from abscess.

Another important contribution provided by these imaging modalities is the detection of surgically correctable abnormalities of the urinary tract. Investigation should be considered in patients at the greatest risk of having critical surgically correctable abnormalities. Patients included in this higher risk category are those with pyelonephritis, regardless of age, who relapse after therapy. The routine use of noninvasive renal ultrasonography in women with acute uncomplicated pyelonephritis appears excessive because focal complications are rare and underlying

structural abnormalities occur in only about 5% of cases.[276,283] Women with bacteriuria of pregnancy in whom eradication of infection is difficult should be evaluated. Whereas ultrasonography can be safely performed during pregnancy, accurate delineation of the urinary tract should be delayed until at least 2 months after delivery, by which time the physiologic alterations to the urinary tract that occur during pregnancy should be reversed.[145] Ultrasound examination is also useful in diagnosing lower urinary tract obstruction and quantifying residual volume of urine in the bladder. A radionuclide diethylenetriaminepenta-acetic acid (DTPA) scan with furosemide to increase urine flow is useful in determining whether there is structural as opposed to functional ureteropelvic junction obstruction.

In addition to delineating lesions amenable to surgical correction, imaging frequently provides information previously unknown to the patient or physician. For example, unsuspected renal scarring may be seen, suggesting the possibility of undiagnosed (or even diagnosed) UTI in childhood. Occasionally, an unusual or unsuspected type of renal infection such as tuberculosis, papillary necrosis, or XGP may be discovered.[275] Two major radiologic patterns of XGP are seen, a localized mass and diffuse nodularity (Fig. 72.16). When a mass lesion is present, differentiation from pyogenic abscess, tuberculous abscess, or avascular carcinoma may not be possible. Additional findings include nephromegaly, thickening of the Gerota fascia, and infiltration into the perinephric space and surrounding retroperitoneal tissues.

Children with UTI are evaluated with imaging studies to identify those with congenital anomalies who may be at risk of chronic renal damage and those who require corrective surgery to prevent recurrent UTI and preserve renal function (Fig. 72.17).

Imaging protocols in pediatric UTIs are evolving. Renal ultrasound examination is commonly done in children with UTI, particularly those with recurrent UTI. Influenced by the new ability for antenatal diagnosis,

**FIG. 72.15 Renal gallium-67 scan in a young girl with bilateral acute pyelonephritis and increased uptake in both kidneys caused by inflammation.** *(Courtesy Dr. M. Bergeron.)*

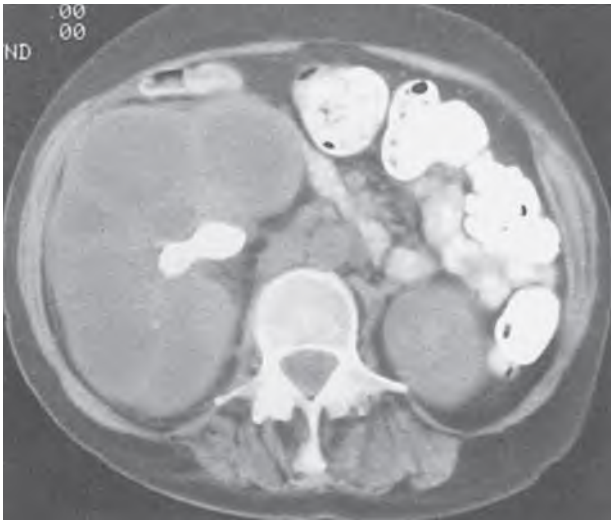



**FIG. 72.16 Computed tomography scan of a patient with right-sided xanthogranulomatous pyelonephritis.** A huge multilobulated inflammatory mass replaces the right kidney. *Proteus mirabilis* was grown from the urine. *(Courtesy Dr. L. E. Nicolle.)*

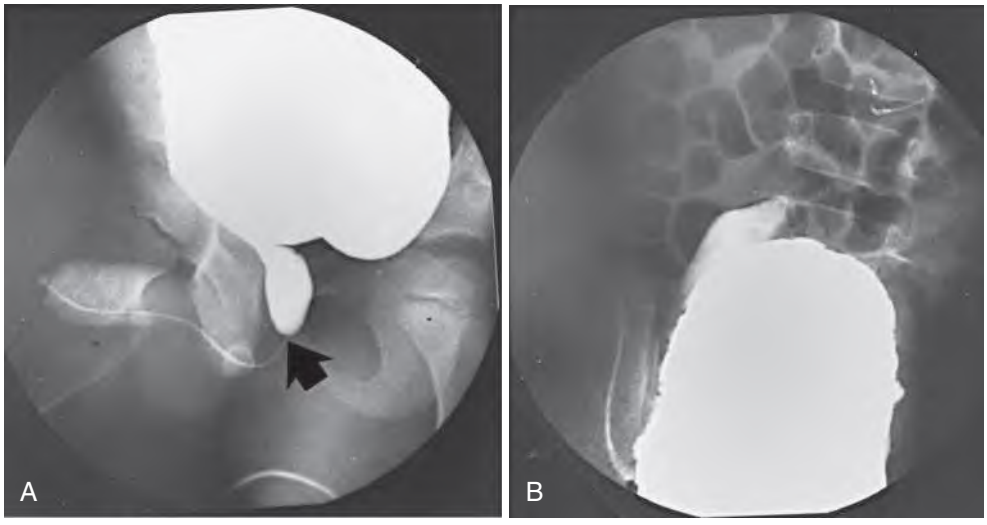



**FIG. 72.17 Voiding cystourethrogram.** (A) Posterior urethral valve on computed tomography scan. Note the discrepancy in size of the anterior *(arrow)* and posterior urethra. (B) There is irregular trabeculation of the bladder, with right ureteric reflux. *(Courtesy Dr. T. Slovis.)*

strategy has changed from extensive investigations, including cystography for all children younger than 7 years with UTI, to strategies focused on children at risk of developing renal damage as indicated by National Institute for Health and Care Excellence recommendations.[284–286] The main focus in the past was identifying vesicoureteral reflux (VUR). Traditional management consisted of prompt treatment of UTI, long-term antimicrobial prophylaxis until VUR resolved, or surgical intervention for those patients with both persistent high-grade VUR and recurrent UTIs in spite of prophylaxis with antimicrobials. What has changed involves questioning recommendations that were not evidence based and recognition of widespread overinvestigation. The debate regarding prophylaxis in children has moved to "selective prophylaxis".[287] The consistent message that emerges is that investigation of the urinary tract in children with UTIs should be limited to identifying a small select population that has a high risk of developing renal complications, with a lesser role for extensive investigation, surgical treatment, and antibiotic prophylaxis for most patients.[288]

As noted, the natural history for lower grades of VUR (grades I, II, and III) as opposed to higher grades is spontaneous resolution at a rate of 13% per year.[289] Furthermore, more recent data have supported the notion that mild and moderate VUR does not significantly increase the incidence of UTIs, pyelonephritis, or serious renal scarring.[290] In one study, the presence of VUR did not identify a susceptible population with an abnormal kidney on DMSA scan. In the context of a normal ultrasound result, cystography contributes little to the treatment of children younger than 1 year with a UTI.[291]

Although DMSA scans are of value in confirming the clinical diagnosis of acute pyelonephritis, the results uncommonly alter management and hence these scans are not routinely recommended. A DMSA scan performed 36 months after UTI may identify permanent loss of renal parenchyma or renal scars (Fig. 72.18).[292] Children at high risk of structural urinary tract abnormalities and of renal damage in whom renal ultrasonography should be obtained are listed in Table 72.5. Some experts believe that children with their first uncomplicated febrile or nonfebrile symptomatic UTI caused by *E. coli* who respond well to treatment do not require imaging unless they have recurrent infection.[284] Most experts, however, recommend ultrasonography of the urinary tract in all children with febrile UTIs. Accordingly, children with nonfebrile UTI do not need an initial imaging of their urinary tracts unless recurrent, in which case imaging that focuses on bladder function would be indicated—that is, prevoiding and postvoiding ultrasonography followed by voiding cystourethrography or indirect radioisotope cystography (Fig. 72.19).[284,293] Indirect cystography (nuclear) is particularly useful for follow-up evaluation. Children with abnormal findings on renal ultrasound likely will need further imaging such as a voiding cystourethrogram and/or a diuretic DTPA renal scan. Even if the renal ultrasound is normal, some experts recommend a DMSA renal scan to determine if the patient should have a voiding cystourethrogram, also called the "top-down approach."[284] A DTPA scan, particularly with furosemide administration, is used for the diagnosis of ureteropelvic junction obstruction. This study visualizes the passage of tracer through the urinary tract.[292] Some specialists think that cystourethrography should be avoided unless imaging (DMSA scan) shows evidence of renal scars.

## Surgical Management

Surgical therapy in the management of UTI consists of the elimination of obstructive lesions or calculi and endoscopic or open surgical correction of severe reflux. An obstruction may be intrinsic (such as renal cysts), or it may be extrinsic anywhere along the urinary conduit from the ureteropelvic junction to the external urethral meatus. Surgical therapy should be directed toward eliminating the obstruction and preserving renal function. After the obstruction is eliminated, the patient should be followed with urine cultures. Urinary tract infection should be treated before surgery to render the urine sterile at the time of surgery; this decreases the possibility of bacteremia occurring in association with the surgery. For the management of perinephric or intrarenal abscess, see "Perinephric Abscess and Intrarenal Abscess" earlier.

## Summary of Treatment Approaches

Fig. 72.20 summarizes the approach to the management of UTI. Table 72.6 summarizes the recommendations for initial therapy of UTI in adult outpatients.

**TABLE 72.5 Findings in High-Risk Children for Whom Radiologic Imaging Is Indicated**

| |
|---|
| Recurrent infection |
| Clinical signs such as poor urinary stream or palpable kidney |
| Unusual organisms (non–*Escherichia coli*) |
| Bacteremia or septicemia |
| Prolonged clinical course with failure to respond fully to antibiotic therapy within 48 h |
| Unusual clinical presentation (e.g., older boy) |
| Known dilatation or abnormality on antenatal ultrasound screening of urinary tract |

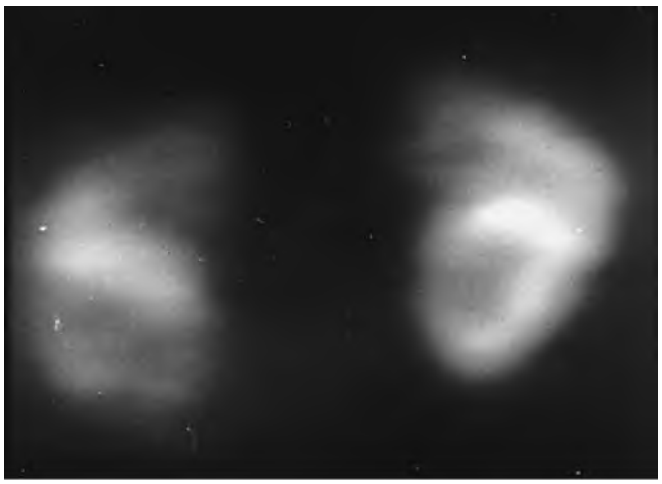


**FIG. 72.18 Acute pyelonephritis.** This technetium-99m glucoheptonate–labeled, single-photon emission computed tomography scan shows markedly decreased visualization of the upper and lower poles of the right kidney. The midportions are normal. *(Courtesy Dr. T. Slovis.)*

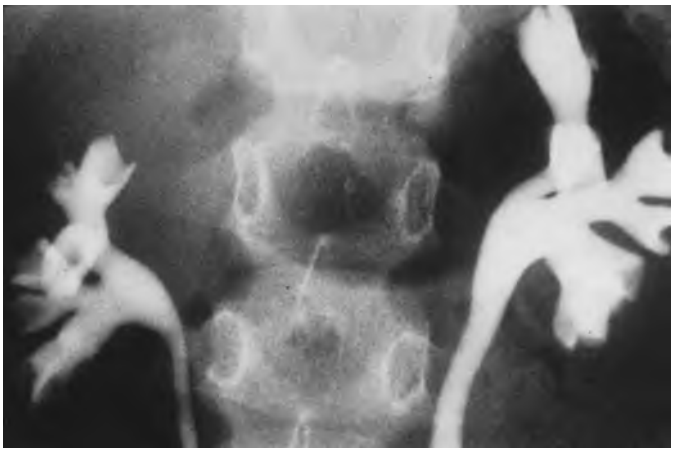
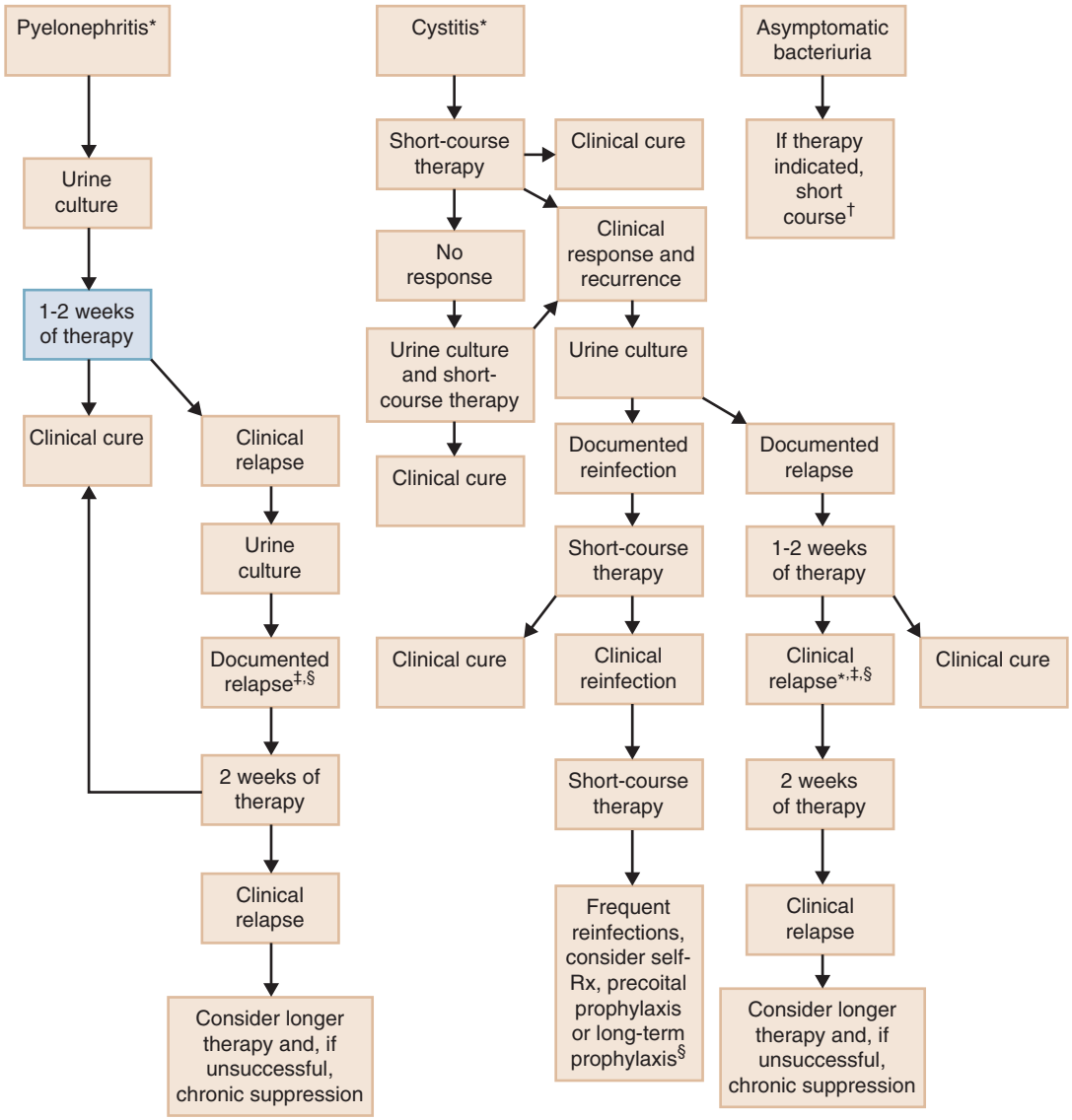


**FIG. 72.19 Grades II and III reflux in a voiding cystourethrographic study from a young boy who presented with recurrent urinary tract infection.** Note early clubbing of the calyces and dilation of the ureter on the left side. *(Courtesy Dr. L. E. Nicolle.)*




*Consider imaging studies in all men and in women with complicated urinary tract infection.
†No therapy except for renal transplant patients or prior to urologic procedures. Follow-up culture only in transplant patients.
‡Evaluate men for chronic bacterial prostatitis.
§Consider imaging studies in women.

**FIG. 72.20 Approach to the management of urinary tract infection in nonpregnant adults.**

**TABLE 72.6 Recommendations for Initial Therapy of Urinary Tract Infection in Adults**

| PARAMETER | ORAL[a] | PARENTERAL (SWITCH TO ORAL WHEN RESPONSE OCCURS) |
|---|---|---|
| **Uncomplicated Pyelonephritis** | | |
| GNB or no urine Gram stain available | CP 7 days, LV 5 days; if cannot use FQ, TMP-SMX 14 days + 1 dose CT or AM | FQ or extended-spectrum β-lactam (e.g., CT) ± AM or carbapenem |
| GPC in chains | Amoxicillin, 14 days | Ampicillin |
| GPC in clusters | Linezolid or TMP-SMX, 14 days | Vancomycin |
| **Complicated Pyelonephritis** | | |
| Nonpregnant women or men | As for uncomplicated pyelonephritis; duration 10–14 days | Extended spectrum β-lactam ± AM, FQ, carbapenem[d] |
| Pregnant women | Extended spectrum β-lactam; or TMP-SMX[b] only if known sensitive; both for 14 days | Extended spectrum β-lactam ± AM |
| **Uncomplicated Cystitis** | | |
| Nonpregnant women | Nitrofurantoin, 5 days; or fosfomycin, 1 dose; or TMP-SMX, 3 days; or pivmecillinam, 3–7 days | |

**TABLE 72.6 Recommendations for Initial Therapy of Urinary Tract Infection in Adults—cont'd**

| PARAMETER | ORAL[a] | PARENTERAL (SWITCH TO ORAL WHEN RESPONSE OCCURS) |
|---|---|---|
| **Complicated Cystitis** | | |
| Women or men | FQ or nitrofurantoin, 7 days; or fosfomycin, 1 dose | |
| Pregnant women | Cephalexin, 3–5 days; or fosfomycin, 1 dose; or nitrofurantoin,[c] 7 days; or TMP-SMX,[b] 3 days if sensitive | |

[a]Preferred if the patient is reliable, compliant, hemodynamically stable, and able to take oral therapy.
[b]TMP-SMX should be avoided in the first and third trimesters.
[c]Nitrofurantoin should be avoided in the first trimester.
[d]Ceftazidime-avibactam is a potential option for infections due to carbapenem-resistant Enterobacteriaceae or multidrug-resistant (MDR) *Pseudomonas;* ceftolozane-tazobactam is another potential option for MDR *Pseudomonas.*
*GNB,* Gram-negative bacilli; *GPC,* gram-positive cocci.
Oral Drugs and Dosages:
CP, ciprofloxacin 500 mg bid or 1000 mg daily.
LV, levofloxacin 750 mg daily.
TMP-SMX, trimethoprim-sulfamethoxazole 160/800 mg bid.
FQ, fluoroquinolone—ciprofloxacin 500 mg bid or 1000 daily or levofloxacin 750 mg daily.
Oral Drugs and Dosages:—cont'd
Amoxicillin 875 mg bid.
Linezolid 600 mg bid.
Nitrofurantoin 100 mg bid.
Fosfomycin 3 g once.
Pivmecillinam 400 mg bid.
Cephalexin 500 mg qid.
Parenteral Drugs and Dosages:
FQ, fluoroquinolone—ciprofloxacin 400 mg q12h or levofloxacin 500 mg daily.
CT, ceftriaxone 2 g/d.
AM, aminoglycoside (e.g., gentamicin 5 mg/kg/day).
Ampicillin 2 g q4h.
Vancomycin 15 mg/kg bid.
Carbapenem (e.g., imipenem 500 mg q6h or ertapenem 1 g daily).

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*The complete reference list is available online at Expert Consult.*


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# E Sepsis

# 73 Sepsis and Septic Shock

*Tom van der Poll and Willem Joost Wiersinga*

## SHORT VIEW SUMMARY

### Definition
- Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.

### Clinical Signs and Symptoms
- Pneumonia, peritonitis, urinary tract infections, and soft tissue infections are—in descending order—the most important sources of sepsis.
- Organ failure is the hallmark sign of sepsis and most frequently occurs in the respiratory and cardiovascular systems, followed by renal, central nervous system, hematologic, and hepatic dysfunction.

### Epidemiology
- The incidence of sepsis has increased at least in part due to the aging population and aggressive therapies for chronic diseases.
- The case-fatality rate of sepsis has decreased, at least in high-income countries, likely in part through implementation of the Surviving Sepsis Campaign guidelines and improvement of standard intensive care.
- The risk of acquiring sepsis is influenced by age, sex, comorbidity burden, and socioeconomic status.

### Microbiology
- A causative microorganism can be identified in up to two-thirds of patients admitted to an intensive care unit for sepsis.
- Gram-negative bacteria are identified in 38% to 62% of cases, gram-positive bacteria are identified in 40% to 52%, and fungi are identified in 5% to 19%. Viral infections are detected in 1% to 7% of cases.

### Pathogenesis
- Pattern-recognition receptors are essential for sensing invading bacteria and subsequent initiating of the immune response. These receptors recognize both pathogen-associated molecular patterns (conserved motifs expressed by pathogens) and danger-associated molecular patterns or alarmins (host molecules released during inflammatory stress).
- The host response to sepsis is characterized by both proinflammatory and antiinflammatory reactions and varies among individuals. Proinflammatory responses include cytokine release and activation of the complement system, coagulation system, and vascular endothelium; antiinflammatory responses can result in immunosuppression at least in part due to apoptotic loss of lymphoid cells.
- The host response to infection and noninfectious injury is not fundamentally different.

### Diagnosis
- There is no gold standard for diagnosing sepsis. A clinical pattern based on the patient's history and physical examination combined with laboratory, radiology, and microbiology testing is typically required for the diagnosis.
- Host response biomarkers can be of diagnostic value, discriminating infectious from noninfectious conditions or determining the causative pathogen; of prognostic value, assigning risk profiles and predicting outcome; or of theranostic (combining diagnosis and therapy) value, aiding in selection and monitoring of therapy (see Fig. 73.6).

### Therapy
- Implementation of the Surviving Sepsis Campaign guidelines for management of sepsis has been associated with improved outcome.
- Intravenous antibiotics should be started as soon as possible after recognition of sepsis and within 1 hour for septic shock.
- The choice of empirical antibiotic treatment depends on the suspected source of infection, global geography, setting (e.g., community or hospital), comorbidity, and local microbial susceptibility patterns.

### Prognosis
- Patients who survive sepsis often have long-term complications including cognitive and physical impairments, higher readmission rates, and increased mortality.

Sepsis is a life-threatening condition with organ failure caused by a dysregulated host response to an infection. Septic shock is sepsis accompanied by persistent hypotension. The most common infections causing sepsis and septic shock are pneumonia and peritonitis. Any infection that overrides the protective innate immune response initiated in response to a potential pathogen can result in sepsis. Sepsis is most often caused by bacteria, but fungal and viral infections can also instigate sepsis. A key pathogenic feature of sepsis is that the multifaceted innate immune response fails to return to normal homeostasis in the context of an unsuccessful attempt to eradicate the invading pathogen. Concurrent hyperinflammation and immunosuppression ensue, affecting different cell types and organs. The case-fatality rate of sepsis has improved in recent years, probably as a result of better general clinical practices and development and implementation of sepsis treatment guidelines. Nonetheless, sepsis continues to be the most frequent cause of death in hospitalized patients, and it is expected to remain an important clinical problem in the future, owing to the aging population, aggressive therapies for chronic diseases, and antimicrobial resistance. Moreover, with more patients surviving sepsis, attention has been directed toward long-term sequelae, which include cognitive and physical impairments and cardiovascular disease.

## DEFINITION

Sepsis is a broad term used for an incompletely understood process, and there is no gold standard for its diagnosis. The term *sepsis* originates from the ancient Greek word *sêpsis* ("putrefaction" or "decay of organic matter") and was first used in a medical context in Homer's *Iliad,* written more than 2700 years ago. In the early 1990s sepsis was clinically defined by a consensus definition generated by a group of key experts.[1] The Sepsis-1 definition was centered around four systemic inflammatory response syndrome (SIRS) criteria consisting of tachycardia (heart rate >90 beats/min); tachypnea (respiratory rate >20 breaths/min); fever or

hypothermia (temperature >38°C or <36°C); and leukocytosis (white blood cells >1200/mm$^3$), leukopenia (white blood cells <4000/mm$^3$), or bandemia (≥10%) (Table 73.1). Sepsis-1 was defined as (documented or suspected) infection leading to the onset of SIRS as reflected by the presence of two or more SIRS criteria. Severe sepsis was defined as sepsis complicated by organ dysfunction, which could progress to septic shock, defined as "sepsis-induced hypotension persisting despite adequate fluid resuscitation."[1] By incorporating the SIRS criteria in the definition, the Sepsis-1 definition sought to capture the then-prevailing view that sepsis resulted from a systemic inflammatory response to infection. In 2001 a new task force was assembled to readdress the definition of sepsis.[2] Although the limitations of Sepsis-1 were recognized, alternatives were not offered owing to absence of supporting evidence. The Sepsis-2 definition expanded the list of diagnostic criteria, encompassing a set of 24 general, inflammatory, hemodynamic, organ dysfunction, or tissue perfusion parameters. In the Sepsis-2 definition the criteria for severe sepsis remained similar, whereas septic shock was defined more explicitly as refractory hypotension (systolic blood pressure <90 mm Hg or mean arterial blood pressure <70 mm Hg) despite adequate fluid resuscitation.[2]

The most recent Sepsis-3 definition, published in 2016,[3] seeks to confine important limitations of Sepsis-1 and Sepsis-2, which include a disproportionate emphasis on inflammation, poor specificity and sensitivity of the SIRS criteria, and the incorrect concept that sepsis follows a continuum through severe sepsis to shock. The Sepsis-3 definition, in contrast to Sepsis-1 and Sepsis-2, partially relies on large data sets, which were used to obtain quantitative information in support of the new criteria. The new definition abandoned the use of SIRS criteria in the diagnosis of sepsis. In addition, in the new definition the presence of organ dysfunction is a requirement for a sepsis diagnosis, and therefore the term *severe sepsis* was eliminated in Sepsis-3. According to the Sepsis-3 definition, sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[3] In the clinic, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more; the baseline SOFA score should be presumed zero unless the patient is known to have preexisting organ dysfunction before the onset of infection (Table 73.2). Septic shock is now defined as a subset of sepsis in which strong circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone; these patients can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

The 2016 Task Force also introduced the quick SOFA, or qSOFA, score, composed of three components that are easy to measure at the bedside: respiratory rate of 22 breaths/min or greater, altered mentation, and systolic blood pressure of 100 mm Hg or less.[3] Evidence indicated that in out-of-hospital, emergency department, and general hospital ward settings, adult patients with suspected infection and a higher risk for poor outcomes typical of sepsis can be rapidly identified by the presence of at least two qSOFA criteria. Importantly, qSOFA is *not* part of the new definition of sepsis. Moreover, failure to meet two or more SOFA or qSOFA criteria should not lead to a delay of

**TABLE 73.1 Sepsis Definitions**

| TERM | DEFINITION |
|---|---|
| **1991 Consensus Conference[1]** | |
| SIRS | At least two of the following:<br>• Temperature >38°C or <36°C<br>• Heart rate >90 beats/min<br>• Respiratory rate >20 breaths/min or arterial $CO_2$ <32 mm Hg<br>• White blood cell count >12 × 10$^9$/L or <4 × 10$^9$/L or >10% immature forms |
| Sepsis | Infection[a] + SIRS |
| Severe sepsis | Sepsis + acute organ dysfunction |
| Septic shock | Sepsis + persistent hypotension after fluid resuscitation |
| **2001 International Sepsis Definitions Conference[2]** | |
| No significant changes from 1991 definitions, with the addition that signs and symptoms of sepsis are more varied than captured by 1991 definitions; this resulted in the presentation of a list of these signs and symptoms for the diagnosis of sepsis | |
| **2015 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[3]** | |
| Sepsis[b] | • Life-threatening organ dysfunction caused by dysregulated host response to infection<br>• Organ dysfunction can be identified as acute change in total SOFA score ≥2 points |
| Septic shock | • Sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality<br>• Clinically defined as sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mm Hg and with serum lactate >2 mmol/L |

[a]Suspected or proven.
[b]In the new sepsis definition, the presence of organ dysfunction is central and a requirement; previously, organ dysfunction identified "severe" sepsis, a term that was abandoned in the Sepsis-3 definition.
*$CO_2$,* Carbon dioxide; *SIRS,* systemic inflammatory response syndrome; *SOFA,* Sequential [Sepsis-related] Organ Failure Assessment.

**TABLE 73.2 SOFA Score**

| ORGAN SYSTEM | SCORE |
|---|---|
| Respiration | |
| $Pa_{O_2}/Fi_{O_2}$, mm Hg (kPa) | |
| <400 (53.3) | 1 |
| <300 (40) | 2 |
| <200 (26.7) with respiratory support | 3 |
| <100 (13.3) with respiratory support | 4 |
| Central nervous system | |
| GCS score | |
| 13–14 | 1 |
| 10–12 | 2 |
| 6–9 | 3 |
| <6 | 4 |
| Cardiovascular | |
| MAP or use vasopressors (μg/kg/min) | |
| MAP <70 mm Hg | 1 |
| Dopamine <5 or dobutamine (any dose)[a] | 2 |
| Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1 | 3 |
| Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 | 4 |
| Liver | |
| Bilirubin, mg/dL (μmol/L) | |
| 1.2–1.9 (20–32) | 1 |
| 2.0–5.9 (33–101) | 2 |
| 6.0–11.9 (102–204) | 3 |
| >12.0 (204) | 4 |
| Coagulation | |
| Platelets, × 10$^3$/μL | |
| <150 | 1 |
| <100 | 2 |
| <50 | 3 |
| <20 | 4 |
| Renal | |
| Creatinine, mg/dL (μmol/L) or urine output, mL/day | |
| 1.2–1.9 (110–170) | 1 |
| 2.0–3.4 (171–299) | 2 |
| 3.5–4.9 (300–440) or <500 | 3 |
| >5.0 (440) or <200 | 4 |

*$Fi_{O_2}$,* Fraction of inspired oxygen; *GCS,* Glasgow Coma Scale (scores range from 3 to 15; higher score indicates better neurologic function); *MAP,* mean arterial pressure; *$Pa_{O_2}$,* partial pressure of oxygen; *SOFA,* Sequential [Sepsis-related] Organ Failure Assessment.
The SOFA score can be used to measure the severity of organ dysfunction. The aggregate score is calculated by summing the worst scores for each of the organ systems.
[a]Catecholamine doses are given as μg/kg/min for at least 1 hour.
*From Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.* Intensive Care Med. *1996;22:707–710.*

treatment of infection or any other intervention deemed necessary by physicians.

The Sepsis-3 definition and qSOFA have limitations, and criticism exists regarding their use in clinical practice. Although large cohorts were used to support Sepsis-3 and qSOFA, patient data were almost exclusively derived from high-income countries (especially the United States), which leaves uncertainty with regard to extrapolation to resource-poor settings. In addition, supporting data were generated in adult patients and cannot be readily extrapolated to pediatric sepsis. The measurement of serum lactate is required for the diagnosis of septic shock, which is not feasible in many areas of the world. Finally, the Sepsis-3 definition does not entail a molecular or pathogenic component that may stratify patients into more homogeneous subgroups based on their predominant pathophysiologic abnormality and thereby guide individualized therapies.

## CLINICAL SIGNS AND SYMPTOMS

Correctly recognizing a septic patient can be challenging, as clinical signs and symptoms at presentation can be variable and nonspecific.[4,5] The manifestations of sepsis depend on the source of infection, the causative pathogen, the type and extent of organ dysfunction, drug use and comorbidity of the patient, and the delay before consulting a physician or before start of treatment. The most common underlying comorbidities of patients admitted for sepsis include chronic obstructive pulmonary disease, neoplasm, human immunodeficiency virus (HIV) infection, chronic liver disease, chronic renal disease, diabetes, peripheral vascular disease, and autoimmune disease.[6] General variables include fever, tachycardia, tachypnea, altered mental status, significant edema, or positive fluid balance (>20 mL/kg over 24 hours).[2] Hypothermia is observed in 9% to 35% of patients with sepsis and is associated with adverse outcomes.[7,8]

### Source of Sepsis

Pneumonia is the most common source of sepsis in adults, followed by abdominal, urinary tract, and skin/soft tissue infections (Fig. 73.1A).[6,9,10,11,12] These preferred sites account for 80% to 90% of all adult sepsis cases, the remainder being caused by bone/joint infections, ear-nose-throat infections, and others. More than one source is found in approximately 6% of episodes.[9] The primary source of infection often depends on the comorbidity of the patient and the presence of indwelling catheters or devices. For instance, the presence of obstructive lung disease is a significant predictor of hospitalizations caused by respiratory tract infections but not of hospitalizations due to infections outside the respiratory system.[13] Likewise, in patients on long-term renal replacement therapy, sepsis more often is caused by central venous catheter infections, peritonitis, or an ischemic bowel.[14] However, in most series, no obvious source of infection can be found in one-sixth of patients.[6,9,10,11,12]

### Organ Failure in Sepsis

Organ failure is the hallmark sign of sepsis, and respiratory and cardiovascular failure most frequently occurs, followed by renal, central nervous system (CNS), hematologic, and hepatic failure (Fig. 73.1B).[5,6,10,15,16] Respiratory failure, shock, and kidney failure are the most common reasons for admission to the intensive care unit (ICU).[10,15] Most patients have failure of a single organ, whereas approximately 20% have failure of two organs, and approximately 5% have acute failure of three or more organs.[6,11] There is a direct relationship between the number of organs failing in patients with sepsis and mortality.[10] A study from across Europe showed mortality rates were 26% among patients with dysfunction of two organs on ICU admission, whereas mortality rates were 65% among patients with failure of four or more organs.[10] Severity of organ dysfunction has been assessed with various scoring systems that quantify abnormalities according to clinical findings, laboratory data, or therapeutic interventions.[3] The predominant system in current use is the SOFA score (see Table 73.2).[17] A higher SOFA score is associated with an increased probability of mortality.[18]

### Acute Lung Injury

Respiratory failure commonly manifests as acute respiratory distress syndrome (ARDS), defined as hypoxemia and bilateral infiltrates of noncardiac origin (Fig. 73.2).[19] ARDS can be classified as mild (200 mm Hg < partial pressure of arterial oxygen [$Pao_2$]/fractional inspired oxygen [$Fio_2$] < 300 mm Hg), moderate (100 mm Hg < $Pao_2/Fio_2$ ≤ 200 mm Hg), or severe ($Pao_2/Fio_2$ ≤ 100 mm Hg).[19] The underlying pathology is diffuse alveolar epithelial injury, with increased barrier permeability and exudation of protein-rich fluid into the interstitial and airspace compartments.[20] Neutrophils and monocytes accumulate in the lungs and may form cellular aggregates in pulmonary vessels. Significant right-to-left shunting occurs. Dead space volume increases and compliance decreases, augmenting the work of breathing. Mechanical ventilation is needed in most severe cases. In the past 2 decades, mortality among patients with ARDS has decreased from approximately 60% to 25%, which can be accounted for in part by the application of a lung-protective ventilation strategy (with low airway pressure and low tidal

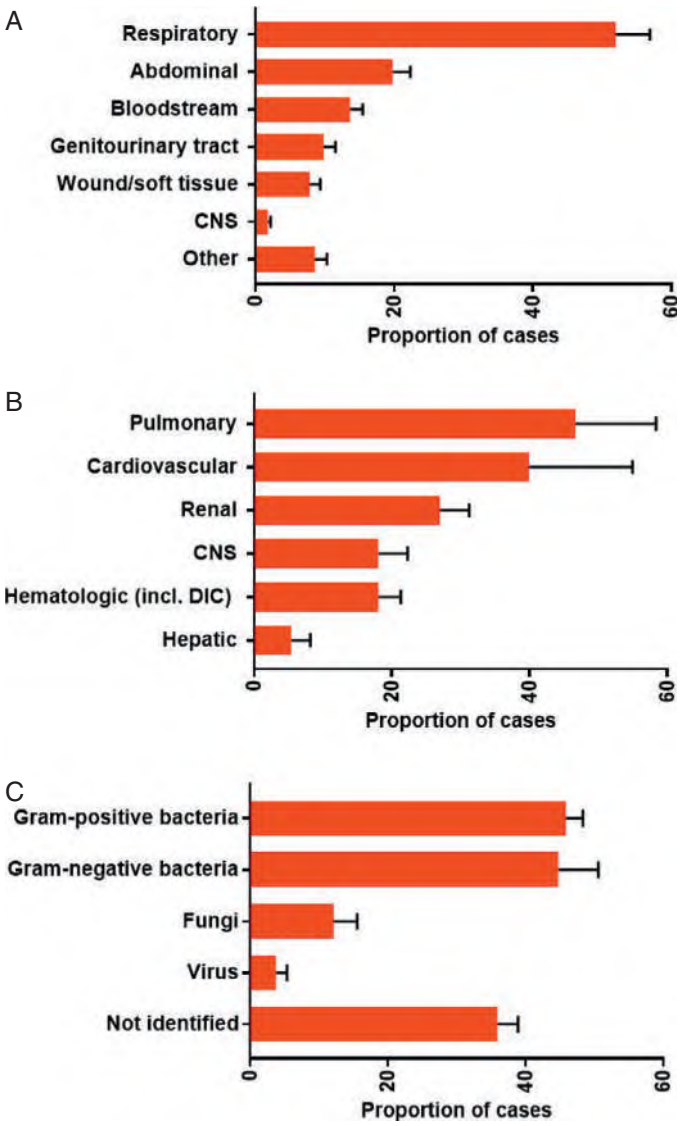


**FIG. 73.1 Most common sites of infection, types of organ failure, and causative organisms identified in patients with sepsis.** (A) Most common sites of infection. Bars show the means plus standard error of data from six representative studies.[6,9,10,11,12,70] The lung and abdomen are the most common primary sites. (B) Most common types of organ failure in sepsis. Bars show means plus standard error of data from four representative studies.[6,10,15,16] The definitions used to diagnose organ dysfunction varied from study to study. Central nervous system *(CNS)* dysfunction was uncommon in some series and very common in others. (C) Incidence of sepsis by causative organism. Bars show means plus standard error of causative organisms isolated in patients with sepsis from four representative studies.[10,16,57,70] A significant number of patients have two or more causative organisms identified. *DIC,* Disseminated intravascular coagulation.

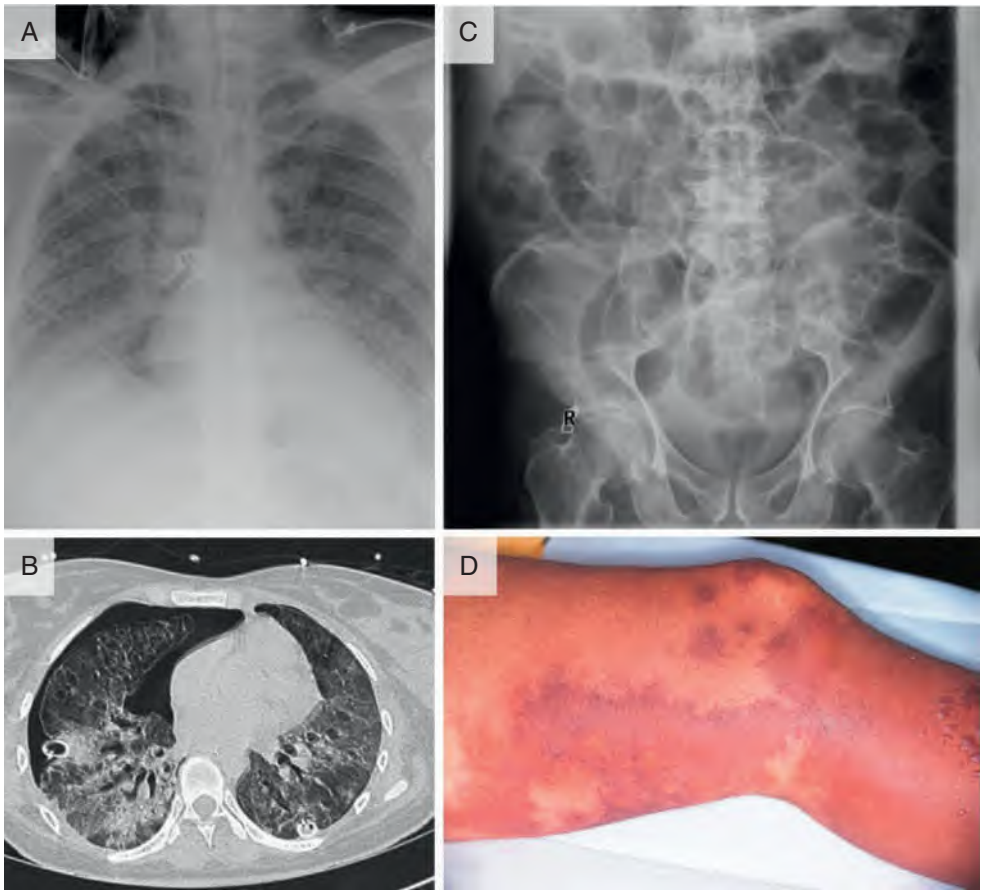


**FIG. 73.2 Common complications of sepsis.** The most common sepsis complications include brain dysfunction, acute lung injury, acute kidney injury, ileus, cardiovascular dysfunction (including shock), disseminated intravascular coagulation (with thrombocytopenia), and liver injury. (A) Typical chest x-ray and (B) computed tomography scan of acute respiratory distress syndrome showing patchy opacification, loculated pneumothoraces, and bilateral chest drains. (C) Plain abdominal x-ray showing an ileus (note dilated loops of small and large bowel with no cutoff). (D) Purpura as a manifestation of severe disseminated intravascular coagulation. *(A from Khan A, Kantrow S, Taylor DE. Acute respiratory distress syndrome.* Hosp Med Clin. *2015;4:500–512; B from Randhawa R, Bellingan G. Acute lung injury.* Anaesth Intensive Care Med. *2007;8:477–480; C from Glancy DG. Intestinal obstruction.* Surgery. *2014;32:204–211; D from Piette WW. Purpura. In: Callen JP, Jorizzo JL, Zone JJ, Piette W, Rosenbach MA, Vleugels RA, eds.* Dermatological Signs of Systemic Disease. *5th ed. Philadelphia: Elsevier; 2017:109–116, courtesy Dr. Neil A. Fenske, Tampa, FL.)*

volumes) in addition to better supportive care in the ICU.[21] However, up to half of patients who recover from ARDS may have significant functional impairment related to the healing process, which can produce restrictive defects, reduced diffusing capacity, and an inability to return to work.[21,22]

## Cardiovascular Dysfunction

The cardiovascular impact of sepsis has two components: myocardial dysfunction and relative hypovolemia resulting from vasodilation.[23,24] Sepsis-associated myocardial dysfunction includes reduced left and right ventricular ejection fractions, increased left and right ventricular end-diastolic volumes, and an elevated heart rate and cardiac output. The cardiac depression associated with septic shock reflects the effects of inflammatory mediators on cardiac myocyte and microcirculatory function, is not caused by ischemia, and usually does not require inotropic therapy. However, if hypovolemic shock cannot be reversed by administering intravenous fluids, the use of vasopressors is indicated to restore tissue perfusion pressure.

Adrenergic agonists are the first-line vasopressors, norepinephrine being the first-choice agent.[25] In cases of refractory septic shock, another vasopressor with a different mechanism of action (nonadrenergic) can be added. Mechanisms implicated in the development of sepsis-induced myocardial depression include alterations in calcium homeostasis, mitochondrial dysfunction, apoptosis, circulating cardiosuppressant mediators, and nitric oxide. A postmortem study found that cardiac myocyte cell death was rare, whereas sepsis-induced focal mitochondrial injury was present in many cells.[26]

## Renal Dysfunction

Acute kidney injury (AKI) is characterized by decreased urinary output with increasing serum creatinine levels; many patients with sepsis require renal replacement therapy.[27] Sepsis-associated AKI is associated with a high burden of morbidity (e.g., dependency on dialysis at the time of hospital discharge) and mortality in patients with critical illness. The renal abnormalities range from minimal proteinuria to profound renal failure; postmortem studies have found focal acute tubular injury and minimal glomerular damage.[26] The underlying pathogenic mechanisms include hypovolemia, hypotension, renal vasoconstriction, and toxic drugs (e.g., aminoglycosides) or contrast agents used for medical imaging.[27] In most patients, sepsis-induced renal injury is largely reversible. Nonetheless, even small acute increases in serum creatinine are associated with decreased long-term survival in critically ill patients.[28] Not surprisingly, survival in patients with septic shock is directly linked to the severity of AKI.[29]

Novel promising biomarkers in urine and plasma for the early diagnosis of sepsis-associated AKI include cystatin C, neutrophil gelatinase-associated lipocalin, tissue inhibitor of metalloproteinase 2, and insulinlike growth factor–binding protein 7. At the present time, however, data on these biomarkers are insufficient to support their use in clinical management of patients with sepsis-associated AKI.[30]

## Dysfunction of Brain, Peripheral Nerves, and Muscles

Brain dysfunction in sepsis may manifest as coma or delirium. Formally, sepsis-associated encephalopathy (SAE) is defined as diffuse cerebral dysfunction that accompanies sepsis in the absence of direct CNS infection, structural abnormalities, or other types of encephalopathy.[31] Delirium occurs in 30% to 50% of patients with severe sepsis. In general, the severity of SAE parallels the severity of other manifestations of sepsis. Because there are no specific markers for SAE, the diagnosis relies on excluding primary CNS infections and other causes of encephalopathy. Proposed underlying mechanisms include microscopic brain injury, blood-brain barrier and cerebral microcirculation dysfunction, altered CNS metabolism, and impaired cholinergic neurotransmission. Patients who experience severe sepsis may have cognitive and functional defects that last for years.[32] Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) are other common complications in patients with prolonged ICU stay. Clinical features include difficulty in weaning from a ventilator, generalized wasting of the limbs, and diffuse weakness.[33] The diagnosis of CIP and CIM relies on clinical, electrophysiologic, and muscle biopsy investigations.[33] The septic inflammatory response is thought to play an important role in their pathogenesis.[34] CIP and CIM are associated with prolonged ICU stays and increased mortality.[33,34]

## Coagulopathy and Disseminated Intravascular Coagulation

Sepsis is frequently complicated by coagulopathy. Abnormalities range from subclinical coagulation disorders to prolongation of clotting times (most notably prothrombin time and partial thromboplastin time), low platelet counts, and elevated D-dimer levels. In patients with sepsis the reported prevalence of the most severe form of coagulopathy, disseminated intravascular coagulation (DIC), is 35%.[35] Commonly used screening assays for DIC include (1) a reduced or downward trend in the platelet count (usually <100,000/mm$^3$); (2) the presence of fibrin-related markers including fibrin degradation products, D-dimers, or soluble fibrin in plasma; (3) prolongation of PT or APTT (>1.2 times the upper limit of normal); and (4) low plasma levels of endogenous anticoagulants such as antithrombin and protein C.[36] Clinically, severe DIC can be characterized by widespread thrombosis in small and midsize vessels with simultaneous hemorrhage from various sites (Fig. 73.2). Earlier studies have shown that the development of DIC in patients with sepsis can double the risk of death.[35] At the present time, no specific therapy for DIC exists apart from treatment of the underlying disorder.[25] Studies on the potential benefit of the use of antithrombin (of which the plasma activity is decreased in patients with sepsis and DIC), soluble thrombomodulin, or heparin in patients with sepsis and DIC were negative or are still ongoing.[37–39] Recombinant activated protein C, which was originally recommended in the 2004 and 2008 Surviving Sepsis Campaign guidelines, was not shown to be effective in adult patients with septic shock in the PROWESS-SHOCK trial and was subsequently withdrawn from the market.[25,40]

## Gastrointestinal Tract and Hepatic Injury

Gastrointestinal tract injuries include disruption of the intact intestinal epithelium, which may lead to the translocation of inflammatory mediators; the occurrence of erosions of the gastric and duodenal mucosa that predispose to upper gastrointestinal bleeding; and the development of ileus, which may persist for several days after the resolution of septic shock (Fig. 73.2).[41,42] The gut microbiota of patients with sepsis are characterized by lower diversity, lower abundances of key commensal genera, and in some cases overgrowth by one bacterial genus, a state otherwise known as dysbiosis.[42] Preclinical work underscores the role of the microbiota in maintaining gut-barrier function and suggests that impaired communication across the gut-organ axes is associated with brain, lung, and kidney failure.[42]

Hepatic dysfunction includes cholestatic jaundice characterized by elevations in conjugated and unconjugated bilirubin, often seen in association with elevated levels of alkaline phosphatase and aminotransferase levels. Preexisting liver disease can aggravate these values. A "shock liver" is unusual, but if the duration of septic shock is prolonged, a massive rise in serum transaminases may follow hypoxic necrosis of centrilobular liver cells.

At the end, the function of every organ may be affected. Skin manifestations of sepsis include a cutaneous reaction at a local inoculation site (pustule, eschar), lesions that appear at sites of hematogenous seeding of the skin or underlying soft tissue (petechiae, pustules, ecthyma gangrenosum, cellulitis), diffuse eruptions caused by bloodborne toxins (e.g., toxic shock syndrome toxin), and hemorrhagic or necrotic lesions. Other common manifestations of sepsis include altered glycemic control, adrenal dysfunction, and sick euthyroid syndrome.[5]

# EPIDEMIOLOGY

In May 2017 the World Health Organization recognized sepsis as a global health priority by adopting the "Improving the Prevention, Diagnosis, and Management of Sepsis" resolution, underscoring the recognition of the substantial burden of sepsis at the individual, health system, and societal level.[43,44] Nonetheless, the true burden of sepsis remains unknown. There is substantial variability in the reported incidence and mortality of sepsis depending on the case definitions and diagnosis codes used to identify patients.[45,46]

## Incidence

The current global estimates of 31.5 million episodes of sepsis per year comes from a systematic review that extrapolated data from selected high-income countries (United States, Germany, Australia, Taiwan, Norway, Spain, and Sweden).[47] For these countries, the aggregate population incidence rate of sepsis hospitalization was 270 per 100,000 person-years with a large confidence interval.[47] Estimates for the incidence of sepsis in the United States range from 300 to more than 1000 cases per 100,000 person-years depending on method of database abstraction.[48] There are no population-level sepsis incidence estimates from lower-income countries, which limits the prediction of global cases and deaths.

In high-income countries, sepsis represents approximately 6% of adult hospitalizations and 10% to 37% of ICU admissions.[6,10,49] The overall incidence rate of hospitalization among emergency medical services encounters is greater for sepsis than for acute myocardial infarction or stroke.[50] A retrospective cohort study of 173,690 adult patients with sepsis admitted to hospitals across the United States in 2014 showed that 54.7% required ICU care during hospitalization, and 15.8% had septic shock.[49] Median ICU length of stay was 5 days (range, 2–6 days).[49] Median hospital length of stay was 10 days (range, 8–12 days).[49] The cost of treating sepsis in US hospitals was estimated to be $24 billion in 2013, making it the most expensive condition treated in US hospitals in that year.[44]

## Mortality

Sepsis is estimated to account for more than 5.3 million deaths around the world each year.[47] In the United States, sepsis contributes to one in every two to three in-hospital deaths[51] and represents the most frequent cause of death in noncoronary ICUs.[46] The case-fatality rate depends on the setting and severity of disease. US data from 2014 show that of all patients admitted for sepsis, 15.0% died in the hospital, and 6.2% were discharged to a hospice.[49] Data from Australia and New Zealand show hospital fatality rates for sepsis and septic shock of 14% and 22%, respectively.[52] The extent and number of organ failures are the strongest denominators of mortality in sepsis.[46,49] There are significant differences in reported acute mortality rates around the globe. As an example, a 1-day point prevalence study among 227 ICUs in Brazil identified 794 patients with sepsis, in whom mortality was observed in more than 50%.[53] In this setting, low availability of resources and adequacy of treatment were independently associated with mortality.[53]

## Trends in Time: Incidence and Mortality

In the past 2 decades, numerous studies have suggested that the incidence of sepsis is increasing over time, while mortality is decreasing.[52,54–57] An observational study from the period 2000–2012 using an ICU registry of more than 100,000 patients with severe sepsis in Australia

and New Zealand provided compelling evidence for gradually declining mortality rates from 35% in 2000 to 18.4% in 2012.[52] Each year absolute mortality decreased 1.3% throughout the study period. In the absence of comorbidities and older age, the case-fatality rate of severe sepsis or septic shock was less than 5% in 2012.[52] This key investigation, which used strict diagnostic criteria during the entire observation period, confirmed the declining mortality rates derived from large retrospective analyses.[46]

In contrast, one more recent study from the United States that used clinical data from electronic health record systems of greater than 170,000 sepsis cases from 2009 to 2014 could not demonstrate any change in the incidence of sepsis or mortality.[49] The shorter observation period in this study together with differences in coding and registration practices can partly explain the variation in the reported incidence and mortality of sepsis compared with previous studies.[5,46,49,52]

The steady decrease of sepsis-related mortality over time most likely reflects the overall improvement in ICU practice in the last 20 to 30 years. This is supported by the finding from the above-mentioned Australian and New Zealand ICU registry study that the observed annual reduction in mortality did not differ between patients with severe sepsis and other diagnoses.[52] Key factors that contribute to the overall rise in the worldwide incidence of sepsis include the aging of the population, the emergence of antimicrobial resistance, the growing use of immunosuppressive drugs and therapies, and the increased number of patients who are at risk for developing sepsis.

## Risk Factors

Any infection can trigger sepsis in a susceptible host. People at the highest risk of developing sepsis include infants and elderly adults as well as patients with chronic or serious illnesses such as diabetes and cancer and patients with an impaired immune system.[46] The most important risk factors for the development of sepsis are listed in Table 73.3.

Demographic risk factors for sepsis include age, male sex, and black race. Patients 65 years of age and older account for nearly 65% of sepsis cases.[58] In addition, advancing age is a major risk factor for poor outcome, which is explained in part by the presence of comorbidities and immunosenescence, which refers to the gradual age-related deterioration of the immune system.[58,59] Most studies report a lower risk for women to develop sepsis,[6,52,57,60] although it is uncertain whether this decreased risk is caused by a relative protection against the acquisition of an infection or the development of organ failure. Potential explanations for this sex difference include gender dissimilarities in behavior, social factors, chronic comorbidities, and the effect of sex hormones.

Sepsis occurs more frequently in blacks than in whites.[61] Moreover, reported sepsis-related ICU case-fatality rates are also higher in blacks than in whites.[61] These racial differences in sepsis are explained by both a higher infection rate and a higher risk of acute organ dysfunction in blacks relative to whites.[62] A study in the United States showed that mortality rates adjusted for patient characteristics were higher for patients in all minority groups compared with white patients.[63] In this cohort, racial disparities in sepsis mortality could be explained by differences in hospital characteristics for white, black, and Hispanic patients but not for Asian/Pacific Islanders.[63] The fact that racial differences are not entirely explained by differences in socioeconomic factors or access to care suggest that genetic variation plays a role.

Environmental factors and socioeconomic status also influence the incidence of sepsis. For example, poor socioeconomic status enhances the risk for bloodstream infection.[64] Data from the United States illustrate that communities with higher poverty rates as determined by ZIP codes have a higher incidence of sepsis.[61] In addition, infections causing sepsis show seasonal variation, with pneumonia occurring more frequently in the winter and genitourinary tract infections occurring more often in summer.[46,65] The outcome of sepsis also shows seasonal differences, with higher case-fatality rates in winter despite comparable disease severity.[65]

Chronic comorbidities are present in most patients with sepsis.[66] Certain diseases increase the risk for sepsis including chronic obstructive pulmonary disease, chronic renal or liver disease, diabetes, cancer, and HIV infection. Patients with cancer have a threefold to fourfold increased risk to be hospitalized for sepsis compared with the overall population.[67] This risk can even be 10 times higher in patients with certain hematologic malignancies. The risk of death in patients with cancer compared with patients without cancer who acquire sepsis is approximately 50% higher.[67,68] Similarly, the use of immunosuppressive therapies increases the likelihood of infection and thereby sepsis. Even so, there is evidence that chronic comorbidities have an impact on both infection risk and sepsis outcome. For example, patients with diabetes have an increased risk of developing infections and sepsis.[69] Most common among diabetic patients with sepsis are urinary tract and skin/soft tissue infections compared with nondiabetic patients.[66] The influence of diabetes on sepsis outcome is less clear, however. Some studies have shown an association with increased mortality, others found no effect, and still others found improved survival.[69]

**TABLE 73.3 Risk Factors for Sepsis**

| |
|---|
| **Demographic Factors** |
| Older age (>65 years old) |
| Male sex |
| Black race |
| Nutrition |
| Vaccination status |
| Genetic polymorphisms |
| **Environmental Factors** |
| Poor socioeconomic status |
| Seasonal variation and contacts |
| Disease outbreaks |
| Travel |
| **Comorbidities** |
| Diabetes |
| Chronic obstructive pulmonary disease |
| Cancer |
| Chronic renal disease |
| Chronic liver disease |
| Human immunodeficiency virus |
| Use of immunosuppressive agents |
| **Hospital Factors** |
| Duration of hospitalization |
| Antibiotic resistance |
| Catheters (e.g., urine catheters, intravenous lines) |
| Complications of surgery (wound infection, emergency vs. elective surgery) |

# MICROBIOLOGY

Virtually any microbe can trigger sepsis. Most cases today occur in patients with previous morbidities and are caused by opportunists from the patient's own microbiome.[4] It is important to determine the exact cause of sepsis, investigate microbial resistance both in a given patient and in the population, and have insights into how these microorganisms express their pathogenicity by means of their virulence.

## Main Causative Agents

A causative microorganism can be identified in up to two-thirds of patients admitted to an ICU for sepsis.[5,10,70] Blood cultures are positive in approximately one-third of patients.[5] An epidemiologic study of sepsis showed that during the period 1979–2000, the incidence of sepsis caused by gram-positive microorganisms steadily increased and overtook gram-negative microorganisms as the predominant causative microorganisms.[57] However, a large survey done in 2007 that aimed to investigate the patterns of infection in ICUs and included more than 14,000 patients from 75 countries showed that gram-negative bacteria accounted for 62% of positive isolates in the ICU, gram-positive bacteria accounted for 47%, and fungi accounted for 19% (Table 73.4).[70] An aggregate of recent representative studies on the main groups of causative agents in patients with sepsis is shown in Fig. 73.1C. Viral infections account for 1% to 7% of cases.[10,57,70] In a significant number of patients, two or more microorganisms are identified. The most common isolated gram-positive

bacterial pathogens are *Staphylococcus aureus, Streptococcus pneumoniae,* and *Enterococcus* spp.; the most common gram-negative pathogens are *Escherichia coli, Klebsiella* spp., *Pseudomonas* spp., and *Acinetobacter* spp.[10,57,70] In patients with multiple comorbidities or sepsis acquired in the ICU, an increase in the incidence of antimicrobial-resistant staphylococci, *Acinetobacter* spp., *Pseudomonas* spp., and *Candida* spp. is seen.[10,70]

Significant differences in these patterns are seen around the globe. Compared with Western Europe and North America, the prevalence of gram-negative infections in Eastern Europe, Central and South America, and Asia is significantly higher, mainly caused by higher numbers of *Klebsiella* spp., *Pseudomonas* spp., and *Acinetobacter* spp. (see Table 73.4).[70] Regional differences can show an even more diverse picture. For example, in northeast Thailand, melioidosis is among the most common causes of community-acquired sepsis, as illustrated by the finding that its causative agent, *Burkholderia pseudomallei,* is the cause of 20% of community-acquired bloodstream infections.[71] A meta-analysis that included greater than 15,000 patients admitted to hospitals across Africa for a bloodstream infection showed that *Salmonella enterica* was found in 29% of isolates, making it the most prevalent nonmalaria bloodstream infection.[72] Most of these isolates were nontyphoidal *Salmonella* spp.[72]

The increase of fungal infections over the last 2 decades could not be prevented by the introduction of new antifungals.[57,73] This is worrisome, as fungal sepsis is associated with a high mortality. *Candida* spp. are the most prominent of all the fungi that can cause sepsis. Reported ICU mortality is more than 1.5 times higher in patients with *Candida* bloodstream infections compared with bacterial bloodstream infections.[74] Important risk factors for candidemia include immunosuppressed or neutropenic state, prior intense antibiotic therapy, indwelling vascular catheters, prolonged ICU stay, and colonization in multiple sites.

## Virulence Factors of Bacteria Causing Sepsis

Invading microorganisms employ multiple mechanisms to escape antimicrobial defenses and overwhelm the host in the cascade of events that can lead to sepsis. First, they must adhere to and traverse the mucosal barrier, after which they must multiply and overcome antimicrobial host defense systems.[75] To do so, these pathogens have a formidable armory of virulence factors.

Bacteria can coordinate their gene expression according to the density of their local population in a process known as quorum sensing.[76,77] Through these signaling networks, individual bacteria communicate with each other by releasing and sensing small signal molecules. Activation of quorum sensing can help a bacterial population to remain inactive and not express virulence factors to avoid detection by the host or—at the other side of the spectrum—increase the expression of virulence factors and launch a coordinated overpowering attack on the host.[77] Quorum sensing activation can also lead to the production and maintenance of biofilms (slimy layers of bacteria that can protect themselves against the immune system and antibiotics), the production and release of proteins needed for tissue invasion, and the activation of toxins.

Pathogens can also injure the host by the expression of toxins that damage natural barriers such as the mucosa to enable further bacterial spread. Toxic shock syndrome is caused by the production of so-called superantigens during an invasive streptococcal infection or a localized staphylococcal infection. The bacterial production of these exotoxins cause nonspecific activation of T cells, resulting in the massive release of proinflammatory cytokines.[78] *S. aureus* secretes 24 different superantigens, and group A streptococcal strains are capable of producing 11 superantigens.[78] These bacterial toxins can be injected into the cytosol of host cells by specialized nanosyringes called type III secretion systems.

Lastly, microorganisms that cause sepsis express multiple pathogen-associated molecular patterns (PAMPs) that are able to inflict damage to host tissues through the generation of an excessive and damaging host inflammatory response.[73] Examples of bacterial PAMPs are lipopolysaccharide (LPS), peptidoglycan, lipopeptides (constituents of many pathogens), lipoteichoic acid (a cell wall component of gram-positive bacteria), flagellin (factor in the mobility of bacteria), and bacterial DNA. Systemic release of these PAMPs can activate innate immune cell

**TABLE 73.4 Distribution in Percentages of Identified Organisms in Culture-Positive Infected Patients Included in the EPIC II Study According to Geographic Region**

| ORGANISM | WESTERN EUROPE | EASTERN EUROPE | CENTRAL/SOUTH AMERICA | NORTH AMERICA | OCEANIA | AFRICA | ASIA |
|---|---|---|---|---|---|---|---|
| **Gram-Positive** | | | | | | | |
| *Staphylococcus aureus* | 20% | 22% | 19% | 27% | 28% | 30% | 16% |
| *Staphylococcus epidermidis* | 11% | 12% | 9% | 12% | 8% | 15% | 9% |
| *Streptococcus pneumoniae* | 5% | 5% | 3% | 4% | 3% | 6% | 2% |
| *Enterococcus* spp. | 13% | 15% | 4% | 10% | 9% | 0% | 6% |
| Other | 7% | 4% | 4% | 11% | 9% | 7% | 4% |
| **Gram-Negative** | | | | | | | |
| *Escherichia coli* | 17% | 15% | 14% | 14% | 13% | 11% | 17% |
| *Enterobacter* | 7% | 8% | 9% | 8% | 3% | 7% | 5% |
| *Klebsiella* spp. | 10% | 21% | 16% | 9% | 12% | 19% | 21% |
| *Pseudomonas* spp. | 17% | 29% | 26% | 13% | 15% | 15% | 30% |
| *Acinetobacter* spp. | 6% | 17% | 14% | 4% | 4% | 15% | 19% |
| Other | 18% | 15% | 17% | 11% | 21% | 20% | 15% |
| Anaerobes | 5% | 3% | 1% | 8% | 3% | 2% | 3% |
| **Fungi** | | | | | | | |
| *Candida* | 19% | 19% | 13% | 19% | 13% | 11% | 16% |
| *Aspergillus* | 2% | 1% | 1% | 3% | 2% | 0% | 1% |

Parasites accounted for 1% or fewer of all isolates in all regions. Percentages do not necessarily equal 100 because patients may have had more than one type of infection or microorganism.

*Data from Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units.* JAMA. *2009;302:2323–2329.*

signaling, coagulation, and complement activation and eventually can contribute to the induction of septic shock.

## Antimicrobial Resistance Trends in the Setting of Sepsis

The widespread emergence of antibiotic resistance genes among bacteria, viruses, fungi, and even protozoa has led to enormous challenges in the treatment of sepsis. Not only will empirical antibiotic treatment be less efficient, the same holds true for the chosen definitive antibiotic treatment. Equally worrisome is the finding that antibiotic-resistant bacteria can increase the total burden of sepsis.[79] For example, a Dutch study that analyzed trends in nosocomial bloodstream infections from 1998 to 2007 found an increase in nosocomial bloodstream infections due to antibiotic-resistant bacteria that occurred in addition to—instead of in replacement of—infections caused by antibiotic-susceptible bacteria.[79] As a result, the total disease burden increases.[79]

This clinical implication of the increasing antimicrobial resistance rates is best illustrated by the results from a recent surveillance study conducted in Malawi between 1998 and 2016 in which 29,183 pathogens derived from 194,539 blood cultures were analyzed.[80] In this 18-year time period, extended-spectrum β-lactamase resistance increased from 1% to 30% in *E. coli* and from 12% to 90% in *Klebsiella* spp. Resistance to ciprofloxacin rose from 3% to 31% in *E. coli* and from 2% to 70% in *Klebsiella* spp.[80] By contrast, more than 92% of common gram-positive pathogens remained susceptible to either penicillin or chloramphenicol. Methicillin-resistant *Staphylococcus aureus* (MRSA) represented 18% of *S. aureus* isolates (an increase from 8%). A similar study from India analyzed 18,695 bacterial pathogens from 35,268 blood cultures derived from a large private laboratory network in the period 2008–2014.[81] Carbapenem resistance increased in both *E. coli* (8%–12%) and *Klebsiella pneumoniae* (42%–57%). Carbapenem resistance was 70% for *Acinetobacter* spp. and 49% for *Pseudomonas aeruginosa*.[81] MRSA rates were relatively stable at 44%. These results highlight the growing challenge of bloodstream infections that are effectively impossible to treat in resource-limited settings.

Regional differences in the prevalence of antibiotic resistance are significant. In the Netherlands, for example, the proportion of extended-spectrum cephalosporin-resistant *E. coli* and *K. pneumoniae* isolates in blood samples collected from 2008 to 2012 increased from 4% to 7% and from 6% to 10%, respectively.[82] MRSA prevalence in blood culture isolates remains low (<1%).[82]

Increasing resistance has been associated with higher mortality rates. In ICU patients, MRSA infection was reported to be independently associated with an almost 50% higher likelihood of hospital death compared with methicillin-resistant *S. aureus* infection.[83] A retrospective cohort study from the United States also reported increased hospital stays and increased mortality when the initial antibiotic therapy was inappropriate in patients with gram-negative sepsis.[84] However, other studies were unable to demonstrate a link between antibiotic resistance and outcome. As an example, a study from Western Europe did not find an association between inadequate treatment and mortality of *S. aureus* bacteremia.[85] Moreover, a retrospective analysis of the EPIC II study demonstrated that being hospitalized in an ICU in a region with high levels of antimicrobial resistance (Greece, Israel, Italy, Malta, Portugal, Spain, and Turkey) was not associated with a worse outcome compared with countries with low resistance levels (Denmark, Finland, the Netherlands, Norway, and Sweden).[86]

# PATHOGENESIS

Sepsis is the result of a dysregulated host response that at the very start of the infection was initiated to eliminate invading pathogens.[87] The innate immune system consists of a variety of cell types that are able to "sense" pathogens by virtue of their capacity to recognize PAMPs through a range of pattern-recognition receptors (PRRs).[88] Cells involved in the early response to pathogens include not only leukocytes but also parenchymal cells such as epithelial and endothelial cells and especially populate parts of the body from which they constantly can sample their surroundings. In most cases the first encounter between pathogens and host innate immune cells results in a balanced reaction that entails inflammatory, antiinflammatory, and repair responses, with elimination of microorganisms and return to normal homeostasis. In sepsis the pathogen has succeeded in evading protective immunity, while continuing to stimulate host cells, resulting in an unbalanced and harmful immune response and a failure to return to homeostasis. Knowledge of the course of immune dysregulation during infection is almost exclusively derived from animal studies, which are limited by lack of sufficient relevance for sepsis in humans. Most investigations on the host response in patients during sepsis have been done on admission to the hospital, thereby not affording information about the time course and character of the immune response before clinical recognition of severe disease and the diagnosis of sepsis.

Patients with sepsis show signs of both hyperinflammation and immunosuppression, two seemingly opposite reactions that involve partially different cell types and organ systems (Fig. 73.3). Likely, this disturbed immune response is not only the result of persistent stimulation by pathogens and their virulence factors but also the release of damage-associated molecular patterns (DAMPs), or alarmins, which are molecules derived from host cells released into the extracellular environment on injury. DAMPs can trigger many of the PRRs that also sense PAMPs, giving rise to a vicious cycle with sustained immune activation and dysfunction.[89] Patients who fail to recover after early therapeutic measures and continue to require intensive care often develop a chronic critical illness that has been named "persistent inflammation, immunosuppression, and catabolism syndrome."[90] The notion that the course of sepsis as seen by clinicians in the hospital nowadays is more chronic than acute is important for understanding the pathophysiologic mechanisms at play. In patients with sepsis with a prolonged clinical course, the disturbances in the host response involve different leukocyte subsets and parenchymal cells, encompassing key functions at both intercellular and intracellular levels, such as barrier function of epithelium and endothelium and cellular metabolism and mitochondrial dysfunction. respectively. In the next section, we describe the most important features of the septic host response.

## Hyperinflammation

### Instigation of Inflammation

PRRs are germline-encoded sensors that are especially expressed by innate immune cells such as macrophages, monocytes, neutrophils, dendritic cells, and epithelial cells. PRRs are grouped according to their localization, ligand specificity, and function. Prominent PRR families include Toll-like receptors (TLRs), C-type lectin receptors, retinoic acid–inducible gene-like receptors, and nucleotide-binding oligomerization domain-like receptors. Nucleotide-binding oligomerization domain-like receptors include inflammasomes, which are cytosolic multimolecular complexes that sense intracellular microbial danger signals and metabolic perturbations. Inflammasome activation results in activation of caspase-1 and the release of proinflammatory cytokines interleukin-1β (IL-1β) and IL-18 as well as cell death. Recognition of pathogens by PRRs is an important defense mechanism against invading pathogens, inducing inflammatory gene transcription and initiation of innate immunity. In sepsis the inflammatory response is disproportional due to concurrent recognition of multiple PAMPs and DAMPs resulting in activation of multiple PRRs and subsequent triggering of downstream signaling cascades. Activation of nuclear factor kappa B is key for induction of the inflammatory response, resulting in the transcription of multiple early activation genes including those encoding cytokines. Cytokines are small proteins (5–20 kDa) that regulate immune responses locally and systemically. Proinflammatory cytokines implicated in sepsis pathogenesis include tumor necrosis factor (TNF), IL-1β, IL-12, and IL-18. These cytokines are released in the circulation in animals challenged with high doses of bacteria or their products, and in these models their inhibition or elimination protects against organ damage and mortality.[91]

Examples of DAMPs involved in proinflammatory responses during sepsis include high mobility group box 1 (HMGB1) and S100A8/9 (calprotectin). HMGB1 is a nuclear protein that is released passively during cell injury or secreted actively on inflammatory stimuli.[92] Depending on specific posttranslational redox modifications, HMGB1 can act as a cytokine via receptors such as Toll-like receptor 4 or as a chemotactic factor. HMGB1 levels are elevated during sepsis, and postponed treatment (24 hours after the challenge) of mice with

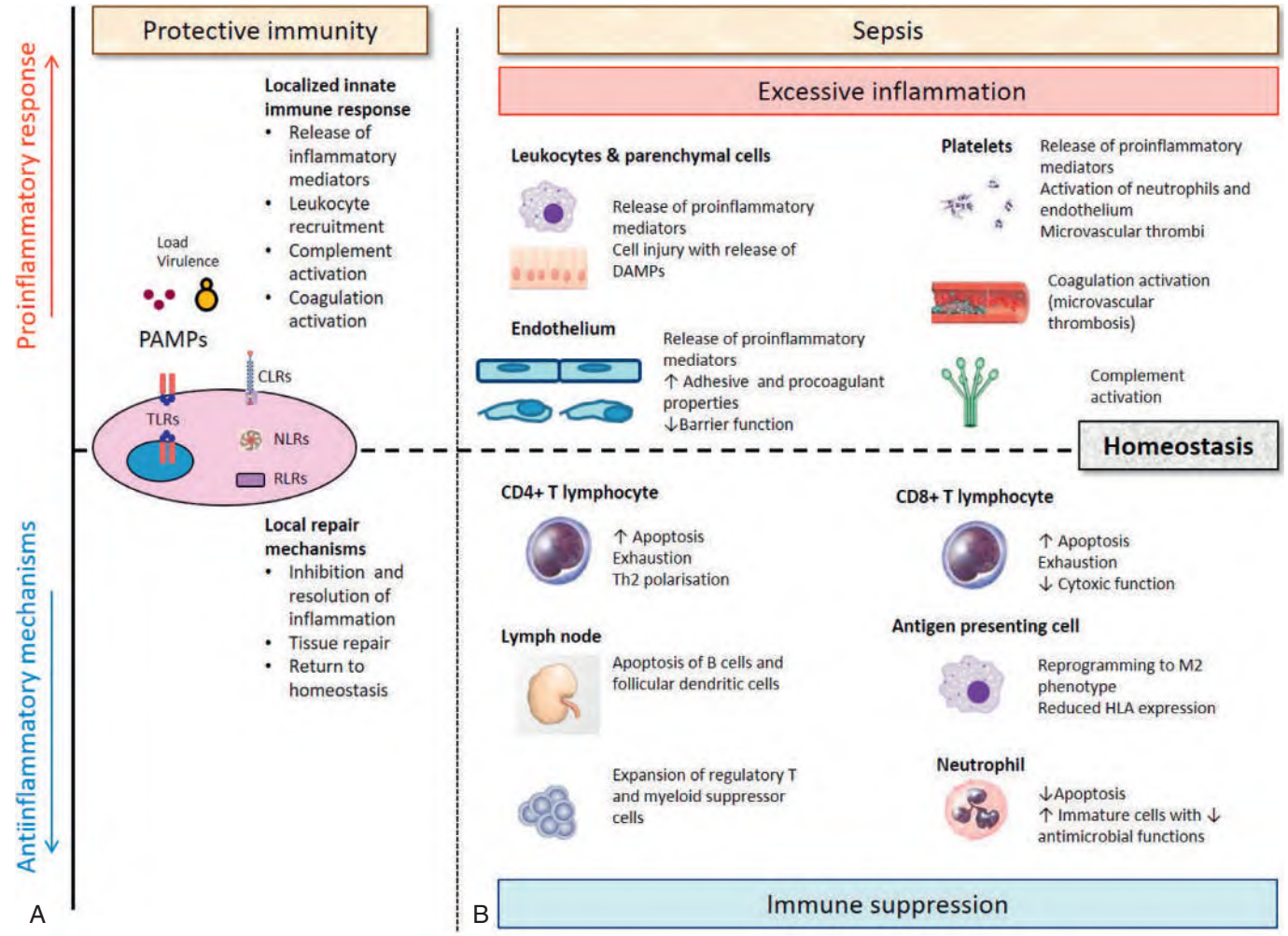


**FIG. 73.3 Host response to infection and during sepsis.** (A) During a protective immune response, innate immune cells recognize invading pathogens by sensing pathogen-associated molecular patterns *(PAMPs)* through a collection of cell surface and intracellular pattern recognition receptors including Toll-like receptors *(TLRs)*, nucleotide-binding oligomerization domain-like receptors *(NLRs)* (which include inflammasomes), retinoic acid–inducible gene-like receptors *(RLRs)*, and C-type lectin receptors *(CLRs)*. A balanced response entails a variety of proinflammatory reactions such as release of cytokines, influx of phagocytes, and local activation of the complement and coagulation systems, followed by a return to homeostasis by a set of compensatory mechanisms aimed at tempering the initial inflammation and tissue repair. (B) If the pathogen succeeds in multiplying, the immune response becomes unbalanced and harmful to the host. The host response during sepsis is characterized by concurrent hyperinflammation *(top)* and immunosuppression *(bottom)*. See text for description of hyperinflammatory and immunosuppressive responses in sepsis. *DAMPs,* Damage-associated molecular patterns.

antibodies to HMGB1 diminished lethality of experimental abdominal sepsis.[92] S100A8/9 is a heterodimeric protein especially expressed in neutrophils.[91] S100A8/9 can stimulate systemic inflammation through activation of Toll-like receptor 4. Patients with sepsis display elevated circulating levels of S100A8/9, and mice deficient for this protein are protected from endotoxin shock and *E. coli*–induced abdominal sepsis.

This harmful hyperinflammatory response, initiated by proinflammatory cytokines and referred to as the "cytokine storm," has long been held responsible for injury and death associated with sepsis, resulting in a large number of clinical trials with antibodies or inhibitors of TNF and IL-1β or other antiinflammatory strategies.[93,94] At the present time, it is appreciated that systemic challenge models in animals have limited relevance for human sepsis, although early mortality in sepsis, generally due to cardiovascular collapse and multiple organ dysfunction, likely is mainly driven by hyperinflammation. Besides cytokines, several other mediator systems have received attention with regard to their potential involvement in sepsis pathogenesis, most notably the complement system, the coagulation system, and the vascular endothelium.

## Activation of the Complement System

The complement system comprises a group of small proteins mostly synthesized by the liver that typically circulate as inactive precursors. The complement system is triggered on exposure to PAMPs and DAMPs, mediated by an interaction with complement components C1q, mannose-binding lectin, and ficolins.[95] Although according to traditional concepts the complement system can be initiated by three distinct pathways (classical, lectin, and alternative), it should be noted that many intracellular proteases (e.g., elastase, neutral proteases) and extracellular proteases (e.g., thrombin, several activated clotting factors) can also generate C3a and C5a, exemplifying the complex nature of inflammation. On complement activation, small activation fragments known as anaphylatoxins are generated, particularly C3a and C5a, which exert strong proinflammatory effects on leukocytes, endothelial cells, and platelets.[95] The main activities of complement activation in protective immunity are opsonization of pathogens by cleavage products of C3 (C3b and iC3b) and C4 (C4b), attraction and activation of leukocytes by C3a and C5a, direct elimination of pathogens through phagocytosis via complement receptors or cell lysis mediated by the so-called membrane attack complex (C5b through C9), and regulation of adaptive immune responses by stimulation of B cells and T cells. Uncontrolled activation of complement can cause collateral damage to surrounding tissues and multiple organ failure at the systemic level. Inhibition of C5a improved the outcome in several animal sepsis models including *E. coli* sepsis in baboons and polymicrobial abdominal sepsis in rats.[96] The C3 convertase inhibitor compstatin

not only suppressed complement activation during *E. coli* sepsis in baboons but also attenuated other inflammatory responses, coagulation activation, and multiple organ failure.[97]

## Activation of Coagulation and Vascular Endothelium

Hemostasis, the termination of bleeding, is a continuous process that under physiologic conditions favors an anticoagulant state. In the early stages of host-pathogen interaction, activation of coagulation elicits immune defense mechanisms including the release of antimicrobial peptides, recruitment and activation of phagocytizing cells, and induction of innate immune responses through activation of protease-activated receptors (PARs).[98] Accordingly, inhibitors of elements of the coagulation system were shown to impair microbial clearance and increase mortality during a variety of experimental infections.[98] The term *immunothrombosis* has recently been proposed to reflect the codependency of the coagulation and innate immune systems.[99]

Sepsis is associated with a strong activation of coagulation, which, together with an impairment of endogenous anticoagulant mechanisms, results in a net procoagulant state and a tendency toward microvascular thrombosis (Fig. 73.4).[100] The most severe manifestation of coagulopathy in sepsis is DIC, which clinically can be associated with both microvascular thrombosis and hemorrhage, owing to widespread fibrin depositions and consumption of clotting factors and platelets, respectively. Tissue factor drives coagulation activation after infection via the so-called extrinsic pathway, which involves activation of factor VII and subsequent formation of factor Xa, thrombin, and fibrin. Perivascular cells such as fibroblasts, pericytes, and epithelial cells express tissue factor constitutively, thereby safeguarding hemostasis and vessel integrity. In sepsis, injury of vessels exposes tissue factor to blood coagulation factors, inducing clotting. Cells in close contact with blood such as endothelial cells and macrophages normally do not express large quantities of tissue factor but can be triggered to do so by PAMPs and proinflammatory cytokines. Tissue factor also can be present in microparticles derived from leukocytes, endothelial cells, vascular smooth muscle cells, and platelets. The interaction between coagulation and inflammation is augmented by virtue of the capacity of tissue factor and clotting factors VIIa, Xa, thrombin, and fibrin to induce proinflammatory signaling. The G protein–coupled PAR family plays a major role herein. Inhibition of the tissue factor–factor VIIa pathway in humans and nonhuman primates strongly attenuated coagulation activation after infusion of endotoxin or bacteria, whereas in a model of otherwise lethal sepsis in baboons, tissue factor inhibition in addition prevented multiple organ failure and mortality.[100]

In addition to the tissue factor–mediated extrinsic route, coagulation can be activated via the so-called intrinsic pathway mediated by the contact system.[101] The contact system is initiated by factor XII, which can activate coagulation via factor XI and thrombin and stimulate inflammation via the kallikrein-kinin system. Inhibition of factor XII limits thrombosis in experimental settings without causing hemorrhage. This has raised interest in factor XII as a therapeutic target, although clinical evaluation in sepsis has not been reported.

The tendency toward thrombosis during sepsis is increased by concomitantly compromised activity of three main anticoagulant pathways: antithrombin, tissue factor pathway inhibitor (TFPI), and protein C system.[100] The anticoagulant properties of antithrombin (the main inhibitor of thrombin and factor Xa) and TFPI (the main inhibitor of the tissue factor–factor VIIa complex) are supported

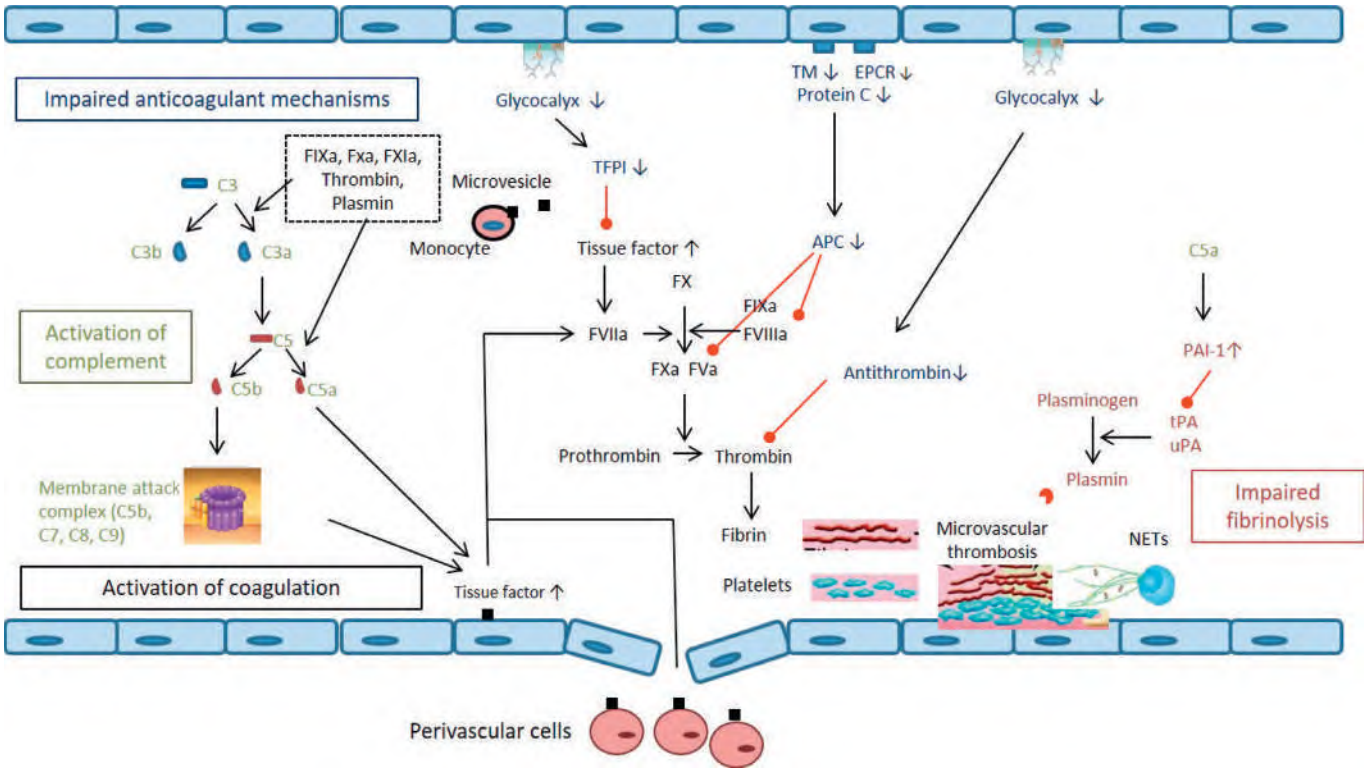


**FIG. 73.4 Activation of the coagulation and complement systems during sepsis.** Sepsis results in a procoagulant state via at least three mechanisms: tissue factor–mediated thrombin generation *(black font)*, dysfunctional endogenous anticoagulant mechanisms *(green font)*, and impaired fibrin removal due to suppression of the fibrinolytic system by plasminogen activator inhibitor 1 *(PAI-1) (red font)*. Besides in cell-associated form, tissue factor can reside in microparticles. The anticoagulant properties of antithrombin and tissue factor pathway inhibitor *(TFPI)* are supported by the glycocalyx, a glycoprotein-polysaccharide layer covering the endothelium, the continuity of which is disturbed in sepsis. Activated protein C *(APC)* is generated from protein C at the surface of resting endothelial cells, a process mediated by binding of thrombin to thrombomodulin *(TM)* and amplified by the endothelial protein C receptor *(EPCR)*. Multiple interactions exist between the coagulation and complement systems, and coagulation proteases can activate the complement system and vice versa. Vascular inflammation and coagulation are augmented by the release of neutrophil extracellular traps *(NETs)* by neutrophils. *tPA,* Tissue-type plasminogen activator; *uPA,* urokinase-type plasminogen activator.

by the glycocalyx, a glycoprotein-polysaccharide layer covering the endothelium. Sepsis is associated with a disruption of the continuity of the endothelial glycocalyx, which impairs the function of antithrombin and TFPI and increases vascular permeability. Activated protein C (APC) is generated from protein C at the surface of endothelial cells by a process that is accelerated by the endothelial protein C receptor (EPCR) and inhibits coagulation by inactivating the coagulation cofactors Va and VIIIa. Many investigations have supported the anticoagulant potency of the protein C system in vivo, showing that weakening its function converts nonlethal bacteremia into lethal sepsis with DIC.[102] APC also has antiinflammatory, antiapoptotic, and vasculoprotective properties,[102] and the anticoagulant effects of APC are not essential for protection against lethality in experimental sepsis as demonstrated in studies using nonanticoagulant APC mutants with selective cytoprotective properties.[103] Considering the impaired activity of antithrombin, TFPI, and the protein C system, there is a clear rationale to supplement these anticoagulant pathways in sepsis. However, clinical trials in patients with sepsis in whom antithrombin, recombinant TFPI, or recombinant APC was infused did not show a consistent benefit.[37,40,104,105]

## Interaction Between Complement and Coagulation Systems

Evidence has accumulated that coagulation proteases can activate the complement system and vice versa (see Fig. 73.4).[106] Components of the coagulation and fibrinolytic systems can activate C3 and C5. Specifically, clotting factors IXa, Xa, and XIa as well as thrombin and the central fibrinolytic protease plasmin can convert C3 and C5 into C3a and C5a, respectively. Proteases of the coagulation cascade can also activate the complement system upstream of C3 and C5; for example, C1 can be activated by factor XIIa, resulting in instigation of the classical complement pathway. Ficolin and mannose-binding lectin can interact with fibrinogen/fibrin, which can modulate the activation of C3 and C4 and complement deposition on the surface of microorganisms. Chondroitin sulfate expressed at the surface of platelets can contribute to binding of C1q and regulators of the complement system C1 inhibitor, C4b-binding protein, and factor H. In a reciprocal way, complement products can activate the coagulation system.[106] C5a and the membrane attack complex can stimulate expression of tissue factor in endothelial cells. Complement products can also cause structural changes in the endothelium that can modify the clotting tendency of blood. For example, C5a can facilitate the release of the endothelial surface proteoglycan heparan sulfate, which can result in a procoagulant shift due to a reduced function of antithrombin.

## Endothelial Dysfunction

In health the vascular endothelium affords a semipermeable barrier that regulates the movement of fluids, solutes, gases, macromolecules, and blood cells. Normal barrier function of the endothelium is preserved by the cell cytoskeleton, the glycocalyx, intercellular adhesion molecules, and other supportive proteins.[107] Connections between cells that comprise the vascular lining are upheld by adherens junctions such as vascular endothelial–cadherin and tight junctions (zona occludens), predominantly consisting of occludins and claudins.[108] On infection, leukocytes and platelets adhere to the vascular endothelium and migrate to locations of proliferating microorganisms. In sepsis, exaggerated inflammation enhances these processes, which can result in barrier incompetency. In fact, sepsis is almost invariably associated with a disruption of the integrity of the endothelial barrier, which can expose underlying collagen fibers and tissue factor to circulating blood, eliciting activation of platelets and the coagulation system. Moreover, sepsis is associated with breakdown of the glycocalyx, further damaging barrier function and in addition impeding anticoagulant mechanisms.[107]

The mechanisms underlying vascular leak have been the subject of many investigations. Activation of PARs has been implicated in alterations in vascular barrier function.[109] PARs can be activated by various serine proteases, a process that involves the cleavage of the N-terminal part of the receptor, which exposes a new previously cryptic sequence. The exposed sequence remains tethered to the receptor, acting as a receptor-activating ligand. Four PARs (PAR1 through PAR4) have been identified, which can either disrupt or protect endothelial barrier function, depending on which intracellular signaling pathway is activated. Each PAR can be activated by several proteases. Thrombin is the best-characterized PAR activator, capable of cleaving PAR1, PAR3, and PAR4; these receptors can also be activated by plasmin, trypsin, or cathepsin G. PAR1 signaling on endothelial cells is controlled by the activating protease and heterodimerization with PAR2 or PAR3. Activation of endothelial cell PAR1 by thrombin can contribute to endothelial dysfunction by inducing cytoskeletal derangements, inducing endothelial cell contraction and rounding and thereby destabilizing cell-to-cell contacts and increasing vascular permeability. Notably, thrombin linked to PAR1 at relatively low doses can protect barrier function by transactivating PAR2 into a PAR1-PAR2 heterodimer.[110] PAR1 can also be activated by APC, which results in antiinflammatory, antiapoptotic, and vasculoprotective signals in endothelial cells when APC remains attached to EPCR, and several studies have shown that the APC-EPCR-PAR1 pathway plays an important cytoprotective role in sepsis and endotoxemia.[102] APC potently inhibits thrombin-induced vascular hyperpermeability by a mechanism dependent on transactivation of the sphingosine 1 phosphate (S1P) receptor 1 (S1P1), whereas thrombin induces vascular hyperpermeability dependent on another S1P receptor, S1P3.[111] Activation of endothelial cell S1P1 preserves vascular integrity through cytoskeletal reorganization, adherens junction, and tight junction assembly. Another mechanism implicated in maintaining vascular integrity is angiopoietin 1–induced activation of the endothelial Tie2 receptor.[107] Angiopoietin 2 is a functional antagonist of angiopoietin 1 that can disrupt endothelial barrier function. Matrix metalloproteinase (MMP) 1 and MMP13 can activate PAR1 on cells through noncanonical sites.[109] MMP1 has been detected at high levels in the circulation of patients with sepsis. Cleavage of PAR1 by MMP1 results in barrier disruption, and MMP1-induced PAR1 signaling is associated with poor outcomes in experimental models of septic shock.[112]

## Neutrophil Extracellular Traps

Vascular inflammation and coagulation are amplified by so-called neutrophil extracellular traps (NETs) released by neutrophils.[113] NETs are composed of histones, DNA, and neutrophil-derived proteases and can contribute to protective immunity by capturing and killing microorganisms. However, NETs have also been implicated in responses that are detrimental to the host, including collateral tissue damage and thrombosis. NETs can facilitate coagulation and thrombus formation by serving as a scaffold for platelets and proteins such as fibrinogen, fibronectin, and von Willebrand factor and by activating the intrinsic pathway of the coagulation system, thereby stabilizing blood clots. Accordingly, disassembling NETs reduced thrombosis in animal models. Bystander injury and thrombus formation caused by NETs are at least in part mediated by their histone components, which can exert cytotoxic effects, induce thrombin generation, and activate platelets.

## Platelets

Platelets are small circulating anucleate cells that are of vital importance in hemostasis. More recently it has become clear that platelets also play an important role in inflammation and immunity (Fig. 73.5).[114,115] Sepsis is associated with activation of platelets through a variety of mechanisms.[114] Thrombin, generated as a consequence of coagulation activation, is an important platelet activator via PAR1, PAR3, and PAR4. In addition, von Willebrand factor can activate platelets by binding platelet glycoprotein Ibα. During normal hemostasis, von Willebrand factor stabilizes the adhesion of platelets at sites of vascular injury, a process regulated by ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif 13), which cleaves large von Willebrand factor multimers. Sepsis is accompanied by a relative deficiency of ADAMTS13, resulting in increased concentrations of ultra-large von Willebrand factor multimers, which facilitate platelet adhesion to injured endothelium. Additional platelet activation during sepsis can be induced by subendothelial collagen (via platelet glycoprotein VI), complement products (via the C1q receptor), bacteria, and DAMPs (e.g., histones).[114] On

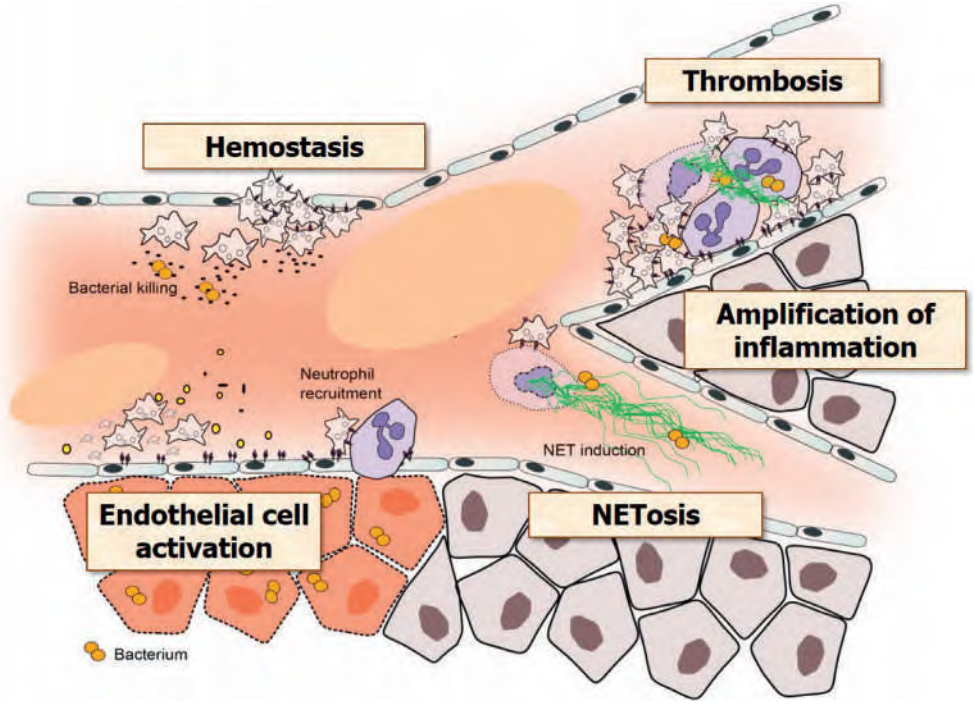


**FIG. 73.5 Role of platelets in sepsis.** Activated platelets release several regulatory proteins including cytokines, chemokines, coagulation mediators, and antimicrobial peptides. Platelets play an important role in hemostasis and maintenance of the endothelial barrier, and platelets bound to endothelium support adhesion of neutrophils following selectin-mediated tethering and rolling, thereby guiding neutrophils to transmigrate. Platelets can amplify inflammation by interacting with leukocytes and by facilitating the formation of neutrophil extracellular traps. Platelets play an additional role in immunothrombosis, in which platelets and products of the coagulation pathway regulate the effector function of innate immune cells and recruit additional cells. *NET,* Neutrophil extracellular trap. *(Illustration by Sacha de Stoppelaar.)*

activation, platelets release molecules such as thromboxane $A_2$ and adenosine diphosphate, which further augment platelet activation. Platelet activation triggers platelet-platelet aggregation, platelet-leukocyte complex formation, and the release of granular content, which includes coagulation factors, chemokines, adhesive proteins, mitogenic factors, and regulators of angiogenesis.

Low platelet counts are independently associated with mortality in patients with sepsis,[116] and thrombocytopenic mice demonstrated an impaired host defense during pneumonia-derived sepsis.[117] Platelets likely play a protective role in the initial stages of an infection by virtue of their capacity to release bactericidal products, to activate leukocytes, and to induce the formation of NETs. However, during sepsis, excessive platelet activation contributes to the development of complications such as DIC, acute lung injury, and AKI. Platelets have been implicated in the pathogenesis of organ failure in sepsis by contributing to leukocyte recruitment and hyperinflammation, by driving the development of vasoocclusive thrombi in the microvasculature, and by direct cell toxic effects of platelets and platelet-derived microparticles.[114] Several antiplatelet agents improved survival in sepsis models, and prior use of the platelet inhibitor acetylsalicylic acid was associated with reduced mortality of sepsis in a recent meta-analysis.[118] The potential therapeutic effect of platelet inhibitors in human sepsis has not been investigated in randomized trials.

## Antiinflammatory Mechanisms and Immunosuppression

A balanced immune response to an infection entails early induction of antiinflammatory reactions meant to limit excessive and potential harmful activity of inflammation as well as resolution of inflammation and instigation of tissue repair. In sepsis, sustained antiinflammatory reactions can result in immunosuppression involving different cell types and caused by a variety of pathologic mechanisms. Patients admitted to the ICU with sepsis show signs of concurrent hyperinflammation and immunosuppression; a clear separation in time between SIRS and so-called compensatory antiinflammatory response syndrome, a concept for a two-staged host response to sepsis proposed in the late 1990s,[119] does not seem to exist. Rather, as discussed earlier, patients with sepsis who continue to require intensive care experience a condition referred to as persistent inflammation, immunosuppression, and catabolism syndrome.[87,90] Although the inflammatory response during early sepsis likely is mainly driven by PAMPs and DAMPs, the etiology of persistent inflammation is relatively unknown. Sustained release of DAMPs probably plays a role.

Clinically the consequences of sustained immunosuppression may be the occurrence of secondary infections often caused by weakly virulent organisms such as *Stenotrophomonas, Acinetobacter, Enterococcus,* and *Candida* and by reactivation of latent viruses such as cytomegalovirus and herpes simplex virus.[120] We discuss the main features of immunosuppression and their underlying mechanisms in sepsis further on.

### Suppression of Innate Immune Cell Functions

Several cell types involved in innate immunity show strong phenotypic and functional changes in patients with sepsis.[87,120] Although neutrophils clearly contribute to sepsis-induced inflammation, at least in part through the release of NETs, they also demonstrate dysfunctional features that impair their antimicrobial capacities. Key findings in sepsis are delayed apoptosis of neutrophils, defects in neutrophil chemotaxis and recruitment to sites of infection, and an impaired capacity of neutrophils to produce essential effector molecules such as reactive oxygen species and cytokines. In addition, antigen-presenting cells such as monocytes, macrophages, and dendritic cells display a reduced expression of HLA-DR and a diminished capacity to release proinflammatory cytokines on stimulation. Although this latter phenomenon has been referred to as "immunoparalysis" or "endotoxin tolerance," these terms are not correct, as these cells seem reprogrammed rather than generally suppressed. Indeed, certain functions remain intact or even are enhanced, such as the release of antiinflammatory mediators (e.g., IL-10). Alterations in the function of antigen-presenting cells during sepsis are at least in part caused by epigenetic changes. Regulation of gene transcription occurs

through organization of gene loci on chromatin into transcriptionally active or silent states.[121] Histones "wrap" DNA in a chromatin structure, and specific histone modifications can wind or unwind chromatin to make it inaccessible (heterochromatin) or accessible (euchromatin) for transcription, respectively. Histone acetylation of lysines typically promotes transcription, whereas methylation can support either active euchromatin or silent heterochromatin formation, depending on the lysine that is methylated.[121] Immune cell function can also be regulated at the posttranscriptional level by noncoding RNAs including microRNAs that can reduce protein expression through targeted degradation of specific messenger RNAs.

The term *trained immunity* has been introduced to reflect the fact that the function of innate immune cells can be influenced by previous encounters with pathogens or their products.[122] Previous exposure to microbial products can render macrophages less responsive to a second stimulation (endotoxin tolerance) but can also prime them for stronger second responses. Both phenotypes are mediated by specific alterations in cellular metabolism and epigenetic reprogramming. Manipulation of trained immunity may reverse some of the effects of immunosuppression in sepsis, as suggested by a more recent study reporting that induction of trained immunity by β-glucan can restore the epigenetic, transcriptional, and functional program of monocytes during endotoxin-induced tolerance.[123] Alterations in cellular metabolism have been linked to reprogramming of antigen-presenting cells in sepsis.[124] A shift from oxidative phosphorylation to glycolysis (the so-called Warburg effect) leads to succinate accumulation, which stabilizes hypoxia-inducible factor 1α to increase IL-1β transcription. Whereas LPS induces a classic Warburg effect, whole microorganisms can trigger an increase in both glycolysis and oxidative phosphorylation in monocytes.[125] Likewise, the defects of monocyte metabolism in patients with sepsis with immunosuppression not only involve glycolysis but also entail a broad inhibition of metabolic processes including glycolysis, fatty acid oxidation, and oxidative phosphorylation.[126] Hence, although a disbalance in cellular metabolism is involved in immunosuppression in sepsis, the mechanisms seem more complex than a simple shift between oxidative phosphorylation and glycolysis.

Inhibition of inflammation can occur through the so-called neuroinflammatory reflex, which involves peripheral sensory input transmitted through the afferent vagus nerve to the brainstem, with subsequent stimulation of the efferent vagus nerve and activation of the splenic nerve in the celiac plexus. This results in norepinephrine release in the spleen and acetylcholine secretion by a subset of $CD4^+$ T cells.[127] Acetylcholine limits proinflammatory cytokine release by macrophages. In experimental endotoxemia, vagotomy increases proinflammatory cytokine release and lethality, whereas stimulation of the efferent vagus nerve attenuates systemic inflammation.[127] Whether the neuroinflammatory reflex contributes to immunosuppression in sepsis remains to be established.

### Suppression of Adaptive Immune Cell Functions

Sepsis is associated with a profound reduction in the number of $CD4^+$ and $CD8^+$ T cells, B cells, and dendritic cells caused by apoptosis (programmed cell death).[120,128] Postmortem studies of patients who died of sepsis in addition demonstrated signs of T-cell exhaustion; T cells obtained from the spleen shortly after death produced lower amounts of interferon-γ (IFN-γ) and TNF than splenic T cells harvested from patients who had died of a noninfectious cause.[128] Inhibition of lymphocyte apoptosis improved the outcome of sepsis in several experimental models, suggesting a causal role for the loss of lymphocytes in sepsis lethality. Checkpoint molecules may be an appealing target for therapeutic intervention in patients with immunosuppression. Checkpoint molecules are normally expressed at low levels on various cell types and can be upregulated in a variety of circumstances. Examples important for sepsis include programmed cell death 1 (PD-1) and its ligand (PD-L1), which are found mainly on surfaces of T cells and antigen-presenting cells, respectively. An interaction between PD-1 and PD-L1 results in broad immunosuppressive effects. $CD4^+$ T cells of patients with sepsis displayed enhanced expression of PD-1, whereas macrophages and endothelial cells displayed enhanced expression of PD-L1, which may impair T-cell function at the local tissue level.[128] Inhibition of the PD-1–PD-L1 pathway improved survival in experimental sepsis, pointing at an unfavorable causal role for T-cell exhaustion and identifying the PD-1–PD-L1 axis as a potential therapeutic target in sepsis.[129] Another mechanism that may contribute to reduced T-cell function is an increase in the fraction of regulatory T cells (Tregs) and expansion of myeloid-derived suppressor cells, which are immature myeloid cells that can impede immune responses, particularly T-cell functions. Tregs can also inhibit monocyte and neutrophil functions, and blocking of Tregs improved immune function and increased microbial killing in experimental sepsis.[120]

## DIAGNOSIS

There is no gold standard for diagnosing sepsis. A clinical pattern based on the patient's history and physical examination combined with laboratory, radiology, and microbiology testing is typically required for the diagnosis. Once the diagnosis of sepsis is made, it is critical to determine the cause of the underlying infection and the extent of organ dysfunction. We present a set of tools consisting of some basic laboratory, microbiology, and imaging examinations that are important to help establish the diagnosis, detect any level of organ failure, and identify the causative agent. In addition, host response biomarkers can be of diagnostic value (to discriminate infection from noninfectious conditions or to determine the causative pathogen), of prognostic value (assigning risk profiles and predicting outcome), and of potential theranostic value (aid in selection and monitoring of therapy).[130]

### Hematologic and Biochemical Evaluation

All patients suspected to have sepsis should have blood drawn for a complete blood count, metabolic panel, renal and liver function, and coagulation parameters. Inflammatory variables classically used as helpful criteria for the diagnosis of sepsis include leukocytosis (white blood cell count, >12,000/$mm^3$), leukopenia (white blood cell count, <4000/$mm^3$), normal white blood cell count with >10% immature forms, an elevated plasma C-reactive protein (>2 SD above the upper limit of the normal range), and elevated plasma procalcitonin (>2 SD above the upper limit of the normal range).[5]

High procalcitonin levels are associated with bacterial infection and sepsis.[130] However, the usefulness of procalcitonin in diagnosing sepsis is limited; a meta-analysis reported a sensitivity of 0.77 and specificity of 0.79 of procalcitonin to differentiate between sepsis and noninfectious critical illness,[131] which is not good enough for the decision to start or withhold antibiotics in patients admitted to the ICU with suspected sepsis. Procalcitonin may, however, help to guide the decision on when to stop antibiotic treatment in critically ill patients with infections. Procalcitonin guidance to reduce the duration of antibiotic treatment has been shown to be feasible and safe in patients with an established diagnosis of sepsis.[132,133]

First signs of AKI are an increase in creatinine (>0.5 mg/dL or 44.2 μmol/L) with or without acute oliguria (urine output <0.5 mL/kg/h for at least 2 hours despite adequate fluid resuscitation).[5] Marked hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 μmol/L) can indicate liver dysfunction. Renal and liver tests should be monitored during the course of sepsis.

Thrombocytopenia (platelet count <100,000 $\mu L^{-1}$) is seen in up to 50% of patients with sepsis.[116] Low platelet counts can suggest DIC, which is also characterized by coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 seconds), low fibrinogen levels, and elevated markers of fibrinolysis (fibrin degradation products or D-dimer levels).[36] Coagulation disorders in sepsis are discussed in more detail in "Pathogenesis."

Lactate levels can be elevated (>1 mmol/L or >9 mg/dL, or twice these values in septic shock) and signal poor tissue perfusion. High levels are associated with poor outcome.[134] Arterial blood gas analysis often shows a metabolic acidosis with compensatory respiratory alkalosis; acidosis and hypoxia are markers of severe disease. Other laboratory features often seen in sepsis include hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes and low albumin levels due to capillary leakage, altered hepatic metabolism, or poor nutrition.

## Pathogen Detection

Routine microbiologic cultures (blood, urine, sputum, wound, cerebrospinal fluid, joint fluid) should be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock.[25] Two sets of blood cultures (aerobic and anaerobic) should always be included. In patients with an intravascular catheter (in place >48 hours), at least one blood culture set should be obtained from the catheter (along with simultaneous peripheral blood cultures) to assist in the diagnosis of a potential catheter-related bloodstream infection.[25]

The culprit pathogen can be identified only in approximately 60% to 65% of patients with sepsis.[5] Often the reason for this will be the start of antibiotic treatment before cultures were obtained. In addition, culture-based pathogen identification is relatively slow, and sensitivity can be low. To overcome these problems, rapid culture-independent diagnostic methods including matrix-associated laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (MS), polymerase chain reaction (PCR), and microarrays have been introduced.[135] These methods can be very helpful for quicker and more accurate identification of microorganisms. MALDI-TOF MS has received much attention, permitting fast and correct identification of bacteria and fungi based on the generation of unique mass spectral protein fingerprint signatures. A recent investigation has suggested that use of MALDI-TOF MS may reduce the time to appropriate antibiotic therapy, the length of ICU stay, and the mortality of patients with bacteremia.[136] Early detection of antimicrobial resistance is essential to reduce the risk of inappropriate therapy. MALDI-TOF MS coupled with a PCR-based rapid diagnosis of MRSA diminished unnecessary coverage of MRSA.[137] A study in six European countries in critically ill patients with bloodstream infections or pneumonia showed the enhanced sensitivity to identify a pathogen when using the combination of PCR and electrospray ionization MS compared with standard culture techniques.[138] Using PCR/electrospray ionization MS also demonstrated the ability to rule out infection with a negative predictive value of 97% at 6 hours from sample acquisition.[138] Several studies have evaluated the use of rapid point-of-care testing for respiratory viruses showing its benefit in better pathogen detection and improved use of antimicrobials.[139,140] As these techniques are emerging, their clinical value and cost-effectiveness have to be assessed as well as their potential to determine antimicrobial resistance for which isolation and direct testing of viable pathogens remain key. Nevertheless, these molecular assays are expected to eventually replace present-day conventional microbiologic techniques for the detection of infections causing sepsis.

Regarding invasive fungal infections, blood cultures are positive in a minority of cases and often late in the course of infection. Non–culture-based laboratory techniques may contribute to early diagnosis. The use of galactomannan and β-D-glucan to assist in the assessment of invasive *Aspergillus* (and a broad range of fungal pathogens) has become well accepted in patients with high-risk hematologic conditions.[141] Regarding invasive candidiasis, the value of antigen-based tests that target the *Candida*-specific cell wall component mannan or the nonspecific fungal element β-D-glucan is still poorly defined in an ICU population.[142] The same applies for the use of *Candida*-specific PCR in blood and serum.

## Diagnostic Imaging

Imaging studies should be performed promptly to confirm a potential source of infection.[25] In addition to chest radiography for the evaluation of pneumonia, standard computed tomography can be helpful to assess infection in the sinuses, lungs, liver, and abdomen. Ultrasonography may be useful for evaluating gallbladder and kidney dysfunction.

## Host Response Biomarkers

Biomarkers are molecules, genes, or other factors that can assist in the identification of physiologic or pathologic processes.[130] The ideal biomarker provides specific and sensitive information about a process or disease state and can be measured rapidly by a point-of-care test with low production costs. To be clinically useful, a biomarker needs to assist the physician in therapeutic decision making. Biomarkers that have been evaluated in patients with sepsis can be arbitrarily divided into diagnostic and prognostic markers (Fig. 73.6). Diagnostic biomarkers can aid in distinction between sepsis and noninfectious critical illness or between causative organisms; such biomarkers could be helpful in antibiotic stewardship and reduction of inadequate use of antibiotics. Prognostic biomarkers can help to predict adverse outcomes, including specific complications. In recent years, efforts have been made to use biomarker profiles to stratify patients with sepsis in different subgroups or endotypes based on particular pathophysiologic features; this approach likely is key for personalized medicine with implementation of individualized treatment based on the patient's unique characteristics.[87] The term *theranostics* has been introduced to indicate biomarker-guided selection of patients for a specific therapy followed by biomarker-guided assessment of treatment response.

Despite the fact that numerous host response biomarkers have been evaluated in sepsis, none are routinely used in sepsis management,[143] and the Surviving Sepsis Campaign guidelines list procalcitonin only as potentially useful in guiding antibiotic treatment in critically ill patients.[25] Other well-studied protein sepsis biomarkers include C-reactive protein, LPS binding protein, IL-6, soluble triggering receptor expressed on myeloid cells 1, and soluble urokinase-type plasminogen activator receptor, all with a lower sensitivity and specificity relative to procalcitonin.[130] To date, the most robust biomarkers of sepsis-induced immunosuppression have been measured by flow cytometry.[144] Of these, decreased expression of monocyte HLA-DR is considered a good surrogate marker of monocyte anergy. Reduced monocyte HLA-DR expression is an independent predictor of mortality in patients with sepsis and has been used as an inclusion criterion for immunostimulatory trials. Overexpression of PD-1 on lymphocytes and overexpression of its ligand PD-L1 on monocytes have also been used as markers of immunosuppression and risk prediction.[144]

In more recent years the search for sepsis biomarkers has moved from individual proteins to sets of (potential) markers using systems-based approaches.[87,130] The "omics" field includes genomics, epigenetics, transcriptomics, proteomics, and metabolomics. Increasingly, "omics"-based methodologies are used to study host-pathogen interactions and biomarkers in sepsis.[87,145] Especially transcriptomics has been used for the discovery of biomarkers that can discriminate between sepsis and noninfectious causes of critical illness,[146–148] and one such test has been registered in the United States with this indication.[146] Host gene expression signatures may also help in identifying causative pathogens in patients with infections; for example, in adults presenting to the emergency department with suspected community-acquired acute respiratory tract infections, different RNA signatures were revealed in patients with diseases of bacterial, viral, or noninfectious origin.[149] Blood leukocyte gene expression profiles that can assist in the discrimination between bacterial and viral infection have also been reported in other clinical

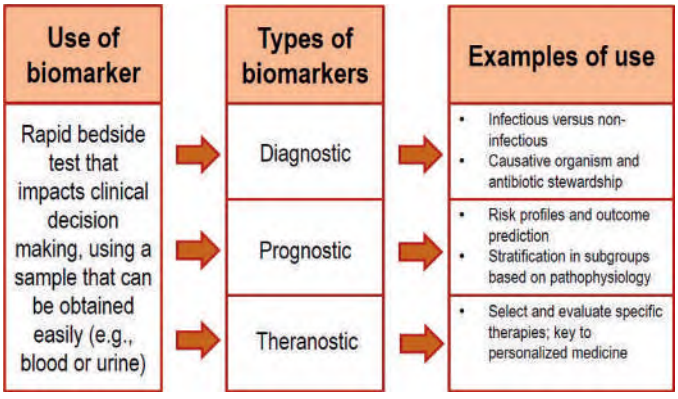


**FIG. 73.6 Sepsis biomarkers.** Biomarkers can be used to differentiate sepsis from noninfectious critical illness or to determine causative pathogens, thereby contributing to antibiotic stewardship. Furthermore, biomarkers can assist in stratifying patients based on risk profiles, predicting outcome, or identifying pathophysiologic pathways that can be the target for personalized therapy. Theranostics entails biomarker tests that select and monitor specific therapies.

settings including in the ICU.[150] In addition, transcriptomic signatures have been used to stratify patients with sepsis into endotypes with pathophysiologic and prognostic significance.[151,152] These signatures could be the key to targeted therapy and theranostics in the future. RNA biomarkers can be incorporated in PCR-based bedside tests with limited or no hands-on time, which—if proven valuable—make them attractive for implementation in clinical practice. Proteomics, metabolomics, and lipidomics represent other new areas of biomarker research.[153]

## THERAPY

Sepsis is a medical emergency. Early clinical suspicion, rigorous diagnostic measures, aggressive initiation of appropriate antimicrobial therapy, comprehensive supportive care, and measures aimed at reversing predisposing causes are the cornerstones of successful management.

### Surviving Sepsis Campaign Guidelines

The Surviving Sepsis Campaign consists of a group of international critical care and infectious disease experts that aims to improve the outcome of sepsis and septic shock. The third revision of the Surviving Sepsis Campaign guidelines was published in 2017.[25] Of note, this last revision was conducted before publication of the Sepsis-3 definitions[3] and does not incorporate them. Adherence to the Surviving Sepsis Campaign guidelines has been associated with reduced hospital mortality rates.[154,155,156] Table 73.5 summarizes key recommendations for the initial management of sepsis, which are aimed to provide rapid cardiorespiratory resuscitation and diminish the immediate danger of the underlying infection.

Cardiorespiratory resuscitation involves intravenous fluids, vasopressors, and mechanical ventilation where needed. Compared with the 2012 version of the guidelines,[157] the current version deemphasizes protocolization of care and invasive monitoring, instead suggesting that patients be reevaluated frequently. An earlier landmark study from 2001 showed that early goal-directed therapy (EGDT), a well-defined intervention to guide hemodynamic resuscitation according to targets for central venous pressure, mean arterial blood pressure, urinary output, and central venous oxygen saturation, decreased mortality of patients with severe sepsis and septic shock.[158] However, follow-up multicenter, randomized controlled trials from the United States (ProCESS),[159] Australia (ARISE),[160] and the United Kingdom (ProMISe)[161] could not demonstrate a survival benefit of EGDT compared with usual resuscitation in patients with septic shock. Also, measurements of central venous pressure and central venous oxygen saturation were not beneficial in patients with lactate values greater than 4 mmol/L.[159,160,161] Finally, a patient-level meta-analysis of the ProCESS, ARISE, and ProMISe trials not only confirmed that EGDT did not result in better outcomes than usual care but also showed that this strategy was associated with higher hospitalization costs.[162]

The initial management of infection involves identifying the most likely source of infection, obtaining cultures (whenever possible before start of antibiotic therapy), administration of empirical antimicrobial therapy, and source control (*ubi pus, ibi evacua* ["where there is pus, there evacuate it"]) where appropriate. The importance of source control cannot be overstated.[163] Common occult sources are found in the lungs, urinary tract, or abdomen (e.g., diverticulitis, cholecystitis). Signs of septic arthritis, endocarditis, and osteomyelitis should be looked for. Intravascular access devices that are a possible source of sepsis should be promptly removed after other vascular access has been established. The same holds true for urinary catheters. The Surviving Sepsis Campaign recommendations on antimicrobial therapy and source control are listed in Table 73.6.[25] It should be noted that the formulation of these recommendations has stirred an ongoing debate.[164]

### Empirical Antibiotic Therapy

The Surviving Sepsis Campaign guidelines recommend that intravenous antibiotics should be started as soon as possible after recognition and within 1 hour for both sepsis and septic shock.[25] If the patient is infected and is severely ill or has shock, there is little margin for error. However, in patients with less severe disease, this recommendation has been criticized, as uncertainty exists if a 1-hour delay in the administration of antibiotics will negatively impact outcome in all patients with sepsis.[165] A recent study from the Netherlands could not demonstrate an effect on survival in patients with sepsis if prehospital antibiotics were already administered in the ambulance.[166] In addition, one may fear that using a fixed time period may lead to antibiotic overuse.[165] In patients who are not critically ill there is often more time to generate additional diagnostic information and—in some cases—prevent the administration of broad-spectrum antibiotics to patients who do not have infections but present with a sepsis-like syndrome. Taken together, the benefits of treating patients with infections need to be balanced against the harms of treating patients who at first appear as if they may have infections but in fact do not.[164] Other guidelines have proposed that a 3-hour target for the initiation of empirical antibiotic therapy for sepsis is reasonable.[164] One should keep in mind that the recognition of sepsis can be difficult; broad-spectrum antibiotics given to patients with syndromes that look like infections who do not actually have infections should be stopped as soon as possible.

Inadequate empirical antibiotic therapy in patients with sepsis is associated with increased mortality,[167] indicating that antibiotics covering all probable pathogens should be given as early as possible. The choice of empirical antibiotic treatment depends on the suspected source of

**TABLE 73.5 Key Recommendations of the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016**

- Sepsis and septic shock are medical emergencies, and treatment and resuscitation should begin immediately.
- Routine microbiologic cultures are obtained before starting antimicrobial therapy in patients with suspected sepsis. These always include at least two sets of blood cultures (aerobic and anaerobic).
- Patients with hypoperfusion should receive at least 30 mL/kg of IV crystalloid within 3 hours and should be reassessed frequently.
- For patients who require vasopressors, initial target mean arterial pressure should be 65 mm Hg.
- Norepinephrine is the first choice for patients who need vasopressors. Vasopressin or epinephrine can be added. For patients who remain unstable, dobutamine is recommended.
- IV hydrocortisone (200 mg/day) is suggested for patients who are hemodynamically unstable despite fluids and vasopressors.
- Blood transfusion should be reserved for patients with hemoglobin concentration <7.0 g/dL except in special circumstances such as hemorrhage and myocardial ischemia. Platelets should be given if the platelet count is <10,000/$mm^3$ or <20,000/$mm^3$ with bleeding.
- Mechanical ventilation with a target tidal volume of 6 mL/kg predicted body weight is recommended compared with 12 mL/kg in adult patients with sepsis-induced ARDS. An upper limit goal for plateau pressures of 30 cm $H_2O$ over higher plateau pressures is recommended in patients with sepsis-induced severe ARDS. The use of higher PEEP over lower PEEP is recommended in patients with sepsis-induced moderate-to-severe ARDS.
- A protocolized approach to blood glucose management in ICU patients with sepsis is recommended, initiating insulin dosing when two consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucose level ≤180 mg/dL.
- Either continuous or intermittent renal replacement therapy can be used in patients with sepsis and acute kidney injury.
- Sodium bicarbonate should not be used for most patients with pH ≥7.15.
- Pharmacologic prophylaxis against venous thromboembolism with unfractionated heparin or LMWH should be given in the absence of contraindications for these agents.
- Stress ulcer prophylaxis should be given to patients with sepsis or septic shock who have risk factors for gastrointestinal bleeding.
- Administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings is not recommended in critically ill patients who can be fed enterally. The administration of parenteral nutrition is not recommended over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not feasible.
- Goals of care and prognosis should be set and discussed with patients and families as early as feasible.

See Table 73.6 for specific recommendations on antimicrobial therapy and source control.

*ARDS, Acute respiratory distress syndrome; ICU, intensive care unit; IV, intravenous; LMWH, low-molecular-weight heparin; PEEP, positive end-expiratory pressure.*

*Data from Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.* Crit Care Med. *2017;45:486–552.*

**TABLE 73.6 Surviving Sepsis Campaign Recommendations on Antimicrobial Therapy and Source Control**

| | RECOMMENDATION | GRADE |
|---|---|---|
| | **Antimicrobial Therapy** | |
| 1 | Intravenous antimicrobials should be initiated as soon as possible after recognition and within 1 hour for both sepsis and septic shock. | Strong recommendation, moderate quality of evidence |
| 2 | Empirical broad-spectrum therapy is recommended with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage). | Strong recommendation, moderate quality of evidence |
| 3 | Antimicrobial therapy should be narrowed once pathogen identification and sensitivities are established or adequate clinical improvement is noted. | Best practice statement |
| 4 | Sustained systemic antimicrobial prophylaxis is not recommended in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury). | Best practice statement |
| 5 | Dosing strategies of antimicrobials should be optimized based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock. | Best practice statement |
| 6 | It is suggested to use empirical combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogens for initial management of septic shock. | Weak recommendation, low quality of evidence |
| 7 | It is suggested that combination therapy is not routinely used for ongoing treatment of most other serious infections including bacteremia and sepsis without shock.[a] | Weak recommendation, low quality of evidence |
| 8 | The use of combination therapy for routine treatment of neutropenic sepsis/bacteremia is not recommended.[a] | Strong recommendation, moderate quality of evidence |
| 9 | If combination therapy is used for septic shock, it is recommended to deescalate with discontinuation of combination therapy within the first few days in response to clinical improvement or evidence of infection resolution. This applies to both targeted (for culture-positive infections) and empirical (for culture-negative infections) combination therapy.[a] | Best practice statement |
| 10 | Antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock. | Weak recommendation, low quality of evidence |
| 11 | Longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus,* some fungal and viral infections, or immunologic deficiencies including neutropenia. | Weak recommendation, low quality of evidence |
| 12 | Shorter courses are appropriate in some patients, particularly patients with rapid clinical resolution following effective source control of intraabdominal or urinary sepsis and patients with anatomically uncomplicated pyelonephritis. | Weak recommendation, low quality of evidence |
| 13 | Daily assessment for deescalation of antimicrobial therapy in patients with sepsis and septic shock is recommended. | Best practice statement |
| 14 | Measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients. | Weak recommendation, low quality of evidence |
| 15 | Procalcitonin levels can be used to support discontinuation of empirical antibiotics in patients who initially appeared to have sepsis but subsequently have limited clinical evidence of infection. | Weak recommendation, low quality of evidence |
| | **Source Control** | |
| 1 | A specific anatomic diagnosis of infection requiring emergent source control should be identified or excluded as rapidly as possible in any patient with sepsis. Required source control interventions should be implemented as soon as medically and logistically possible. | Best practice statement |
| 2 | Prompt removal of intravascular access devices that are a possible source of sepsis or septic shock is recommended after other vascular access has been established. | Best practice statement |

[a]Combination therapy is defined in these guidelines as the use of multiple antibiotics with the specific intent of covering the known or suspected pathogen or pathogens with more than one antibiotic (e.g., piperacillin/tazobactam and an aminoglycoside or fluoroquinolone for gram-negative pathogens) to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Other proposed applications of combination therapy include inhibition of bacterial toxin production (e.g., clindamycin with β-lactams for streptococcal toxic shock) or potential immunomodulatory effects (macrolides with a β-lactam for pneumococcal pneumonia). These statements do not preclude the use of multidrug therapy to broaden antimicrobial activity. Consult local guidelines.
Recommendations according to Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.[25] Uncertainty about the effect of some of these recommendations on clinical outcome has resulted in widespread variation in clinical practice. See text for a summary of the criticism of some aspects of these guidelines.[164]
*Data from Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.* Crit Care Med. *2017;45:486–552.*

infection, global geography, location where the infection was acquired (e.g., community, nursing home, or hospital), medical history, and local microbial susceptibility patterns. As a result empirical antibiotic guidelines for sepsis are different in different parts of the world. It should be emphasized that local guidelines should be referred to first. For example, multidrug empirical antibiotic therapy is appropriate for patients with risk factors for multidrug-resistant organisms but are often not required for patients with less severe disease who present to a hospital with low levels of antibiotic resistance.[164] Once culture results become available, deescalation of initial broad-spectrum antibiotic therapy is safe and may reduce the appearance of resistant microorganisms, possible drug toxicity, and costs.

Empirical antifungal therapy should be limited to patients at high risk for invasive candidiasis. A randomized trial from France showed that among nonneutropenic critically ill patients with ICU-acquired sepsis, *Candida* spp. colonization at multiple sites, and multiple organ failure, empirical treatment with micafungin did not increase fungal infection–free survival at day 28 compared with placebo.[168] Novel biomarkers or clinical risk algorithms are needed to identify patients who would benefit from empirical antifungal therapies.

## Immunomodulation

Based on the assumption that sepsis mortality is driven by excessive inflammation, many trials have been performed with a variety of

antiinflammatory agents. None of these trials showed benefit, strongly suggesting that inhibition of specific components of the inflammatory response does not improve survival in all-comers with sepsis selected based on severity of disease.[93,94] Following the more recent observations of sustained immunosuppression in patients with sepsis, several investigators now suggest use of immunostimulants in the treatment of sepsis, arguing that this would restore normal immune functions and thereby reduce the incidence of secondary infections and late sepsis mortality.[120,169] However, a recent investigation estimated that overall sepsis mortality in the ICU is only 10% attributable to secondary infections.[170] Although this finding in Dutch ICUs needs to be confirmed in different settings, including settings with higher incidences of antimicrobial resistance, it does raise doubt about the potential benefit of immunostimulation in unselected sepsis populations. The key to success of any type of immunomodulation, either antiinflammatory or immunostimulatory, is to identify the patients who may benefit from a particular intervention. Considering the complexity of the host response during sepsis and the diversity of pathophysiologic mechanisms at play, it is unlikely that the present "one-target" and "one-size-fits-all" strategy will ever be successful. In addition, clinical researchers who support inhibiting inflammation and clinical researchers who propose stimulating the immune system in sepsis may well both be right. Subgroups of patients with sepsis may benefit from combined treatments that seek to constrain certain inflammatory responses, while stimulating others. Ideally, each therapeutic should be connected with a specific biomarker that provides insight into the expression of the target, a strategy referred to as theranostics as noted earlier. In the following paragraphs we discuss therapeutics that have been tested in patients with sepsis, roughly divided into antiinflammatory and immunostimulating agents.

### Therapeutics That Seek to Inhibit Hyperinflammation

The Surviving Sepsis Campaign guidelines suggest the use of hydrocortisone (200 mg/day intravenously) for patients who are hemodynamically unstable despite fluids and vasopressors.[25] This recommendation is graded as weak with low quality of evidence. Indeed, several systematic reviews that have examined the use of low-dose hydrocortisone in septic shock have shown contradictory results.[171–,173,174] The most recent randomized controlled trial on this subject, a trial from Australia comprising 3800 patients with septic shock undergoing mechanical ventilation, could not demonstrate a 90-day survival benefit of a continuous infusion of hydrocortisone at a dose of 200 mg/day given for 7 days compared with placebo.[175] In addition, low-dose hydrocortisone in patients with septic shock can cause hyperglycemia and hypernatremia as side effects.[175]

Other antiinflammatory agents tested in clinical sepsis trials over the past decades include corticosteroids, TNF antibodies, soluble TNF receptors, IL-1 receptor antagonist, nitric oxide inhibitors, and platelet-activating factor inhibitors; none of these improved mortality.[93,94] Moreover, clinical trials that determined the efficacy of antithrombin, APC, and TFPI (anticoagulants that also exert antiinflammatory effects) showed no consistent benefit in patients with sepsis.[37,40,104,105] Several techniques have been developed seeking to remove bacterial and host inflammatory products from the circulation of patients. Strategies to remove LPS from blood include polymyxin B hemoperfusion, of which the effect on the outcome of patients with sepsis was not consistent.[176–178] CytoSorb is an extracorporeal cytokine adsorber that was evaluated in a small randomized trial in 100 patients with sepsis.[179] Hemadsorption did not lower plasma IL-6 concentrations, and 60-day-mortality was higher in the treatment group, although the difference was not significant after adjustment for baseline imbalances.[179] AB103 is a peptide that impedes the interaction between bacterial superantigens and the T-cell receptor CD28.[180] Besides reducing mortality in mouse models of superantigen-induced shock, AB103 also improved outcome of experimental polymicrobial sepsis,[180,181] suggesting that this peptide may have activity beyond T cells. AB103 is currently being evaluated in patients with necrotizing soft tissue infections.[182] Other antiinflammatory therapeutics studied in clinical sepsis trials are a humanized anti-C5a monoclonal antibody (CaCP29; phase II) and soluble recombinant human thrombomodulin (ART-123; phase III). An attractive therapeutic strategy in sepsis is to restore endothelium barrier function. Several agents have been studied in patients with diseases other than sepsis, including angiopoietin-1/Tie-2 modulators, S1P1 agonists, fibrinopeptide $B\beta_{15–42}$, and a PAR1 pepducin.[107]

### Therapeutics That Seek to Stimulate the Immune System

Several interventions that may stimulate the immune system in sepsis have been evaluated in small clinical trials.[120,169] Immunostimulating cytokines have been studied most extensively in this regard. IFN-γ primarily targets antigen-presenting cells and can enhance the capacity of phagocytosis and killing of phagocytes. IFN-γ administration to patients with sepsis partially reversed two hallmark features of immunosuppression—reduced HLA-DR expression on monocytes and the diminished capacity of blood leukocytes to produce proinflammatory cytokines on stimulation.[183,184] IL-7 targets T cells and may reverse immunosuppression in sepsis by stimulation of T-cell proliferation, inhibition of lymphocyte apoptosis, and augmentation of the expression of adhesion molecules resulting in improved cell trafficking.[185] Addition of IL-7 to T cells from patients with sepsis was associated with enhanced proliferation and IFN-γ production, mediated at least in part through alterations in cellular metabolism initiated by mechanistic target of rapamycin activation,[186,187] suggesting that IL-7 may impact T-cell dysfunction in human sepsis. Recombinant IL-7 had a good safety profile in patients with HIV infection and patients with cancer and increased $CD4^+$ and $CD8^+$ T-cell counts[188] and is currently being tested in small trials in patients with sepsis. Granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances the production of neutrophils, monocytes, and macrophages. GM-CSF administration to patients with sepsis restored several features of immunosuppression in the patients, enhancing monocyte HLA-DR expression and the capacity of blood leukocytes to release TNF-α on stimulation,[189,190] which in children with sepsis was associated with a diminished incidence of secondary infections.[190] A larger trial assessing the ability of GM-CSF to avert secondary infections in patients with sepsis with reduced monocyte HLA-DR expression is ongoing. Granulocyte colony-stimulating factor, which enhances the production of granulocytes, did not impact sepsis mortality in several trials.[191] So-called checkpoint inhibitors have been suggested as sepsis treatment as a method to restore T-cell functions.[120] In this respect antibodies against PD1 and PD-L1 have received the most attention. These antibodies have been widely used in patients with cancer,[192] and an anti-PD-L1 antibody is now being studied in patients with sepsis. Thymosin alpha 1 is a thymic peptide that increased HLA-DR expression on blood monocytes and tended to reduce mortality in patients with sepsis.[193]

### Mesenchymal Stem Cells

Administration of allogeneic mesenchymal stem (or stromal) cells (MSCs) represents a potential immunomodulatory therapy in sepsis that cannot be readily classified as antiinflammatory or immunostimulatory. MSCs improved survival in animal models of sepsis by mechanisms that comprise antimicrobial, antiapoptotic, immunomodulatory, and barrier-preserving properties.[194] Administration of MSCs to humans appears to be safe, and their effect is currently being studied in patients with sepsis or ARDS or both.

## PROGNOSIS

Patients who survive sepsis often have long-term complications after admission, a higher readmission rate for sepsis, and an increased mortality. The magnitude of this problem increases as the number of patients who survive sepsis treatment increases. Impaired quality of life in the physical and mental domains can persist for months to years after a sepsis episode.[195] Sepsis survivors have an increased risk for physical disability, cognitive impairment, renal failure, and cardiovascular events. In the year after sepsis, cardiovascular events were reported to occur in 30% of patients, which was higher compared with matched control populations.[195] As a result, health care use will increase nearly threefold compared with levels before sepsis.

One study from the United States comprising almost 3500 patients with severe sepsis found that 43% of survivors were rehospitalized within 90 days.[196] The most common readmission diagnoses included heart failure, pneumonia, chronic obstructive pulmonary disease exacerbation,

and urinary tract infections. Readmissions for a primary diagnosis of infection (sepsis, pneumonia, urinary tract infection, and skin/soft tissue infection) occurred in 12% of severe sepsis survivors compared with 8% of patients with matched acute medical conditions.[196] Of the patients readmitted with sepsis within 90 days, about two-thirds have an infection at the same site as their initial admission.[197]

Sepsis increases the risk of death for up to 5 years after the initial sepsis episode even after accounting for comorbidities.[195] Not surprisingly, survival after sepsis is strongly modified by age; for instance, reported 1-year survival was 94% for patients <45 years old and 54% for patients ≥85 years old in a retrospective study from California.[198]

Taken together, these poor long-term outcomes in terms of physical and cognitive impairment add to the total burden of sepsis-related death and disability.[195] Recently, more emphasis has been placed on recovery from sepsis. Suggestions made to enhance sepsis recovery include early referral for treatment of new physical, mental, and cognitive problems and thorough evaluation of treatable conditions that commonly result in hospitalization such as infection, heart failure, renal failure, and aspiration. Rehabilitation with physical and occupational therapy may benefit a subset of patients after sepsis.[195] An observational study from Taiwan that included more than 15,000 ICU patients who survived sepsis and received rehabilitation within 3 months after discharge showed that referral to rehabilitation within 90 days of hospital discharge was associated with lower risk of 10-year mortality compared with propensity-matched control subjects.[199]

## FUTURE PERSPECTIVES

Despite the recent decline in case-fatality rates, sepsis will remain a major health burden worldwide due to its increasing incidence and the emergence of antibiotic resistance. Better recognition of the sepsis syndrome, faster administration of antibiotics and cardiopulmonary resuscitation, and a general increase in the standard of ICU care most likely all have contributed to the better early survival of patients with sepsis.

Nonetheless, many questions remain. Main research topics include faster detection of causative microorganisms, development of novel treatment strategies that save lung and kidney function, and development of more individualized treatment approaches. The development of new biomarkers will be essential for any personalized medicine approach in sepsis. Fig. 73.7 gives an overview of current and future advances in

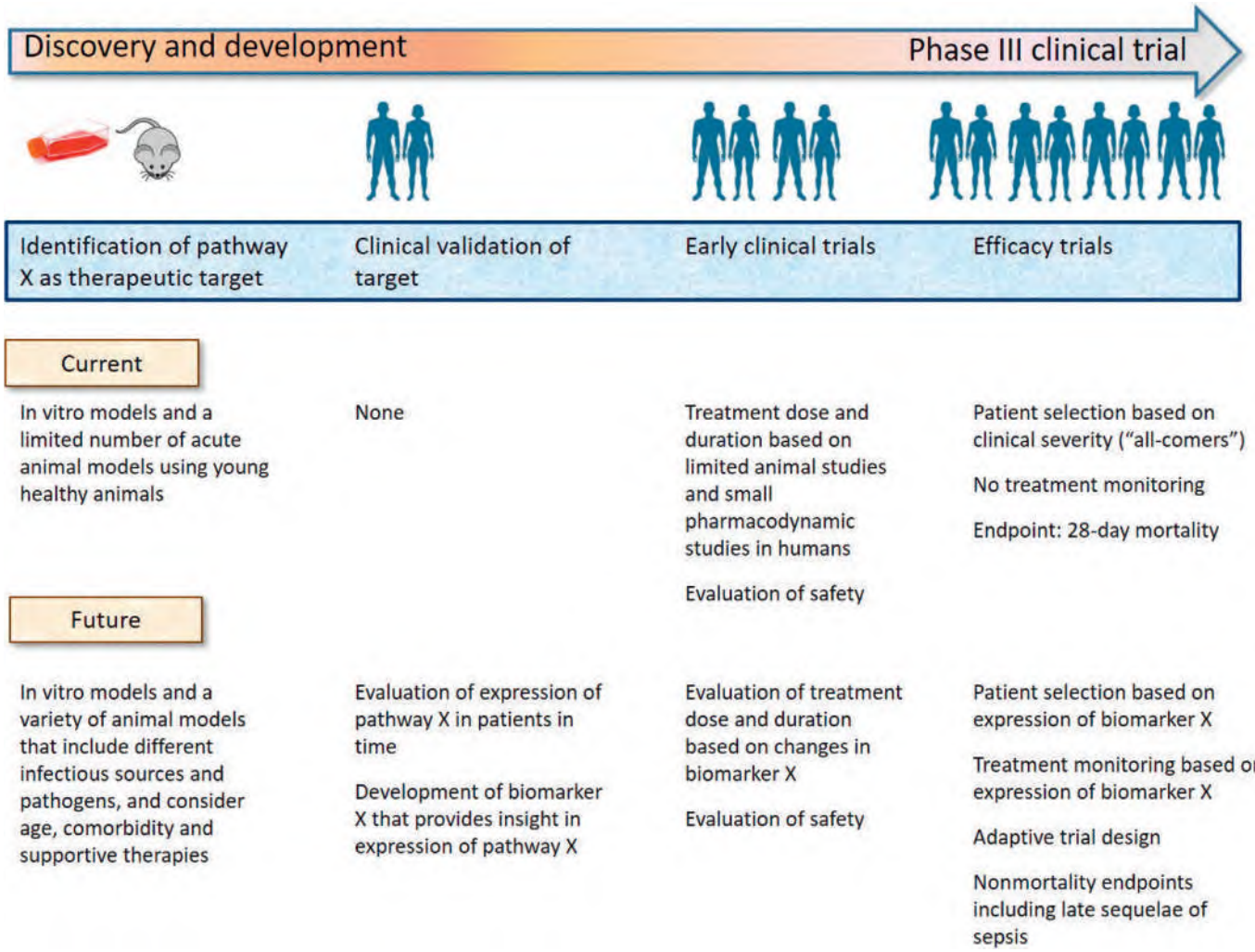


**FIG. 73.7 Current and future advances in sepsis therapy development.** Therapeutic targets for sepsis have traditionally been identified by studies in animals challenged with high-dose endotoxin (or other bacterial components) or viable bacteria or subjected to infection of the lungs, abdomen, or other body sites. Although such animal sepsis models may be useful in finding potential therapeutic targets, they do not adequately resemble the lengthy course of sepsis in patients and usually do not include common variables in human sepsis such as old age, comorbidities, and supportive therapies. Possible therapeutic targets derived from animal models should be verified in patients by detailed measurements over time, which is also important to develop host response biomarkers that afford insight into the expression of the targeted pathway. Such biomarkers could be implemented in inclusion of patients and treatment monitoring, an approach that has been termed theranostics. Thus far clinical sepsis trials used 28-day all-cause mortality as their primary end point. However, many patients with sepsis are still hospitalized at day 28. Adaptive trial designs and end points that take into account late physical and cognitive sequelae could alter the focus for drug development, moving away from efforts to modify the early host response and instead aiming to support faster and more complete recovery.

sepsis therapy development. Prevention of sepsis is an emerging research area. A better understanding of the long-term health sequelae of sepsis will be instrumental to develop therapies that truly enhance sepsis recovery.

In the future, for any patient presenting with a sepsis-like illness, rapid bedside genetic sequencing of known causative pathogens and simultaneous analysis of the host immune response could be performed with a blood sample. The results—combined with the clinical signs and symptoms and laboratory, imaging, and other phenotype data—could be analyzed with smart computer tools that use continuing learning algorithms to design individualized treatment options, which will help the attending physician, patients, and family members to initiate and monitor the optimal treatment to improve the outcome of sepsis.[200]

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*The complete reference list is available online at Expert Consult.*


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# F Intraabdominal Infections

## 74 Peritonitis and Intraperitoneal Abscesses

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### SHORT VIEW SUMMARY

**Definition**

- Infection in the abdominal cavity encompasses a wide spectrum of entities and may involve any intraabdominal organ or space.
- Peritonitis is an inflammatory response within the peritoneal cavity as the result of contamination with microorganisms, chemicals, or both.
- Infective peritonitis is classified as either diffuse or localized, and primary *(spontaneous),* secondary, or tertiary, and is further characterized as community acquired or health care acquired, and "uncomplicated" or "complicated."
- In primary peritonitis there is no intraabdominal source, whereas in secondary peritonitis there is an intraabdominal source of infection.
- Uncomplicated infections are contained within a single organ without anatomic disruption. Complicated infections involve extension beyond the organ, either localized or generalized peritonitis, with spillage of microorganisms into the sterile peritoneal space. Community-acquired infections may be further subdivided into low- or high-risk infections depending on the probability of involvement of drug-resistant bacteria and severity of infection (mild, moderate, severe), together with any significant comorbidities the patient may have.
- Peritonitis is a common complication occurring in patients undergoing continuous ambulatory peritoneal dialysis (CAPD).
- Intraperitoneal abscesses are focal collections of pus complicating either primary or secondary peritonitis, with locations generally related to the site of primary disease and the direction of dependent peritoneal drainage.
- The majority of intraabdominal infections (80%) are "community acquired" and are graded from "mild to moderate" to "more severe" on the basis of physiologic scoring systems (Acute Physiology and Chronic Health Evaluation II [APACHE II]), the patient's comorbid conditions, underlying immune status, and an inability to achieve adequate source control.
- Health care–associated intraabdominal infections are most commonly acquired as complications of previous elective or emergency abdominal operations.

**Epidemiology**

- Primary peritonitis accounts for approximately 1% of all peritonitis cases.
- Adult patients usually have cirrhosis and ascites and are at greater risk if there is a coexisting gastrointestinal hemorrhage, previous episode, or low ascitic protein concentration.
- Secondary peritonitis is the most common intraabdominal infection (80%–90%) and is caused by microbial or chemical contamination of the sterile peritoneal cavity from multiple disease processes (see Table 74.3).
- Tertiary peritonitis refers to a persistent or recurrent infection without a surgically treatable focus, may be due to a disturbance in the host's immune response, and often is associated with less virulent and potentially resistant microorganisms.
- CAPD peritonitis is the major complication of peritoneal dialysis and most often is due to touch contamination or catheter-related infection.
- CAPD peritonitis recurs in 20% to 30% of patients and is the primary reason for a switch to hemodialysis.
- Intraperitoneal abscesses occur secondarily as a consequence of diseased organs, penetrating trauma, or a surgical procedure.

**Microbiology**

- Primary peritonitis is a monomicrobial infection; more than 60% of episodes in cirrhotic patients are caused by gram-negative enteric bacteria.
- In children, hematogenous spread of *Streptococcus pneumoniae* and other streptococcal species is more frequent.
- *Staphylococcus aureus* is rarely isolated in primary peritonitis.
- Variants of primary peritonitis include ascites that grows a single type of organism but has fewer than 250 polymorphonuclear (PMN) white blood cells (WBCs) per cubic millimeter (monomicrobial nonneutrocytic bacterascites) or has more than 250 PMN WBCs/$mm^3$ with negative cultures (culture-negative neutrophilic ascites).
- Secondary peritonitis is characteristically polymicrobial (see Table 74.4) and depends on the microflora associated with the primary disease process, which may be altered by previous antibiotic therapy, other medications, and specific host factors.
- Enterococci and *Candida* spp. can often be isolated; the significance of this is controversial, but treatment is warranted under certain circumstances.
- CAPD peritonitis is caused by gram-positive organisms (*Staphylococcus epidermidis, S. aureus,* and *Streptococcus* spp.) in 60% to 80% of cases.
- Gram-negative bacteria (e.g., Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp.) make up 15% to 30% of cases, often derived from urinary tract, bowel, skin, or contaminated water.
- Fungal and mycobacterial species are occasionally involved.
- Polymicrobial peritonitis in CAPD is assumed to be secondary to an intestinal process (e.g., bowel perforation).
- Intraperitoneal abscesses are mostly polymicrobial and involve the same microorganisms that cause secondary peritonitis.
- Pathogens include obligate anaerobic species (e.g., *Bacteroides fragilis,* anaerobic cocci, and clostridia) along with facultative gram-negative bacilli (e.g., *Escherichia coli* and *Proteus* and *Klebsiella* spp.)

**Diagnosis**

- Primary peritonitis is diagnosed by excluding a primary source of intraabdominal infection.
- Ascitic fluid studies include WBC count with differential, protein concentration, Gram stain, and culture.
- The difference between serum and ascitic fluid albumin concentration is greater than 1.1 g/dL, which is correlated with portal hypertension.
- Ascitic fluid glucose, amylase, and lactate dehydrogenase measurements may help to distinguish primary from secondary peritonitis.
- Patients suspected of having secondary peritonitis or an intraperitoneal abscess on the basis of clinical findings or peritoneal fluid