CHAPTER

23 Infections of the Upper Urinary Tract

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In the normal urinary tract, ascending upper tract infections are prevented or delayed by the dynamics of urine flow and the interference of the vesicoureteral junction. The microbial etiology of urinary tract infections (UTIs) is similar throughout the urinary system, but the infection site determines the clinical features, the response to therapy, complications, and the ultimate prognosis; therefore, it is appropriate to identify upper tract infections in this chapter as a unique and significant illness. Parasitic, fungal, and mycobacterial infections of the upper tract are discussed in other chapters. Viruses are commonly excreted in the urine, but with the exception of the syndrome of hemorrhagic fever with renal insufficiency, and parvovirus B19 and other infections in renal transplant patients, the role in renal disease is ill defined; therefore, this chapter focuses primarily on bacterial infections. An infection of the upper urinary tract is not readily diagnosed in the absence of the classic clinical features of acute pyelonephritis. As a result, much of the information available is derived from studies in which the diagnosis of renal infection was imprecise. Complicated urinary infections are reviewed in Chapter 25. Uncomplicated upper tract infections in adults is the principal focus of this review, with a discussion of renal infection in patients with complicated urinary infections where relevant.

DEFINITIONS

Acute Pyelonephritis

Acute pyelonephritis is a clinical syndrome of flank pain, renal tenderness, fever, and chills, and is accompanied by bacteriuria. It may be associated with bacteremia and can progress to the systemic inflammatory response syndrome, septic shock, and, rarely, death. Acute nonobstructive pyelonephritis, also called acute uncomplicated pyelonephritis, occurs in women with a normal genitourinary tract.[1] Pyelonephritis may also occur as one clinical presentation of a complicated urinary infection in persons with structural or functional abnormalities of the genitourinary tract.

Chronic Pyelonephritis

Chronic pyelonephritis is a radiologic diagnosis characterized by renal scarring and destructive changes in the calyceal system, presumed to be caused by bacterial infection, vesicoureteral reflux, or both. Although the classic histologic features of chronic pyelonephritis have included interstitial inflammation and fibrosis, this description lacks specificity for bacterial infection and is now recognized as common to a variety of pathologic processes.

Bacteriuria

Bacteriuria is the presence of bacteria in the urine. Kass[2] introduced the term significant bacteriuria to differentiate contaminated from infected urine using quantitative urinary bacterial counts. Significant bacteriuria is the presence of at least 10^5 colony-forming units (CFU) per milliliter or at least 10^8 CFU per liter (International System of Units). Patients with symptomatic upper tract urinary infections occasionally demonstrate lower bacterial counts in their urine.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is bacteriuria without accompanying signs or symptoms attributed to urinary infections.[3] Pyuria or a serologic response to the infecting organism often accompanies asymptomatic bacteriuria, suggesting the patient is infected and not simply colonized. In females, two voided urine samples with at least 10^5 CFU per milliliter of the same organism are required to diagnose asymptomatic bacteriuria. In men, only one urine culture is necessary. Any quantitative count of a single specimen obtained by catheterization or suprapubic aspiration in men or women is also sufficient.

Recurrent Urinary Infection

Persons who experience one episode of a UTI have a greatly increased risk for a subsequent infection. A recurrent urinary infection is considered a reinfection when a new bacterial strain is isolated in the subsequent infection and is considered a relapse if the strain isolated posttherapy is similar to the

pretherapy isolate. When a relapse occurs, the infecting strain is presumed to have persisted within the genitourinary tract.

Pyuria

Pyuria is the presence of more than 5 polymorphonuclear leukocytes per high-power field (HPF) on a microscopic examination of spun urine sediment, or the presence of more than 10 polymorphonuclear leukocytes per microliter of unspun urine.[4]

HISTORICAL PERSPECTIVES

The initial description of pyelonephritis is attributed to a 9th century Arabic physician. By the mid-19th century, the associations of pyelonephritis with pregnancy and chronic pyelonephritis with a history of recurrent urinary infection were described. In 1881, Roberts[5] noted bacteria in the urine of patients with urinary symptoms, and in 1894, Escherich[6] identified "Bacillus coli" in the urine of children with urinary infections. During the preantibiotic era, recurrent urinary infection was identified as a cause of progressive renal impairment, bilateral contracted kidneys and death from uremia in girls,[7] of long-term complications of hypertension and atrophic pyelonephritis in women,[8] and of hypertension and progression to end-stage renal disease following acute pyelonephritis of pregnancy.[9] Kass,[2] in 1956, revolutionized the study of urinary infection by introducing the quantitative assessment of bacteriuria, and also identified the importance of asymptomatic bacteriuria during pregnancy. The introduction of effective antimicrobial therapy in the middle of the last century has subsequently profoundly altered the impact and adverse outcomes associated with renal infection.

PATHOGENESIS

Bacteriology

Escherichia coli is responsible for 80% or more of 16 cases of acute nonobstructive pyelonephritis (Table 23.1). Strains isolated from renal infection belong to a restricted number of O:K:H serotypes characterized by an array of virulence factors that include toxins, such as hemolysin; iron binding proteins, such as aerobactin; and specific adhesin proteins that bind to receptors on uroepithelial cells.[17,18] These and other virulence genes are often clustered within the genome in pathogenicity islands.[17] Over 95% of strains of E. coli isolated from patients with acute nonobstructive pyelonephritis contain genes for the pap G class II allele of the P fimbria adhesin.[17] The P fimbriae family is one of the mannose resistant adhesins, with a binding specificity for the gal (α1–4) gal-β disaccharide galabiose, which mediates adherence to uroepithelial cells. Specific clonal groups of E. coli, some of which are multidrug resistant, have caused global

23.1 Distribution of Bacterial Species Isolated in Patients with Acute Uncomplicated Pyelonephritis

Number of Isolates (%)						
	Urine Culture				Blood Culture	
Organism	Safrin et al.[10]	Pinson et al.[11]	Schloes et al.[12]	Talan et al.[13]	Stamm et al.[14]	Valesco et al.[15]
Escherichia coli	140 (80.9)	63 (77)	199 (85)	136 (85)	54 (85)	133 (90.5)
Klebsiella spp.	5 (2.9)	(6)	4 (1.7)	3 (1.9)	2 (3.1)	
Citrobacter spp.	-	-		2 (1.3)		1
Enterobacter spp.	-	3 (4.0)	3 (1.3)	10 (6.3)	-	1
Proteus mirabilis	2 (1.2)	2 (2.0)	2 (1)	3 (1.9)	1 (1.6)	1
Pseudomonas spp.	-	4 (5.0)				
Staphylococcus aureus	-	1 (1.0)		1 (0.6)	-	
Staphylococcus saprophyticus	8 (4.6)	4 (5.0)	8 (3)	5 (3.1)	3 (4.7)	
Enterococcus faecalis	1	-			-	1
Other	-	6		-	4 (6.3)	

outbreaks of uncomplicated urinary infection, including pyelonephritis.[19] For instance, Prats and colleagues[20] described a uropathogenic clone (E. coli 015:K52:H1) isolated during a 1-year period in Barcelona, Spain, which was overrepresented in patients with acute pyelonephritis.

Other gram-negative rods, including Klebsiella spp., Proteus mirabilis, and Enterobacter species, are isolated in a few patients with community-acquired renal infections but are much more common in patients with complicated infections. P. mirabilis accounts for more than 40% of infections in infant boys.[21] P. mirabilis is particularly significant as a renal pathogen because of its propensity to promote struvite calculi.[18] Coagulase-negative staphylococci and Enterococcus faecalis each cause 2% to 3% of invasive renal infections. The latter is a more important pathogen in elderly men. Group B streptococci are isolated in less than 1% of urinary infections, but appear to have a propensity for patients with diabetes and pregnant women.[22] Group A streptococci, Streptococcus pneumoniae, and Neisseria spp. are rare upper tract pathogens. Some patients with Staphylococcus aureus bacteremia from other sites will have S. aureus bacteriuria, with or without associated renal infection.[23] Although Staphylococcus saprophyticus is an important cause of acute cystitis in women, its role in invasive upper tract infections is uncertain. Both Mycoplasma hominis and Ureaplasma urealyticum have infrequently been isolated as the sole pathogen in patients with classic acute pyelonephritis; increases in specific antibody titers to these agents support a role for infection.[24]

Some relatively uncommon organisms isolated include Leptospira spp., Brucella spp., and Salmonella spp. A leptospiral infection usually involves the kidneys and has pathologic changes of interstitial inflammation, hemorrhage, and tubuloepithelial damage.[25] The pathogenesis of these lesions is attributed to leptospiral proteins together with hypotension, hypovolemia, and hyperbilirubinemia. Although renal insufficiency is common, localized renal symptoms are unusual; plasma creatinine and blood urea nitrogen (BUN) usually normalize in the second week of illness. A culture of urine on special leptospiral media is usually positive during the acute illness; a polymerase chain reaction or serology are also useful diagnostic tests, if available. Brucella spp. infection may, rarely, be associated with bacterial pyelonephritis and may also present as glomerulonephritis or interstitial nephritis.[26] Salmonella spp. are also a rare cause of pyelonephritis, although renal dysfunction is reported to occur in up to 36% of infected adults, usually due to dehydration and rhabdomyolysis.[27,28]

The microbiology of pyelonephritis in patients with a complicated urinary infection, including catheter-associated hospital-acquired urinary infection, is substantially different. E. coli, usually arising from the patient's own gastrointestinal tract, remains the most common urinary pathogen, but many other species are frequently isolated, and bacteria are likely to be of increased resistance. The spectrum of infecting organisms in a patient will be influenced by exposures to the health care environment as well as current or recent antimicrobial exposure. E. coli isolated from pyelonephritis in patients with complicated urinary infection have a much lower prevalence of potential virulence factors, including the P fimbria, consistent with host rather than organism factors being the principal determinants of infection.[29–31] More resistant gram-negative rods, including Pseudomonas aeruginosa and Serratia marcescens, account for 10% to 15% of hospital-acquired invasive upper tract infections in some reports, and may occur in outbreaks.[32] Corynebacterium group D2 has been identified as a unique etiologic agent of nosocomial urinary infection, particularly in catheterized patients.[33] These organisms are urease producers and may be isolated from persistent infections including bladder and renal calculi, pyelonephritis, and bacteremia. They are slow growing and sometimes missed if routine cultures are discarded after 24 hours.

Organisms that are unable to use urine as a nutrient source only rarely cause pyelonephritis. These include most species of obligate anaerobes, for which the relatively high oxygen tension in normal urine also likely inhibits growth. In a prospective study of 5,781 urine specimens, Segura et al.[34] identified only 10 patients with positive urine Gram stains and negative aerobic cultures from which anaerobic bacteria were isolated—an overall prevalence of 1.2% of bacteriuric specimens. All but 1 of these 10 patients had complicated urologic problems. Uropathogens surviving in the kidney without cell walls, also called L forms or protoplasts, have been suggested to contribute to relapsing pyelonephritis by enabling organisms to persist and cause chronic disease in the hypertonic environment of the renal medulla.[35] However, studies have not yet confirmed a role for these bacterial forms in urinary infections.

Host Factors and Host Response

Host factors contributing to pyelonephritis and the host immune and inflammatory response are described in detail in Chapter 21. Behavioral factors associated with acute nonobstructive pyelonephritis in premenopausal women are similar to those for acute uncomplicated cystitis—most importantly sexual intercourse and spermicide use for birth control.[12] There is also a genetic predisposition, as evidenced by a twofold to sixfold increased prevalence of urinary infections in the mothers and female siblings of girls and women with recurrent urinary infections.[36] Women who are nonsecretors of the blood group substance have an increased risk of recurrent acute uncomplicated urinary infections,[37] and selected blood group antigens are associated with an increased frequency of urinary infections in girls without vesicoureteral reflux.[21] Epithelial cell receptors necessary for E. coli binding are glycolipids of the globoseries, the antigens of the P blood group system. Recent studies exploring polymorphisms of effector molecules of the innate immune response have described other potential genetic determinants. In children without vesicoureteral reflux, pyelonephritis is reported to be associated with polymorphisms and mutations of the CXCR1 receptors for interleukin (IL)-8 and GCP-2 in some,[38,39] but not all studies.[40] A single nucleotide polymorphism for IL-8 was associated with severity of pyelonephritis among

children.[40] Genetic variation in the Toll-like receptor (TLR) promoter TLR-4 may also influence susceptibility to pyelonephritis in children,[41] whereas a TLR-1 receptor polymorphism has been reported to be associated with protection from pyelonephritis in women.[42]

Individuals with structural or functional abnormalities of the urinary tract have a greatly increased risk of pyelonephritis, apparently independent of behavioral or genetic factors (Table 23.2). Obstruction at the level of the kidney or ureter may directly inhibit urine flow from the upper tract, allowing bacteria to establish infection behind the obstruction. In addition, voiding abnormalities, such as neurogenic bladders, are frequently associated with reflux, which promotes upper tract infections.

Acute pyelonephritis is characterized by an intense local and systemic inflammatory and immune response.[17] Following the stimulation of epithelial receptors within the urinary tract by bacteria or bacterial products, there is activation of the innate immune response through TLRs. The Pap G adhesin appears to be important in stimulating the epithelial cytokine response.[43] Pyuria occurs early, and urinary and serum cytokines and chemokines including IL-6, IL-8, and others are elevated.[42–45] Alterations in the expression of antimicrobial peptides may be another element of the innate response, but there is a limited evaluation to date of the role of these molecules within the urinary tract.[46] The intensity of the inflammatory response correlates with the severity of symptoms. Pyelonephritis is associated with a greater inflammatory response than a lower tract infection, and urinary cytokines have increased levels in symptomatic compared with asymptomatic UTIs. This inflammatory response resolves promptly with the institution of effective antimicrobial therapy.[47] Renal infection is also associated with both a local and a systemic humoral immune response. An immunoglobulin (Ig)M antibody predominates with the initial infection but subsequent infections are dominated by an IgG response.[17,18] The primary antibody response develops about 7 to 10 days following the initial infection. Local urine antibody includes both an IgA and an IgG response to the infecting bacteria. Whether this humoral immune response has any protective role for subsequent infection remains controversial.

23.2 Abnormalities Associated with Complicated Renal Infections

Associated Systemic Diseases
Renal transplantation
Chronic renal failure
Diabetes mellitus with complications
Neutropenia
Immunosuppression
Underlying Structural Abnormalities
Congenital abnormalities (obstruction and/or stasis)
Acquired obstruction (pelvicalyceal, ureteral, urethral)
Neurogenic bladder
Catheter associated (indwelling or intermittent)
Cystocele
Bladder diverticulae
Renal cyst
Renal calculus
Atrophic or malfunctioning kidney
Less Susceptible Pathogens
Pseudomonas aeruginosa
Proteus mirabilis
Candida albicans

PATHOLOGY

Acute Pyelonephritis

A renal biopsy is contraindicated for patients with acute pyelonephritis. When pathology specimens are available, the histologic hallmarks of acute pyelonephritis include abscess formation and edema in the renal parenchyma with an accumulation of polymorphonuclear leukocytes in and around the tubules. Bacteria are often demonstrable in the foci of acute renal suppuration. In general, glomeruli are spared, although small abscesses may surround them. Areas of infection are characteristically wedge-shaped with the apex in the medulla resembling an infarct. Although tissue destruction is greater in the cortex than in the medulla, the relative smaller size of the medulla means the inflammatory response appears to have a greater effect on medullary anatomy and function. The distribution of wedge-shaped areas of suppuration is characteristically focal, usually corresponding to renal lobes, and sharply demarcated from areas of uninvolved renal parenchyma. In adults, the kidney is unlikely to be uniformly affected unless concomitant obstruction is present.

Chronic Pyelonephritis

Chronic pyelonephritis is a focal parenchymal disease with associated changes of the renal collecting system owing to inflammation and deformation. Fibrosis with atrophy of overlying renal tissue leads to surface depression or scars. Neighboring unaffected renal tissue often undergoes hypertrophy and may appear to be a mass lesion. A sharply defined border between normal and diseased tissue is characteristic of chronic pyelonephritis. The capsule is adherent and the cortical surface is irregular. Calyceal clubbing results from a papillary retraction into the scar. Dilatation, muscular hypertrophy, and fibrotic inflammation causing a thickening of the calyceal system all occur to a variable extent. The two kidneys are usually markedly asymmetrically involved, whereas other diseases that cause interstitial inflammation usually affect both kidneys equally.

The histology of chronic pyelonephritis is the pathology of interstitial or tubulointerstitial nephritis and is characterized by a pleomorphic infiltrate of lymphocytes, plasma cells, and macrophages in the interstitium of the kidney. Polymorphonuclear leukocytes and eosinophils may also be present. The vessels in zones of the normal kidney may be normal or may demonstrate hyaline intimal changes. Histologic features of acute and chronic pyelonephritis can overlap. The relative degrees of edema and fibrosis rather than the interstitial cellular response are the most useful criteria to delineate these entities. Previously, many end-stage kidneys were referred to pathologically by the term chronic pyelonephritis. This is now recognized as being a common end stage for many renal diseases, and is seldom attributable to infection.

PREVALENCE AND INCIDENCE

Symptomatic Pyelonephritis

Bacteriuria occurs in 0.7% of full-term infants, and clinically evident urinary infections occur in 0.3%.[21] Males predominate in the first 3 months of life, and account for almost 80% of neonatal urinary infections. Most of these infections appear to involve the upper tracts. In a retrospective review of 11,655 children born at a Stockholm hospital between January 1, 1979 and June 30, 1982, the annual incidence of pyelonephritis during the first 2 years of life was 34 per 10,000.[48] Acute pyelonephritis occurred after a mean of 5.6 months following discharge, with a range of 1 week to 17 months; only one infant had an underlying malformation of the urinary tract. A more recent report from a Seattle group health cooperative reported hospitalization rates for pyelonephritis were 17/10,000 for girls and 6/10,000 for boys age 0 to 4 years.[49] It is estimated 1% to 3% of all girls 1 to 5 years of age experience an episode of pyelonephritis.[21]

About 250,000 episodes of acute pyelonephritis with over 160,000 hospitalizations occur each year in adult women in the United States.[50] The highest rates of acute nonobstructive pyelonephritis are in young women, many of whom also experience acute uncomplicated cystitis (Table 23.3). Ikaheimo and associates[51] reported an incidence of 2.7 episodes of pyelonephritis per 100 patient years during a 1-year follow-up of women in a family practice in Finland who originally presented with an episode of acute cystitis. The ratio of episodes of cystitis to pyelonephritis was 29:1. Stamm and associates[52] followed 51 American women with recurrent uncomplicated urinary infections for a median of 9 years. The mean infection rate was 2.6 per patient year with the ratio of cystitis to pyelonephritis episodes of 18:1 for women not receiving prophylactic antimicrobials.

Hospitalization for treatment of acute pyelonephritis reported from a Canadian province was 11/10,000 women.[54] Pyelonephritis accounted for 0.4% of all hospital admissions.

23.3 Reported Frequency of Pyelonephritis in Selected Populations

Study Design (with Reference)	Population	Incidence
Retrospective,[48] Sweden	Children <2 years	34/10,000 population
Prospective, 12 months, Finland[51]	179 women initially presenting to GP with acute cystitis	2.7/100 patient years
Retrospective,[52] United States 1969–1985	51 women with recurrent cystitis	0.1 ± 0.3/patient year
Prospective,[53] Canada	Diabetic women with bacteriuria	7.2/100 patient years
Administrative data,[54] Canada, hospitalized	Women—all Women >60 years Men	10.9/10,000 population 14.0/10,000 population 3.3/10,000 population
Administrative data,[50] United States, hospitalized	Women <60 years Women >60 years Men <60 years Men >60 years	7.8–15.0/10,000 population 13.5–23.3/10,000 population 1.1–2.4/10,000 population 6.3–12.9/10,000 population
Administrative data, United States[49]	Hospitalized women men Outpatient women men	12–13/10,000 population 2–3/10,000 population 3–4/10,000 population 1–2/10,000 population

The frequency of hospitalization underestimates the incidence of pyelonephritis because many patients with pyelonephritis, especially healthy young women, are not admitted for treatment. Peak pyelonephritis hospitalization rates occurred in women 20 to 29 years old, and men and women older than 50 years. From 0.3% to 0.7% of all pregnancies required hospitalization for pyelonephritis. Women with diabetes were six to 24 times more likely to be admitted with pyelonephritis than nondiabetic women, stratified by age. An American study reported a similar hospitalization rate of 11.7/10,000 for women,[50] but hospitalization rates were not increased in patients with diabetes. The highest rates were observed in younger women aged 20 to 39 years, with 15 hospitalizations/10,000, and women over 80 years, with 23.3/10,000. For women enrolled in a group health cooperative in Seattle, estimated annual rates of outpatient and inpatient pyelonephritis were 12 to 13/10,000 and 3 to 4/10,000, and the highest incidence of 18 to 20/10,000 occurred in young women.[49]

Pyelonephritis in men usually occurs in the context of complicated urinary infections, but acute nonobstructive pyelonephritis may rarely occur. Krieger and colleagues[55] reported an incidence of uncomplicated symptomatic urinary infection of 4.9/10,000 men per year in a 6-year study of male university students, but most of these were likely lower tract infections. Rates of hospitalization for acute pyelonephritis in men, most with complicated urinary infections, were reported to be 3.3/10,000 per year in Canada,[54] and 2.4/10,000[50] and 1 to 2/10,000[49] in the United States. In selected populations with complicated urinary infections, Waites and associates[56] reported 1.8 episodes per person year of urinary infections presenting with fever and chills, presumably upper tract infections, in 64 spinal cord–injured patients managed with intermittent catheterization or condom drainage. A prospective study of residents in long-term care facilities reported 1.1 episodes of febrile urinary infection per 10,000 resident days.[57] The rate was 0.8/10,000 resident days for individuals without chronic indwelling catheters, and 4.6/10,000 for those with chronic indwelling catheters.

Asymptomatic Upper Tract Infections

Asymptomatic bacteriuria is common in many populations,[3] and frequently involves the upper urinary tract (Table 23.4). Presumably, factors such as the duration of bacteriuria, infecting organisms, associated medical illnesses, the presence of

23.4 Localization of Infection in Bacteriuric Populations

Reference	Method	Population Investigated	Symptoms	Site of Infection		
				Renal	Bladder	Equivocal
58	Ureteral catheterization	95 Women 26 Males	Variable	67	54	—
59	Bladder washout	125 Women	52 Asymptomatic 30 Upper 43 Lower	63	52	10
60	Bladder washout	133 Women	90 Asymptomatic 15 Upper 28 Lower	56	54	23
61	Bladder washout	50 Women	25 Upper 25 Lower	21	22	7
62	Bladder washout	105 Women	60 Asymptomatic 24 Lower 20 Upper	65	39	—
63	Bladder washout	50 Women Mean 80 yr	Asymptomatic	17	14	19
64	Bladder washout	51 Women Mean 80.5 yr	Asymptomatic	34	17	—

vesicoureteral reflux, and urinary obstructions influence the likelihood of a UTI in patients with asymptomatic bacteriuria. At least 50% of institutionalized elderly women with bacteriuria have upper tract localization.[63,64] Bacteriuria in these populations often persists and remains asymptomatic for months to years. Bacteriuria is likely attributable to the same biologic variables as recurrent uncomplicated or complicated symptomatic infection, but bacterial isolates causing bacteriuria are rarely a direct cause of subsequent symptomatic infection in the absence of uroepithelial trauma or obstruction.

NATURAL HISTORY AND CONSEQUENCES

Infection during Infancy and Childhood

The short-term morbidity of acute pyelonephritis in children may include hospitalization, severe sepsis and septic shock, metastatic infection, and, rarely, acute renal failure. Following the introduction of antimicrobial therapy, the outcome for adequately diagnosed and treated children is excellent. However, there remain concerns about the potential for long-term renal damage following acute pyelonephritis in childhood.

Renal scarring is observed in 10% to 30% of children following acute pyelonephritis.[21] Established risk factors for the development of renal parenchymal scarring include vesicoureteric reflux, recurrent infection, delayed treatment, and a young age at the time of initial infection.[65] Parvex et al.[66] observed 88 scars in 50 children at 6 months after acute pyelonephritis; 3 years later, 27% were unchanged, 63% were partially resolved, and 9% were completely disappeared. The number of scars was the most important variable associated with decreased renal growth. Increased serum and urine markers of the inflammatory response at presentation with acute pyelonephritis, including IL-8,[67] IL-6,[68] procalcitonin,[69] and C-reactive protein,[69] are associated with subsequent increased occurrence of renal scarring, regardless of vesicoureteral reflux. Recent studies have suggested that cytokine gene polymorphisms may partly explain the differential inflammatory response.[65,70,71] Studies do not support a role for bacterial virulence factors as predictors of subsequent scarring.[72]

The relative importance of vesicoureteral reflux and pyelonephritis in the development of renal scars and impaired renal function in childhood remains controversial. It is now accepted that congenital vesicoureteral reflux, primarily occurring in males and associated with higher levels of reflux and renal dysplasia, is most likely to progress to renal failure, regardless of infection.[73] Postnatal renal damage may also occur with vesicoureteral reflux associated with an infection, or with acute inflammation from an infection of the renal parenchyma without reflux. Scarring after pyelonephritis in infancy is associated with renal growth arrest in the involved kidney and may be associated with progressive kidney damage.[67,73] The risk of renal failure is significantly greater with high-grade reflux (grade IV through V) and with multifocal or global scarring. A careful follow-up with an immediate diagnosis and the adequate treatment of all recurrent episodes of infection, particularly during infancy and early childhood, are considered necessary to prevent progressive renal impairment.[73]

Asymptomatic bacteriuria occurring in girls 5 years or older with normal kidneys on a study entry is benign.[74] It is not associated with renal scar development regardless of antimicrobial treatment. Thus, programs to screen for bacteriuria in school-age girls and to treat infections, if found, are not worthwhile.

Adult-Onset Infection

Short-Term Morbidity

Potential negative short-term outcomes of acute pyelonephritis are lost days of work, hospitalization, septic shock, requirements for urologic intervention, and sequelae of metastatic infection. For patients with complicated urinary infections, additional morbidity may be attributable to the underlying abnormality, which promotes infection. Women with diabetes have been reported to have more prolonged fever and a higher rate of mortality.[75] Acute renal failure occurring with acute nonobstructive pyelonephritis caused by E. coli is rare, but well described.[76,77] This is usually reversible, may be more common in diabetic patients, and, for some of the reported cases, concomitant nonsteroidal antiinflammatory drugs likely contributed to renal failure.

Mortality

A comprehensive population-based study of the incidence and prevalence of bacteremic acute pyelonephritis from 1977 to 1981 in an urban population of 400,000 reported 22% of community-acquired bacteremias were attributed to invasive urinary infections, with an annual incidence of 15.7 per 100,000.[78] The attributable mortality for bacteremic urinary infections was 4.8%, but all 15 deaths occurred in patients with a significant underlying illness. During the same period, these investigators observed 1,520 episodes of hospital-acquired bacteremia, of which 221 (14.5%) originated from the urinary tract (71% in catheterized patients), thus yielding a rate of 7.3 per 10,000 hospitalized persons.[79] The mortality rate attributed directly to infections in these patients with bacteremic nosocomial pyelonephritis, virtually all with complicated urinary infection, was 12.7%. This mortality rate is one-third that of gram-negative bacteremia originating from other sites. A review of 542 episodes of bacteremic gram-negative urinary infection in Olmsted County, Minnesota, from 1998 to 2007 included 57% that were community acquired, 36% that were health care associated, and 7% that were nosocomial.[80] All cause mortality was 4.9% at 28 days and 15.6% at 1 year. The only independent predictor of increased mortality was increasing age, whereas a lower mortality was associated with community-acquired infections and an isolation of E. coli. In critical care units,

14.6% of patients admitted with septic shock had a urinary source.[81] The 28-day mortality when the urinary tract was the origin of the septic shock was only 18%, compared with 36% for all other sites. Berger et al.[82] described a case series of 65 patients admitted from 1994 to 2007 at one Australian center who required emergency nephrectomies due to severe urosepsis; the mortality in these individuals was 20%. Thus, mortality attributable to pyelonephritis occurs, but virtually only in patients with complicated infections.

Metastatic Infections

Genitourinary sepsis accompanied by bacteremia may be complicated by metastatic infections at other sites. Siroky and colleagues[83] identified 175 patients in whom metastatic infections developed from a primary source in the genitourinary tract. Most patients (86%) were men and the mean age was 57 years. A primary prostatic focus was considered the site for dissemination in many of the men, but in 46 patients the upper urinary tract was the likely source of the bacteremia. One hundred six patients (59%) had infections of the skeletal system; 51 patients (28%) had endocarditis; and 13% involved miscellaneous sites, including the eye and the central nervous system. Almost 70% of the skeletal infections were caused by gram-negative rods, with the vertebral column the most common metastatic site, identified in 83 patients (78%) with skeletal infections. In patients with endocarditis, gram-positive organisms were responsible for two-thirds of the infections, and these patients usually had preexisting heart disease. About one-third of these patients had undergone a manipulation of the upper urinary tract prior to the development of metastatic infections. Underlying host factors that would impair resistance to infections were unusual. In a Danish review of cases of vertebral osteomyelitis from 1978 to 1982, the urinary tract was the most common identified source, with the mean latent period separating an episode of acute urinary infection from the onset of symptoms of vertebral osteomyelitis being 54 days.[84]

Renal Impairment

Adult onset pyelonephritis rarely contributes to chronic renal failure. Abnormalities previously attributed to pyelonephritis in autopsy studies are now recognized as being an end stage of other processes such as vascular disease, papillary necrosis, or medullary cysts, with little contribution from infections. In one autopsy study of patients with renal failure, 13% of subjects were considered to have pyelonephritis, but all had vesicoureteral reflux, analgesic abuse, nephrolithiasis, or obstruction as underlying contributory factors for pyelonephritis.[85]

The Bristol Pyelonephritis Registry followed 375 women for 1 to 13 years after a clinical diagnosis of recurrent pyelonephritis. Only one patient had a radiographic progression of renal scars.[86] Other long-term studies that have reported patients with progression to renal failure also invariably identify alternate diagnoses to explain renal functional deterioration in affected patients. Parker and Kunin[87] retrospectively reviewed 74 cases among 163 women hospitalized for acute pyelonephritis 10 to 20 years previously, in the early antimicrobial era. Continuing clinical illness following the index hospitalization had occurred in more than 40% of patients; 28% had had an operative urologic procedure, and 23% had renal stones. Seventeen percent were bacteriuric at the follow-up examination. One patient died of complications of pyelonephritis, one required a transplantation for end-stage renal disease, and two others had significant renal impairment. Seven patients had undergone unilateral nephrectomy for pyelonephritis. Gower[88] followed 62 adult women with treated infections and a radiologic diagnosis of chronic pyelonephritis for a mean follow-up of almost 5 years. Serial studies demonstrated radiographic progression in 11 women, but persisting infection and analgesic ingestion contributed to progressive radiologic damage in all these cases. Two of the 36 patients with bilateral pyelonephritis had renal failure or died during the follow-up. Alwall[89] described a selected series of 29 women with an initial normal-appearing intravenous pyelogram (IVP) who developed contracted kidneys from 1 to 15 years following acute pyelonephritis. Several went on to end-stage renal disease, but for all these cases, analgesic abuse was a concomitant factor that likely accounted for disease progression.

Raz and colleagues[90] described long-term outcomes for women admitted with acute pyelonephritis to a hospital in Israel between 1982 and 1992. Only 31% of the patients were available for a 10-year follow-up, likely a group representing those with more serious or persistent disease. With technetium ^{99}Tcm–labeled dimercaptosuccinic acid (^{99}Tcm-DMSA) scanning, 46% of these women had evidence of renal scarring. Pregnancy and hypoalbuminemia at hospitalization for pyelonephritis were independent risk factors correlated with the finding of renal scars at a 10-year follow-up. Although four women with scars had a glomerular filtration rate (GFR) of less than 75 mL per minute, none had developed renal impairment. Despite the high proportion of this selected group of women who had renal scarring, there were no clinically relevant adverse outcomes.

These long-term prospective studies support the observation that recurrent UTIs in adult women usually have a benign natural history. Adults with recurrent UTIs and no other complicating illness seldom experience clinically significant renal damage directly attributable to an infection. Persons with infection and renal impairment invariably have significant underlying urologic abnormalities or associated renal diseases.

Hypertension

The long-term follow-up of cohorts that have enrolled large numbers of women have consistently reported no significant differences in blood pressure between patients with bacteriuria and those without bacteriuria.[3] Patients entered into the Bristol Pyelonephritis Registry and followed for up to 13 years developed hypertension at the same rate as the

general population.[86] Raz et al.[90] reported a similar frequency of hypertension in women with and without renal scarring 10 to 20 years after hospitalization for acute pyelonephritis. Thus, evidence does not suggest acute or recurrent pyelonephritis contributes directly to development of hypertension.

Pregnant Women

Acute pyelonephritis occurs in 1% to 2% of all obstetric patients in the absence of screening and treatment programs for bacteriuria.[91] It is the most common medical complication requiring hospitalization during pregnancy. Women with asymptomatic bacteriuria early in pregnancy have a 20- to 30-fold increased risk of acute pyelonephritis in later trimesters.[92] This is attributed to ureteral dilation and urinary stasis resulting from progesterone-induced smooth muscle relaxation, together with mechanical compression by the enlarging uterus. Acute pyelonephritis in pregnancy occurs primarily in the second and third trimesters. Case series have reported 52% of episodes occurring in the second trimester, 46% in the third, and 2% in the first,[93] and 11% occurring in the first trimester and the remainder in the second or third trimester.[94]

Acute pyelonephritis, as with any febrile bacterial illness in late pregnancy, is associated with an increased risk for premature labor, presumably due to systemic inflammation.[95] The attributable risk of acute pyelonephritis for maternal toxemia, prematurity, and perinatal mortality remains controversial.[91] Sever and associates,[96] in data collected from more than 55,000 pregnant women, reported a higher incidence of low-birth–weight infants and stillbirths in the 3.5% of women with documented UTIs. Naeye[97] reported a combined perinatal mortality rate of 42 per 10,000 births in bacteriuric women as opposed to 21 per 10,000 births in nonbacteriuric women. McGrady and colleagues,[98] using birth certificate data from Washington State, showed that the fetal mortality rate was 2.4 times higher for UTI-associated pregnancies. Romero and colleagues,[95] in a meta-analysis, documented an increased occurrence of low-birth–weight and preterm delivery with asymptomatic bacteriuria. Smaill (in a Cochrane review)[99] also showed that antibiotic treatment significantly reduced the risk of low birth weight. Thus, asymptomatic bacteriuria is associated with prematurity and low birth weight, but it is not clear whether acute pyelonephritis is also a risk, or whether any presentation of urinary infection is causative for these outcomes.

Pregnant patients have a reduced GFR following acute pyelonephritis, which reverts to normal within 8 weeks of effective treatment.[100] Long-term follow-up studies of women known to have previously experienced bacteriuria during pregnancy report a benign course for the majority of patients.[101,102] In a follow-up period of 10 to 14 years, almost 40% of 134 women with bacteriuria during pregnancy also had bacteriuria on follow-up cultures. Although pyelography showed renal scarring in 28% of these patients, creatinine clearance was normal for both the bacteriuric and the nonbacteriuric women.[102] Raz et al.[90] reported that pregnancy at hospitalization for acute pyelonephritis was an independent risk factor for the presence of renal scars 10 to 20 years later. Subtle differences in renal function were found in long-term follow-ups between women with and without urinary infection during pregnancy, but these were not clinically significant.

Neurogenic Bladder

Following a traumatic spinal cord injury, patients managed with permanent indwelling catheters have substantial subsequent morbidity and mortality attributable to renal infections. The mortality rate from renal failure was 20% within 3 decades from injury in survivors of World War II spinal injuries. This was a consequence of obstruction, nephrolithiasis, suppurative renal disease, and progressive nonobstructive chronic pyelonephritis.[103] More than one-half of the deaths during the 2nd decade after spinal cord injury were caused by renal failure.[104] The introduction and widespread practice of voiding management to maintain a low-pressure system within the genitourinary tract, including the use of intermittent catheterization, have dramatically altered the occurrence of and mortality from complications of urinary infections in this population. Spinal cord injured patients, however, remain at an increased risk of urosepsis and other complications of infection including urethritis, periurethral abscesses, bladder and renal calculi, vesicoureteral reflux, and renal or perinephric abscesses.

LABORATORY DIAGNOSIS

Urine Culture

Quantitative counts of bacteria isolated from urine collected before the initiation of antimicrobial therapy in patients with acute nonobstructive pyelonephritis exceed 10^5 CFU per milliliter for 95% of patients.[2,105–107] In patients with renal infections, ureteral urine bacterial counts vary between 10^1 and 10^6 CFU per milliliter.[58] The maximum stationary phase growth is reached in the bladder after a period without emptying; thus, whenever possible, urine cultures should be obtained following an overnight "incubation" of urine within the urinary bladder. A number of variables, including diuresis, frequency of voiding, partially effective antibacterial chemotherapy, infection owing to fastidious organisms, obstruction, and extraluminal infection, may reduce bacterial counts to lower levels.

The diagnosis of asymptomatic bacteriuria in women is made with 95% assurance if two consecutive urine cultures are positive for the same organism in counts equal to or greater than 10^5 CFU per milliliter.[2,3] In men, a single positive urine culture establishes the diagnosis of bacteriuria.[3] Urine cultures with more than one organism isolated may be difficult to interpret. Such "mixed cultures" usually reflect contamination or, when urinary devices are in place, biofilm colonization. A true multiple organism infection of the urinary tract is uncommon in patients with acute uncomplicated pyelonephritis, but frequent for some patients with complicated urinary infection, particularly in

patients with foreign bodies or renal stones. Occasionally, different organisms may be present in each kidney. Differential growth rates in the bladder or suppression of one organism by the other may result in a report of a single organism isolated in voided urine despite different infecting organisms in ureteral urine cultures, or even the bloodstream.

Pyuria

Demonstrating the presence of pyuria is the most readily available means of establishing the evidence of a host response, presumably differentiating colonization from infection. Renal infection is usually characterized by a higher urinary leukocyte count than bladder infection.[64,108] However, the sensitivity, specificity, and predictive value of pyuria as a diagnostic test for acute pyelonephritis have not been determined. Leukocytes disintegrate at alkaline pH, potentially leading to false-negative findings for pyuria in patients with infections with urease-producing organisms. In addition, neutropenic patients with symptomatic urinary infections may fail to demonstrate pyuria.

Pyuria is usually identified by the presence of leukocyte esterase on a dipstick screening of urine. The more traditional measurement of pyuria by counting the number of cells in centrifuged urine per high power field is imprecise, with many sources of error.[4] Leukocyte excretion rates are more reproducible, but are not applicable to routine patient care. Excretion rates do correlate well with absolute leukocyte counts of random, unspun urine counted in a hemocytometer; counts in excess of 10/mm^3 represent an abnormal host response.[4]

Other Urinalysis Characteristics

Leukocyte casts indicate intrarenal inflammation. They are present in about two-thirds of patients with invasive renal infection but are nonspecific, also being present in many interstitial and glomerular renal diseases. Microscopic hematuria is common in patients with renal infection but has no documented clinical significance. It usually resolves with adequate treatment. Red blood cell casts are unusual. Persistent hematuria after antimicrobial treatment may require a urologic investigation to exclude other causes. Quantitative proteinuria with a urinary protein excretion rate exceeding 100 mg per 24 hours is unusual in either acute or chronic renal infection unless a second renal disease associated with proteinuria is present.

Bacteremia

Between 15% and 30% of hospitalized patients with acute pyelonephritis have a positive blood culture at presentation and, presumably, are at greater risk of metastatic infection to other sites.[10,11,109] Elderly women, patients with diabetes, and individuals with obstruction are more likely to be bacteremic.[75,110]

The routine collection of blood cultures from all patients presenting to the emergency department with acute pyelonephritis is not clinically useful. McMurray et al.[111] reported that 56 (18%) of 307 patients hospitalized with acute pyelonephritis from 1990 to 1992 had positive blood cultures; 32% of positive blood cultures were coagulase negative staphylococci and were presumed to be contaminants. Only one blood culture grew a pathogenic organism that was not also isolated from urine culture, and clinical management was not altered for any patient by positive blood cultures. Velasco et al.[15] obtained routine blood cultures from outpatients presenting with a diagnosis of acute pyelonephritis at a Spanish hospital. Positive blood cultures were found in 147 (25%) of 583 patients, with only coagulase negative staphylococci isolated in 17 (12%) of these. E. coli grew from 91% of positive blood cultures, and 23% of women with E. coli pyelonephritis had positive blood cultures. The blood culture was consistent with the urine culture result in 98% of cases. Wing et al.[16] pooled data from three randomized controlled trials in pregnant women with acute pyelonephritis, from whom routine blood cultures were obtained at study entry. Among 391 women, 94 (24%) had positive blood cultures and 5 (5.3%) grew only S. epidermidis. Smith et al.,[112] however, retrospectively reviewed results from nonpregnant women admitted with acute pyelonephritis through the emergency department of an urban county teaching hospital where blood cultures were obtained selectively rather than routinely. Bacteremia occurred in 36% of 64 women, and was more frequent in black women, women with genitourinary abnormalities, with higher pulse rates on admission, higher levels of pyuria, and more prolonged fever. Blood cultures were positive in 2 patients with negative urine cultures. van Nieuwkoop and colleagues[113] reported that 23% of patients presenting to emergency departments in the Netherlands with both uncomplicated and complicated febrile UTIs had bacteremia; 95% had concordant blood and urine cultures. Factors independently associated with positive blood cultures but negative urine cultures included the presence of a urinary catheter, any malignancy, and already receiving antimicrobial treatment for urinary infection when the urine culture was obtained.

These studies suggest routine blood cultures obtained from clinically stable women presenting with mild or moderately severe symptoms of acute pyelonephritis are not useful and should not be requested. However, patients who are more severely ill, in whom the diagnosis is uncertain, or when an underlying abnormality is present or suspected, should have blood cultures obtained prior to the institution of antimicrobial therapy. This is particularly the case for pregnant women, where failure to initiate appropriate antimicrobial therapy may have adverse fetal outcomes.

C-reactive Protein and Procalcitonin

C-reactive protein and procalcitonin are elevated in children and adults with acute pyelonephritis.[114,115] These are, however, nonspecific markers for inflammation with limited diagnostic use for differentiating pyelonephritis from other febrile illnesses. Procalcitonin has been suggested to be useful

to identify upper tract involvement in children who present to the emergency department with urinary infections.[114] C-reactive protein and procalcitonin have also been evaluated as prognostic markers. Pratt et al.[115] showed that elevated procalcitonin (using a level of 1 ng per milliliter) correlated with the development of renal scars in children, and was more specific for predicting subsequent scarring than C-reactive protein or leukocyte counts. In adults, a higher C-reactive protein level at admission correlated with prolonged hospitalization, whereas an elevated C-reactive protein at discharge predicted recurrence.[116] Other studies in adults reported that the procalcitonin level at admission in patients with urosepsis predicted bacteremia and bacterial load,[117] but did not predict adverse outcomes at 28 days.[118] The clinical use of these or other inflammatory markers for either the diagnosis or prognosis of acute pyelonephritis remains uncertain, and routine testing is currently not recommended.

INFECTION LOCALIZATION

The clinical presentation of acute pyelonephritis is often straightforward, and a diagnosis of renal infection can be made on the basis of clinical signs and symptoms. However, patients with asymptomatic bacteriuria or only lower tract symptoms may also have a renal infection. Table 23.4 summarizes selected studies performed to localize infections in adults with variable symptom presentations.[58–62] In these studies, as many as one-half of women with asymptomatic infections and a substantial minority of women with only bladder symptoms have a renal infection. However, no epidemiologic studies and few therapeutic studies of bacteriuria and its complications have attempted to prospectively localize renal bacteriuria so the clinical implications, if any, of upper tract localization are not clear. Currently, the localization of the site of infection has a clinical use only for the infrequent patient with relapsing infection where localizing the site of infection may influence clinical management. A large number and variety of different approaches for infection localization have been described (Table 23.5), but most of these methods are now of only historical interest.

Cystoscopy with ureteral catheterization is a direct approach to localization and continues to be the only definitive method for confirming renal localization. It also permits the localization of infection to one kidney and can identify different infecting organisms in each collecting system.[119] In practice, however, this procedure has limited usefulness. Careful urologic manipulation with meticulous attention to avoid contamination is required. A cystoscopy and ureteral catheter insertion are performed in an infected urinary tract because antibacterial therapy is withheld until the urine collections are complete. Infected bladder urine must be removed by repeated washing with sterile irrigating fluid before ureteral catheters are introduced through the bladder.[58] Otherwise, positive ureteral urine cultures may result from the carriage of infected bladder urine into the ureters during catheterization.

23.5 Methods Proposed to Identify Urinary Infection Localized to the Kidney

- Ureteral catheterization with differential urine cultures
- Intravenous pyelography/CT scanning
- Nuclear medicine imaging: ^{67}Ga citrate scanning/^{99}Tcm-DMSA scanning
- Bladder washout
- Renal biopsy with culture
- Fluorescent examination of renal tissue for bacterial antigen
- Serum antibodies to lipopolysaccharide antigen
- Urinary enzymes, cytokines
- C-reactive protein
- Serum procalcitonin
- Tamm-Horsfall protein antibodies
- Maximal renal concentrating ability
- Antibody-coated bacteria (ACB)
- Relapse following short course antimicrobial therapy

CT, computed tomography; Tcm-DMSA, technetium-dimercaptosuccinic acid.

The histopathologic examination of renal tissue obtained by a biopsy or at necropsy is another direct approach to the diagnosis of a renal infection. However, a kidney biopsy is contraindicated in the presence of an acute infection. In addition, pyelonephritis is a focal disease, and a random biopsy may not provide either a pathologic or bacteriologic diagnosis.[120] Percutaneous renal biopsies are seldom used to diagnose chronic pyelonephritis, and bacteriologic studies of renal tissue are rarely helpful. The nonspecificity of the histologic findings and their focal nature further limit the diagnostic use of biopsies because concomitant diseases may distort the gross and histologic features and may therefore make it impossible to attribute changes specifically to bacterial inflammation.

Imaging of the kidneys with ^{67}Ga citrate has been proposed to identify a renal infection. Hurwitz and associates[61] compared imaging with ^{67}Ga citrate to cultures obtained by ureteral catheterization or bladder washout in 47 patients and found a false-positive rate of 15% and a false-negative rate of 13% for the imaging procedure. Radioisotopic localization, particularly with ^{99}Tcm-DMSA, may be a more sensitive procedure for diagnosing a renal infection and assessing renal scarring.[121–123] These tests are often positive in patients with invasive upper tract infections, but are less reliable in those with asymptomatic infection.

The measurement of C-reactive protein has been used as a test to localize renal infections in symptomatic children,[124] but the specific level to differentiate upper from lower tract infections has varied among different studies and is not standardized.[125,126] Serum procalcitonin has also been studied to

diagnose pyelonephritis and UTIs in febrile infants and children. When compared to a DMSA scan, procalcitonin levels >0.5 to 0.6 pg per milliliter[127] had an average sensitivity of 85% and specificity of 76%. Urinary IL-6 is increased in children with acute pyelonephritis, with >15 pg per milliliter reported to have a specificity of 94% and a positive predictive value of 87.5%[128] for upper tract infections. None of these parameters, however, have yet been shown to be of use for routine clinical application.

Measurements of urinary enzymes, including urinary dehydrogenase, leucine aminopeptidase, α-glucuronidase, catalase, lactic dehydrogenase, lysozyme, and urinary α1 microglobulin, have all been reported to be useful for localization in at least one study, but not confirmed in subsequent studies to have adequate sensitivity or specificity to be a reliable diagnostic test. Other localizing methods used in previous studies have included the Fairley bladder washout technique,[60] a measurement of serum or urine antibodies to the infecting bacteria, and the fluorescent antibody-coated bacteria test.[129] None of these has proved to be of sufficient ease of use or reliability for clinical applications. Maximal urinary concentrating ability is reduced in many patients with renal bacteriuria. Fluid deprivation for 24 hours with the administration of antidiuretic hormone achieves maximum urinary concentration of more than 800 mOsm per kilogram of water in more than 80% of patients with bladder bacteriuria, but at least 70% of patients with renal infections are unable to concentrate urine to this level following maximal stimulation.[130] Urinary concentration, however, is altered in a number of pathologic states, and the test is not sufficiently sensitive or specific to be of value for an individual patient.

In practice, clinical presentations are used to assess the site of infection. Smeets and Gower[131] screened 43 symptomatic women with the bladder washout technique. Among these women, only fever higher than 38°C correlated with renal involvement. Two-thirds of the patients with upper tract infections were febrile at the time of localization compared to one-third of patients with lower tract infections. These studies and others suggest that no clinical criteria are uniformly reliable to localize the site of the infection.[132]

A short course of effective antimicrobial therapy will cure most uncomplicated bladder infections in women. It has been proposed that differential outcomes with short-course therapy may localize the site of the infection. Comparisons of single-dose therapy outcomes with other localization methods have documented an association between renal infections and failures of single-dose therapy.[133–135] However, single-dose therapy will fail in 10% to 20% of individuals with lower tract infections, and a small proportion of individuals with covert upper tract infections will be cured by short course therapy. For women with a normal genitourinary tract and repeated relapses following nitrofurantoin therapy, however, a renal localization of infections may be presumed because this agent is effective for sterilizing bladder urine, but it will not eradicate renal infection.

DIAGNOSTIC IMAGING

Acute Pyelonephritis

A plain abdominal film of the kidneys provides limited information in patients with presumed acute pyelonephritis. Renal calculi may be visualized, one or both kidneys may be enlarged, or gross changes such as hydronephrosis or renal atrophy may be apparent from the renal outline. Occasionally, perinephric gas or other changes in the retroperitoneal space provide diagnostic clues.[136] Other findings recognized on abdominal films may lead to diagnoses other than acute pyelonephritis, such as a perforated viscus.

Renal ultrasonography and computerized tomographic (CT) scanning have largely replaced IVP for the initial screening for genitourinary obstruction in patients with acute pyelonephritis.[137,138] In addition to identifying anatomic abnormalities and focal complications such as intrarenal or perinephric abscess, ultrasonography usually shows swollen kidneys, although this may only be appreciated by repeat scanning following antimicrobial therapy. The degree of renal enlargement on ultrasonography has been correlated with prolonged pretherapy symptoms, higher leukocyte counts, and prolonged hospitalizations.[137] However, ultrasonography is less sensitive or specific than CT or magnetic resonance imaging (MRI).[138]

An unenhanced CT scan is usually sufficient and will detect most calculi, gas forming infections, hemorrhage, parenchymal calcifications, obstruction, and inflammatory masses. A contrast-enhanced CT scan may be indicated in acute pyelonephritis if the differential diagnosis includes other intra-abdominal or retroperitoneal pathology, or if there is a delayed response to therapy and the ultrasound is normal or equivocal. With an unenhanced CT scan, global swelling of the infected kidney is present.[138] With contrast-enhanced CT scans, either an enlarged kidney with a uniformly homogeneous nephrogram, a striated parenchymal nephrogram, or wedge-shaped segmental defects are seen.[138] The striated pattern is caused by the localization of inflammatory cells and fluid within the collecting ducts. The wedge-shaped low-attenuation areas include renal parenchyma with impaired function caused by vascular spasm, tubular obstruction, or interstitial edema. Renal enlargement, delayed visualization, and a poor definition of calyceal architecture in the involved kidney are also common findings. Renal parenchymal volume increases by 25% to 50% during an episode of acute pyelonephritis and can take 4 to 6 weeks to regress.[139] For atrophic or chronic pyelonephritis, the involved kidney is irregular in outline and below average size unless hypertrophy has occurred owing to compensatory enlargement. A contrast-enhanced study is necessary to fully define changes in renal excretion that occur as a result of inflammation. A helical (or spiral) CT

scan can provide information addressing specific phases of contrast media excretion.[140,141]

An MRI is also used for the imaging of acute pyelonephritis.[141] Features are consistent with those observed with CT scans, including renal enlargement, perinephric stranding, focal decreased enhancement, and abscess cavities. Typically, an infected area has a low signal intensity on T1-weighted images and increased signal intensity on T2-weighted images with a loss of normal corticomedullary differentiation. The use of gadolinium is essential to correctly identify areas of renal involvement. An MRI may also differentiate acute infections from chronic scars. An MRI may be preferred for some patients because it does not require radiation or iodinated contrast material. A limitation of MRI, however, is poor discrimination for the interpretation of gas-forming collections or calculi.

In children, ^{99}Tcm-DMSA scintigraphy is more sensitive then ultrasound for detecting acute pyelonephritis, cortical lesions, and renal scarring.[140,143] Sattari et al.,[144] however, found contrast-enhanced CT scanning more accurate for identifying acute pyelonephritis than DMSA scintigraphy in adult populations. Small lesions and those localized to the inner layer of the renal cortex were present on the CT scan but were not appreciated with the lower resolution of scintigraphic images. Scintigraphy has also been evaluated in children as a predictor of outcomes at a longer term follow-up. Wallin et al.[145] reported that scintigraphy defects present at the time of an acute infection persist at 6 months in 34% of kidneys, and Agras et al.[146] reported that 38.2% of initial cortical lesions persisted at 6 months, and 17.6% at 12 months. Hitzel et al.[147] evaluated the quantitative analysis of DMSA scintigraphy to predict long-term renal scarring following acute pyelonephritis in children and reported the intensity of abnormality with DMSA scintigraphy at the time that an acute presentation was predictive of subsequent scarring.

The term nephronia refers to a renal mass confined to a single lobe, representing localized inflammation but without suppuration. It is thought to be an intermediate phase in the progression from inflammation to abscess.[148] Gallium scanning demonstrates an increased uptake in the area of the mass, which is usually accompanied by generalized increased activity elsewhere in the same or opposite kidney. Ultrasonography shows a sonolucent ovoid mass that disrupts the normal corticomedullary definition and produces low-level echoes. These findings permit differentiation of nephronia from renal abscess or tumor. In adults, this finding may occur more commonly in diabetics. In children, the presence of acute lobar nephronia was reported to be associated with an increased incidence of renal scarring.[149] Identification of this abnormality on imaging studies, however, does not alter therapeutic approaches.[138]

Radiologic changes induced by acute inflammation are usually reversible with antimicrobial treatment.[61,137,149,150] However, a progressive reduction in renal size or the development of a scar may follow an episode of acute pyelonephritis.[149,150] Scars may involve an entire pole of the kidney or, in patients with atrophic pyelonephritis, the entire kidney. The upper pole is the most common site for scars. In serial studies, the initial abnormality was the loss of the renal cortex, with the renal parenchyma becoming thinned. Calyceal clubbing then developed as the renal papilla is retracted into the scar. The cup of the calyx is no longer a "cup," because the papilla does not project into it. In adults with acute pyelonephritis on a CT scan or an MRI at presentation, a focal lesion with peripheral ring enhancement and without central contrast uptake correlated with subsequent scar development.[150] In men and women with acute nonobstructive pyelonephritis and hypodense images on a CT scan at presentation, abnormalities persisted at the follow-up CT scan in 10 of 44 people.[151] In another study, persistent abnormalities were reported at follow-up in 29% of 55 adult women hospitalized with acute pyelonephritis.[150] Early scar formation was present in two patients, whereas two patients with atrophy had renal biopsies that showed chronic interstitial nephritis.

Indications for Radiologic Investigation

Imaging studies of the genitourinary tract for patients presenting with acute pyelonephritis should be selective.[140] Indications for imaging in individuals with suspected acute pyelonephritis include: (1) to assist with the diagnosis of acute pyelonephritis; (2) to assess whether there are underlying abnormalities present that may require intervention; (3) to assess the severity of infection, including identifying abscesses or emphysematous infections; or (4) in follow-up, to determine the extent of persistent damage such as renal scarring. Patients with atypical presentations, with severe sepsis or septic shock in whom obstruction must be excluded, or with a delayed response to therapy should have prompt imaging studies. Radiologic investigations should also be considered in patients who relapse shortly after discontinuing an adequate course of antimicrobial therapy.

Among 170 patients (163 women, 7 men) with acute pyelonephritis for whom an intravenous pyelogram was routinely obtained, 85 had normal pyelograms and 75 had structural or functional abnormalities that were attributable to the acute infection or represented a risk for relapse, but only 10 (5.9%) had specific disorders identified that resulted in a change of management.[152] In an Australian report, only 1 of 74 patients with acute pyelonephritis who had imaging with an ultrasound or a CT scan at admission had an abnormality identified that required an immediate intervention.[153] van Nieuwkoop et al.[154] prospectively identified patients presenting with febrile urinary infection to eight emergency departments in the Netherlands. There were 346 episodes, 140 (41%) in men, and 138 of these episodes (40%) were considered complicated. For all cases, 245 had an ultrasound or a CT scan; 6% of these showed urologic disorders requiring urgent intervention (pyonephrosis), 32 (13%) had nonurgent urologic disorders (nonobstructive renal stones, urologic malignancy, ureteropelvic junction stenosis, enterovesicle fistula), 175 (71%) had clinically irrelevant or normal results, and 24 (10%) had incidental nonurologic

disorders. They reported that a history of urolithiasis, urine pH ≥7.0, and renal insufficiency were the only variables predicting an abnormality on imaging.

Although contrast-enhanced CT scanning is the preferred imaging test for upper tract infection in adults, renal ultrasonography is rapid and noninvasive and may be more accessible. The intravascular injection of radiologic contrast media has risks of hypersensitivity or contrast media–induced renal failure. The concomitant presence of diabetes mellitus, particularly with renal impairment, is a relative contraindication. In children, the initial screening with ultrasonography or DMSA scintigraphy detects scarring and other renal abnormalities.[121,123] Investigations should be performed in any male infant or boy with a proven bacterial urinary infection, and in girls with a recurrent or complicated infection.[155] A voiding cystourethrogram is added for young children or if there is evidence of upper tract disease.

Unless specific new indications emerge in a given patient, serial periodic imaging studies are redundant in adults with recurring infection. Even among patients with a prior radiologic evidence of chronic pyelonephritis, the development of new findings is unusual.[88] Upper tract pathology rarely develops after the age of 1 year in adequately treated children, and repeated examinations are seldom indicated.[156]

CLINICAL PRESENTATION

Infants and Children

In the neonatal period, UTIs usually present as sepsis. The clinical picture, however, can vary from life-threatening septic shock in association with pyelonephritis to asymptomatic bacteriuria.[21] Nonspecific symptoms potentially associated with urinary infections in infants include fever; inadequate weight gain; gastrointestinal symptoms such as anorexia, emesis, diarrhea, and paralytic ileus; meningitis; seizures; lethargy; irritability; hypotonicity; respiratory irregularity; pallor; cyanosis; abdominal distention; gray skin color; and jaundice. Studies have identified jaundice as the hallmark of ongoing infection in the neonate. The frequent occurrence of generalized sepsis, premonitory symptoms prior to the onset of bacteriuria, and necropsy findings demonstrating cortical infection in the presence of a normal renal pelvis support a hematogenous route of renal infection in neonates. The predominance of males is unexplained. The intestinal tract is the presumptive source.

In older children, the clinical features of urinary infection more closely approximate those in adults.[21] As girls mature, abdominal tenderness, vaginal discharge, vomiting, and anorexia become less common features and fever and flank pain predominate. Asymptomatic UTIs in childhood occur almost exclusively in females.

Adults

The classic clinical presentation of acute upper UTIs in adults include fever, often over 38.5°C, chills, unilateral or bilateral pain in the lumbar flank region, and variable systemic symptoms, including malaise, anorexia, nausea, emesis, diarrhea, myalgia, and headache. The illness may progress rapidly, and many patients seek care within 24 hours of the onset of symptoms. Between 15% and 30% of patients experience concomitant symptoms consistent with a lower UTI, including dysuria, frequency, urgency, and suprapubic discomfort. Renal pain may radiate to the epigastrium or the lower abdominal quadrants. Severe flank pain with radiation to the groin is unusual and suggests a ureteral obstruction. Gastrointestinal symptoms, primarily nausea, vomiting, and diarrhea, occur frequently and predominate in about 10% of patients. Although patients presenting with acute pyelonephritis may be severely ill, the spectrum of disease also includes individuals with low-grade or no fever or only mild flank discomfort. Flank pain or discomfort on palpation or fist percussion is usually present. The physical findings are variable, however, ranging from mild discomfort to severe pain or systemic symptoms including septic shock.

Other diseases, both above and below the diaphragm, can mimic the pain of acute pyelonephritis. The differential diagnosis includes acute bacterial pneumonia, appendicitis, cholecystitis, a perforated viscus, diverticulitis, splenic infarction, acute pancreatitis, and aortic dissection. Acute pelvic inflammatory disease may be misdiagnosed as acute pyelonephritis and should be excluded by a pelvic examination in women at risk of sexually transmitted infections. Varicella-zoster virus reactivation (shingles) in an appropriate dermatome can also mimic renal pain. Renal infarction, acute renal vein thrombosis, obstructive uropathy, and acute glomerulonephritis may each have a clinical presentation that can be confused with acute pyelonephritis.

Pinson and colleagues[105] assessed the use of fever in differentiating acute pyelonephritis from other potential diagnoses. In a retrospective chart review, 93% of women who presented to the emergency department with pyuria and other findings consistent with acute pyelonephritis including leukocytosis, costovertebral angle tenderness, and two or more of abdominal pain or tenderness, back pain, and history of nausea and vomiting, were ultimately diagnosed with acute pyelonephritis when fever was also present. When fever was not present, 35% of hospitalized women with this constellation of symptoms ultimately had an alternate diagnosis. All nonhospitalized patients with fever were ultimately diagnosed with pyelonephritis, but 13% without fever had an alternate diagnosis. They concluded that when patients present with findings compatible with acute pyelonephritis but without fever there should be a high index of suspicion for an alternate diagnosis.

The presenting clinical features of pregnant women are similar to those in nonpregnant women. Septic shock may occur, and acute respiratory distress syndrome is reported in 1% to 8% of these women.[92] Patients with diabetes mellitus may present with deteriorating glycemic control. Renal infections in patients with diabetes mellitus and hyperglycemia may, rarely, present as emphysematous pyelonephritis

owing to carbon dioxide production from fermentation of glucose by gram-negative rods.[136,157] Acute pyelonephritis in patients with diabetes may also be accompanied by papillary necrosis. Fragments of the renal papillae can block the ureter, producing colic and hydronephrosis, often accompanied by gross hematuria. In elderly patients, symptoms of a urinary infection may be more difficult to ascertain and chronic symptoms of dysuria, frequency, urgency, and incontinence often occur unrelated to infection. Flank tenderness is less common in elderly patients, and acute confusion, sometimes with other neurologic symptoms or signs, is more common relative to younger age groups. Despite this, classic features of upper tract infections do occur in most elderly patients with acute pyelonephritis.

The clinical manifestations of chronic pyelonephritis are usually nonspecific. Some patients have recurrent acute symptomatic exacerbations of renal infection. Others have no clear-cut symptoms of infection despite persistent bacteriuria. Sometimes, patients may complain of vague flank discomfort, abdominal pain, or intermittent low-grade pyrexia. The improvement of symptoms after a trial of antimicrobial therapy may clarify an association between mild symptoms and a persistent renal infection.

TREATMENT OF UPPER TRACT INFECTIONS

Therapeutic Principles

The following should be considered whenever an upper urinary infection is diagnosed and treated:

1. A laboratory confirmation of infection is essential. The clinical findings of an invasive upper tract infection can be mimicked by many illnesses and, for patients with pyelonephritis, the antimicrobial susceptibility of infecting organisms must be determined to facilitate optimal therapy.
2. Bacteriuria by itself is a nonspecific finding. Patients with asymptomatic bacteriuria, particularly elderly patients and patients with indwelling catheters, frequently have bacteriuria but without renal infection being present or as a cause for acute clinical deterioration.[3]
3. The initial antimicrobial selection is based on known or presumed organism susceptibility and patient tolerance. The clinical evidence base to support any specific regimen is limited. Many clinical studies enroll patients presenting with both acute nonobstructive pyelonephritis and complicated urinary infection, and the relevance of reported outcomes to acute pyelonephritis alone is difficult to assess.
4. An antimicrobial that provides adequate blood and tissue levels as well as a high urinary level is preferred for the treatment of invasive renal infection. Agents that provide high sustained medullary antimicrobial levels are more effective for upper tract infections.[158]
5. Suppurative and obstructive complications frequently complicate acute pyelonephritis, occurring in 5% to 15% of cases. Patients who present with life-threatening infection, who do not respond within 72 hours of antimicrobial therapy, who deteriorate after therapy is started, or who rapidly recur after therapy is discontinued must be investigated urgently to exclude an obstruction or abscesses that require surgical intervention.
6. If the urine culture subsequently reports growth of an organism resistant to the empiric antimicrobial therapy, the antimicrobial should be changed to a susceptible agent even if there has been a clinical response. Despite apparent improvement, these patients will usually rapidly relapse following the discontinuation of antimicrobial therapy.[13,159]
7. Clinical improvement may not equate with the permanent eradication of bacteriuria. A urinary infection is usually a recurrent disease and patients should be aware of this possibility. However, follow-up urine cultures are not necessary to document a bacteriologic cure unless symptoms recur or if the patient is pregnant.

Acute Pyelonephritis

A suspected clinical diagnosis of acute pyelonephritis requires an urgent assessment and the prompt institution of therapy. Appropriate diagnostic tests, including a urine culture prior to antimicrobial therapy, complete blood count (CBC) and creatinine for all cases, and blood cultures for subjects with more severe presentations, should be obtained. In addition to the prompt institution of empiric antimicrobial therapy and appropriate supportive measures, initial therapeutic decisions include whether hospitalization is required and whether early diagnostic imaging studies are indicated to exclude an obstruction or other complicating factors (Fig. 23.1).

Hospitalization

Only 10% to 30% of nonpregnant women with acute uncomplicated pyelonephritis will require hospitalization[160]; a higher proportion of individuals with a complicated urinary infection presenting as pyelonephritis require hospitalization. Patients with severe clinical presentations, including severe costovertebral angle pain, rigors, high fever (>38.5°C), severe nausea or vomiting, and hemodynamic instability should be hospitalized for the initial investigation and parenteral antibacterial treatment. Intravenous fluids, analgesics and antiemetics, and bed rest are usually prescribed during the initial 24 to 48 hours. Hypotension and diminished urine output should be identified early and managed appropriately. Patients with severe sepsis or septic shock should be cared for in a critical care unit. Women who are pregnant or for whom there is diagnostic uncertainty require a more careful follow-up, and hospital admission is recommended in these cases. Where it is unclear whether hospitalization is necessary, an initial dose of parenteral therapy with observation for 12 to 24 hours is an alternate approach. If the

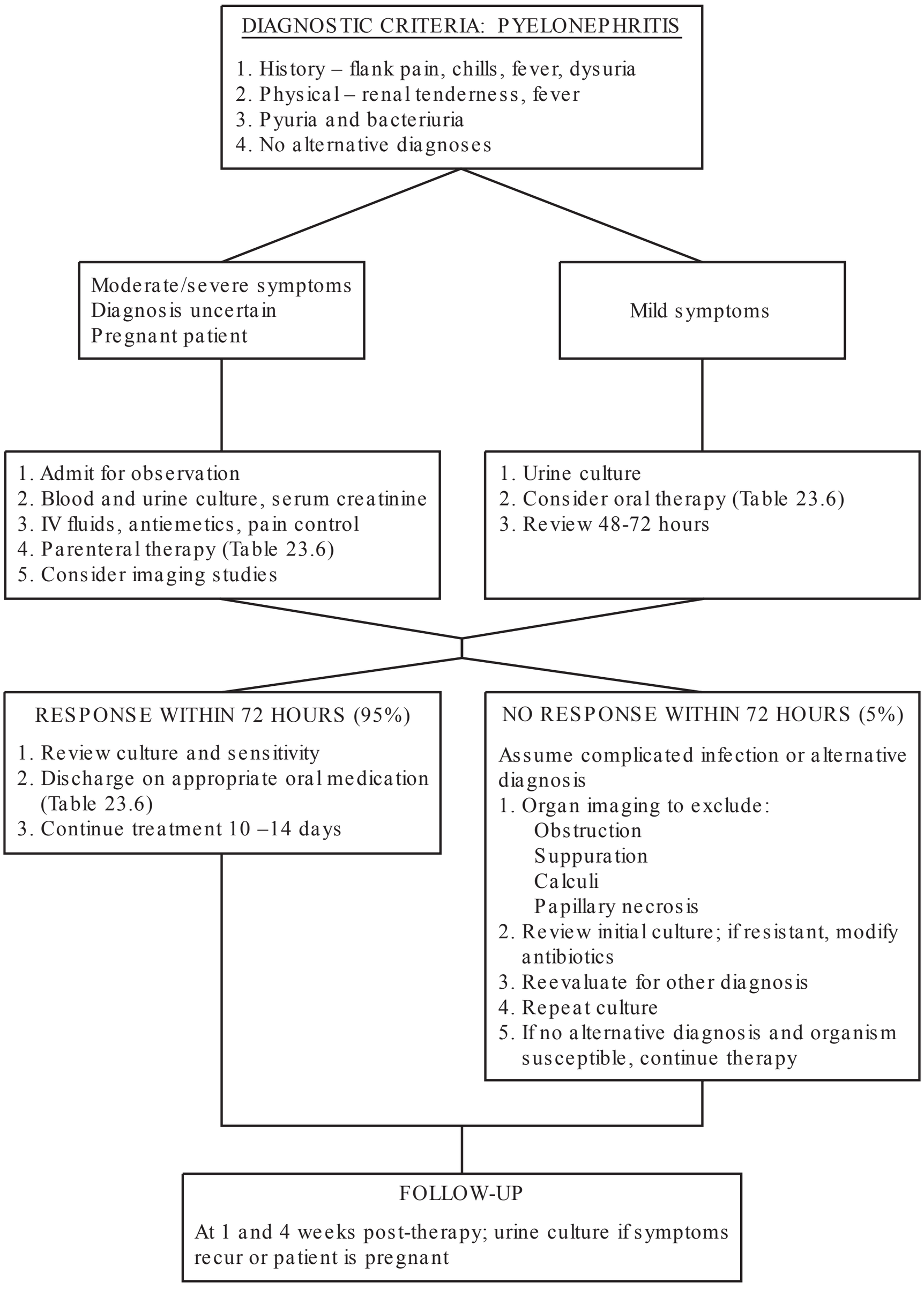

FIGURE 23.1 The management of pyelonephritis.

patient is stable without nausea or vomiting after the initial parenteral therapy and management of systemic symptoms, a discharge home to complete oral therapy is appropriate.

Patients with acute pyelonephritis may be only mildly or moderately symptomatic with low-grade fever, mild flank pain, and few constitutional symptoms. These patients may be managed as outpatients with an oral antimicrobial regimen (Fig. 23.1).[160,161] Specific criteria to identify patients for whom outpatient therapy is appropriate include those who are hemodynamically stable, those who are able to tolerate oral medications, those who are anticipated to be compliant, and those with absent or low-grade fever (38°C or less).

Several studies report similar outcomes for parenteral and oral therapy, with unsatisfactory outcomes in 10% of either group.[10,160,161] Pinson and associates[11] reviewed management and outcomes of 111 febrile women presenting to an emergency room with acute pyelonephritis. Eighty three (75%) were not hospitalized. Women hospitalized for management were older, more frequently had diabetes or known genitourinary abnormalities, and were more ill, as evidenced by vomiting and a higher temperature. Management of nonhospitalized patients usually included a single parenteral antimicrobial dose followed by oral therapy.[11] Nine (12%) of 75 outpatients returned in the follow-up with continuing symptoms of acute pyelonephritis, usually within 24 hours, and 7 of these subsequently required admission but were ultimately cured. The authors concluded that most febrile women with acute pyelonephritis could be treated as outpatients, but an early follow-up after initiation of therapy was recommended. Elkharrat et al.[161] used an algorithmic approach for women presenting to the outpatient department with acute pyelonephritis. All patients received a single intravenous dose of a fluoroquinolone after cultures were obtained, and had an ultrasound examination of the abdomen and pelvis. Patients with normal ultrasonography could be discharged. Of 68 patients, 10 were discharged directly from the emergency ward, 48 after a 12 to 24 hour stay in the observation unit, and 10 were hospitalized. Favorable outcomes occurred in all but one woman.

Parenteral Antimicrobial Therapy

Initial empiric parenteral therapy is indicated for patients with severe symptoms or who cannot tolerate oral therapy. The goal is to step down to oral therapy as soon as the patient is clinically stable and urine culture results are available, usually 48 to 72 hours after the initiation of therapy. A full course of parenteral therapy is necessary only for patients who continue to be unable to tolerate oral therapy or who are infected with a resistant organism for which no oral therapy is available.[162] The Infectious Diseases Society of America (IDSA) guidelines provide evidence-based recommendations for empiric antimicrobial therapy.[163] An aminoglycoside with or without ampicillin, parenteral fluoroquinolone, or extended spectrum cephalosporin or penicillin are recommended as first-line parenteral antimicrobial options. Any empiric regimen for initial treatment of patients with acute pyelonephritis should include in its antibacterial spectrum at least 95% of the potential organisms in the population treated. The selection of a "standard" antimicrobial regimen for empiric therapy requires knowledge of antimicrobial susceptibilities in the community or the individual facility.

A standard approach for initial therapy, pending culture and susceptibility results, is an aminoglycoside, such as gentamicin or tobramycin, in a dose of 3 to 5 mg per kilogram every 24 hours, combined with ampicillin 1 g every 4 hours (Table 23.6). The ampicillin therapy provides coverage for E. faecalis, an uncommon pathogen in younger populations. For the penicillin-allergic patient, an aminoglycoside alone may be adequate empiric parenteral therapy. Aminoglycoside-related nephrotoxicity and ototoxicity are unusual if high sustained trough levels are avoided and the duration of therapy is 4 days or less. Aminoglycoside levels should be monitored if the patient has

23.6 Selected Therapeutic Regimens Appropriate for the Treatment of Pyelonephritis in Patients with Normal Renal Function

Parenteral Therapy
Recommended
Ampicillin,[a] 1 g q4–6h plus aminoglycoside (gentamicin, tobramycin, or netilmicin at 3–5 mg/kg q24h, or amikacin 15 mg/kg q24h)
Ceftriaxone, 1–2 g q24h
Ciprofloxacin, 400 mg q12h
Levofloxacin, 500–750 mg OD
Alternatives
Cefotaxime, 1 g q8h
Ceftazidime, 1 g q8–12h
Ceftizoxime, 1 g q8–12h
Aztreonam, 1 g q8h
Piperacillin-tazobactam, 3.375 g q8h
Ticarcillin-clavulanate, 3 g/100 mg q4h
Ampicillin-sulbactam, 2 g/0.5–1.0 g q6h
Piperacillin, 2 g q6h plus aminoglycoside
Ofloxacin, 200–400 mg q12h
Meropenem, 500 mg–1g q8h
Ertapenem, 1g OD
Oral Therapy
Recommended
Norfloxacin, 400 mg b.i.d.
Ciprofloxacin, 500 mg b.i.d.
Levofloxacin, 500 mg or 750 mg OD
Alternatives
Amoxicillin, 500 mg t.i.d.[a]
Amoxicillin-clavulanate, 500 t.i.d. or 875 mg b.i.d.
Cefuroxime axetil, 500 mg b.i.d.
Cefixime, 500 mg OD
Cephalexin,[b] 500 mg q.i.d.
Ofloxacin, 400 mg b.i.d.
Trimethoprim-sulfamethoxazole,[b] 160/800 mg b.i.d.
Trimethoprim,[b] 100 mg b.i.d.

[a] For Enterococcus spp. or Streptococcus spp.
[b] If the organism is known to be susceptible.
q, every; h, hour; b.i.d., twice a day; t.i.d., three times a day; OD, once daily; q.i.d., four times a day.

renal impairment or will be continued on therapy longer than 5 days. Trough levels should not exceed 2 μg per milliliter for gentamicin and tobramycin or 5 μg per milliliter for amikacin. If a high prevalence of resistance to gentamicin or tobramycin is present, amikacin may be the aminoglycoside of choice for empiric treatment, especially for nosocomial pyelonephritis where more resistant isolates may be anticipated.

Parenteral fluoroquinolones such as ciprofloxacin, ofloxacin, and levofloxacin are also useful agents for the treatment of acute pyelonephritis.[163] The extended spectrum cephalosporins, including ceftriaxone, cefotaxime, ceftizoxime, and ceftazidime, have each been studied as single-agent alternatives to the combination of ampicillin and an aminoglycoside, with cure rates for acute pyelonephritis of about 90% in patients with normal renal function and a normal urinary tract.[163–165] The addition of an aminoglycoside to extended spectrum therapy with cefotaxime did not improve outcomes in women with acute pyelonephritis.[166] Cefazolin should not be used alone for the empiric treatment of invasive renal infection owing to the relatively high prevalence of resistance to first-line cephalosporins among community-acquired and nosocomial pathogens.[163]

Extended spectrum penicillin derivatives have been prospectively compared to the aminoglycoside with ampicillin regimen (Table 23.4).[163–165] In clinical studies reported to date, all regimens appear equivalent. Piperacillin is preferred over the third-generation cephalosporins if Pseudomonas aeruginosa and Enterococcus faecalis are probable etiologic agents. Piperacillin should generally be used in combination with an aminoglycoside but piperacillin/tazobactam may be used alone. Aztreonam is a monobactam β-lactam antibiotic, with an antibacterial spectrum limited to aerobic gram-negative rods, including P. aeruginosa.[167] It has been used successfully to treat patients with acute pyelonephritis. The β-lactam inhibitors in combination with a β-lactam antibiotic are also effective and equivalent to other regimens, and may be drugs of choice for hospital-acquired infections where resistant organisms are a concern. Piperacillin-tazobactam, ampicillin-clavulanic acid, and ticarcillin-clavulanic acid are all effective regimens. The prevalence of infections with an extended spectrum β-lactamase producing E. coli is increasing globally. These strains, if suspected, require empiric treatment with a carbapenem: meropenem, ertapenem, or dorapenem.[168,169] Vancomycin may be required to treat enterococci or staphylococci resistant to the β-lactam antibiotics. Newer parenteral antimicrobial agents are more expensive than the standard therapy of ampicillin plus aminoglycoside and, for susceptible organisms, have not been shown to have improved outcomes. Potential therapeutic advantages must be weighed against the increased expense.

Oral Antimicrobial Therapy

The IDSA guidelines recommend a fluoroquinolone for the initial oral empiric treatment of pyelonephritis.[163] Ciprofloxacin, norfloxacin, ofloxacin, and levofloxacin are all efficacious for the treatment of acute pyelonephritis; fluoroquinolones with limited renal excretion, such as moxifloxacin, should be avoided. Clinical trials document the effectiveness of ciprofloxacin 500 mg twice daily or 1,000 mg extended release daily[13] or levofloxacin 500 to 750 mg daily for acute, uncomplicated pyelonephritis.[170]

A randomized clinical trial compared oral trimethoprim/sulfamethoxazole (TMP/SMX) for 14 days or oral ciprofloxacin for 7 days in 378 women with acute pyelonephritis.[13] For either regimen, an initial parenteral dose of ceftriaxone or ciprofloxacin, respectively, could be given. Therapy was not modified once antimicrobial susceptibilities were obtained (i.e., therapy with TMP/SMX was continued even if the infecting isolate was found to be resistant). The regimens were equally effective when the infecting organism was susceptible to the antimicrobial given. However, TMP/SMX therapy was not effective when given by itself to patients with TMP/SMX-resistant organisms so a higher rate of resistance of E. coli to trimethoprim/sulfamethoxazole resulted in the ciprofloxacin arm being superior overall, with a 96% cure rate at 4 to 11 days and 85% at 22 to 44 days posttherapy. Thus, TMP/SMX is effective therapy but, given the relatively high prevalence of resistance of community-acquired E. coli, this agent is recommended only when the infecting organism is known to be susceptible.

Stamm and colleagues[14] compared 2- and 6-week oral regimens of TMP/SMX or ampicillin for the outpatient management of women with pyelonephritis. They found TMP/SMX to be superior to ampicillin for both treatment durations; the 6-week regimen did not improve cure rates. For TMP/SMX, 83% to 90% of women remained cured at 6 weeks following the discontinuation of antibiotics. Amoxicillin by itself should not be used for nonenterococcal or nonstreptococcal infection because of high community rates of resistance to gram-negative organisms and a tendency to promote colonization with resistant organisms that may cause subsequent infections.[163] However, amoxicillin in combination with the β-lactamase inhibitor clavulanic acid can be prescribed as an oral regimen for selected resistant organisms.

Cronberg et al.[171] enrolled 171 patients, about 60% of whom were women with acute pyelonephritis, into a comparative study of initial cefuroxime for 2 to 3 days followed by ceftibuten 200 mg twice a day (b.i.d.) or norfloxacin 400 mg b.i.d. to complete 10 days once the fever had subsided and the culture results were available. The norfloxacin treatment arm was superior for the eradication of bacteriuria. Sanchez et al.[172] enrolled 105 women into a study comparing ceftriaxone 1 g daily for 10 days or a single initial dose of ceftriaxone followed by oral cefixime for 9 days. The cure rate was 91% for both groups.

Pregnant Women

It is recommended that pregnant women with acute pyelonephritis should be admitted to the hospital, at least for the first several days, to ensure an adequate response to antimicrobial therapy and pending culture results confirming the

infecting organism and susceptibilities.[92] Parenteral outpatient therapy with close monitoring is an option for selected patients in the first and early second trimester.[92] Recommended empiric parenteral regimens are ceftriaxone or an aminoglycoside with or without ampicillin. A prospective, randomized trial of intravenous ampicillin and gentamicin, intravenous cefazolin, or intramuscular ceftriaxone found all three to be equally effective for the parenteral treatment of acute pyelonephritis in pregnancy.[173] Gentamicin has been widely used in pregnant women with no evidence for congenital complications.[92] Extended spectrum penicillins may also be used. Ampicillin or cefazolin, by themselves, are not currently recommended because of the high prevalence of antimicrobial resistance in community isolates. Fluoroquinolones are avoided in pregnancy because of adverse fetal effects, and TMP/SMX should be avoided in the first trimester.

Children

Approaches to the antimicrobial management of acute pyelonephritis in children have recently been critically reviewed in a Cochrane collaboration report.[174] This concluded that initial oral compared with parenteral antimicrobial therapy had similar short-term outcomes of the duration of fever and long-term outcomes of persistent kidney damage at 6 or 12 months. In addition, there was no difference in persistent kidney damage when intravenous was followed by oral therapy or only intravenous therapy was given, each for 7 to 14 days. There was also no difference in outcomes with once or thrice daily aminoglycoside dosing. Thus, the selection of parenteral or oral therapy, or whether to initiate a short initial course of intravenous therapy and complete with oral therapy or treat with oral therapy alone, should be based on clinical evaluation. Infants aged 1 month or less require hospitalization for treatment and investigation because of the very high prevalence of concomitant bacteremia and urologic abnormalities.

For parenteral therapy, aminoglycosides or a third-generation cephalosporin are preferred, with TMP/SMX or amoxicillin/clavulanic acid as first-line agents for oral therapy.[175] Fluoroquinolones are avoided because of potential adverse effects on cartilage. Outpatient parenteral therapy is an option.[176] Although the early treatment of infants and young children will limit the duration of acute symptoms, the earlier institution of antimicrobial therapy has not been shown to decrease the subsequent development of renal scars.[177,178]

The Duration of Therapy and Follow-Up

The appropriate duration of therapy to achieve optimal cure rates in patients with acute pyelonephritis is uncertain, and may differ depending on the antimicrobial used. A minimum of 2 weeks of therapy has been routinely recommended, but 10 days is clearly sufficient in many clinical studies[172] and 7 days of ciprofloxacin[13] or 5 days of levofloxacin[170] have been as effective as longer courses of treatment in controlled clinical trials.

Behr et al.[179] reported, in a series of patients admitted with both complicated and uncomplicated acute pyelonephritis, that 26% remained febrile at 48 hours and 13% remained febrile at 72 hours. The median duration of fever was 34 hours. Johnson et al.[106] reported that 30% of women with acute uncomplicated pyelonephritis remained febrile at 2 days, but virtually all were afebrile by 72 hours. Thus, most patients become afebrile within 72 hours following the initiation of therapy; other clinical findings, including renal-angle tenderness, also rapidly improve.

Treatment in the Presence of Impaired Renal Function

In the management of patients with impaired renal function, antimicrobials, which are effective despite decreased renal perfusion, should be selected, whereas agents that might further compromise function should be avoided if possible. Antimicrobial therapy may ameliorate symptoms but frequently will not cure the infection in the presence of moderate-to-severe renal impairment, presumably because of the failure of antimicrobials to access the site of bacterial infection. Long-term suppressive therapy with an oral antimicrobial may be required in selected cases for the management of recurrent symptomatic episodes.

The β-lactam antibacterials have little dose-related toxicity and are relatively safe in patients with renal failure. Patients with impaired renal function are at increased risk of seizures with imipenem and encephalopathy with cefepime. Interstitial nephritis occurs rarely in patients receiving β-lactam antibacterial agents, but the risk of this complication is not increased by coexisting renal impairment. A dose adjustment for renal impairment is required for most β-lactam agents. No untoward consequences of trimethoprim prescribed without sulfonamide have been reported in patients with moderately advanced renal impairment. The fluoroquinolone antimicrobials—ciprofloxacin, ofloxacin, and levofloxacin—are also effective in renal failure. Dosage adjustments are required for patients with creatinine clearance rates less than 30 mL per minute.

Aminoglycosides should be avoided in patients with renal impairment. In the presence of unstable renal function, a rise in blood urea or creatinine levels may be incorrectly attributed to an aminoglycoside. Doxycycline is relatively safe in renal impairment but usually fails to achieve adequate urine levels. Other tetracyclines are contraindicated. Sulfonamides have been associated with a further loss of renal function and should not be used. Methenamine mandelate or other organic salts also are contraindicated in patients with renal impairment.

Recurrent Upper Tract Infection

In prospective studies, about 5% to 10% of women with acute pyelonephritis have a relapse with the initial infecting organism within 4 weeks of completing therapy.[13,14,170,171] Women with acute nonobstructive pyelonephritis are also

at increased risk of both upper and lower tract urinary reinfection, especially within the first year following the initial episode.[51,52] About 50% of patients with urinary infections in the setting of structural or functional genitourinary abnormalities (Table 23.2) recur with either upper or lower tract infection by 6 weeks after therapy, although most recurrences are asymptomatic. The pattern of recurrence is a predictor of infection site, with relapses predictive of renal infections in women and renal or prostate infections in men. For women with a symptomatic relapse, renal infection is presumed and retreatment with a 2-week course of antimicrobial therapy results in cure for most of those with a normal genitourinary tract. Longer courses of antimicrobial therapy (4 weeks or more) may be considered in patients with repeated relapsing symptomatic infections and chronic renal failure or where progressive renal damage is a concern. Men without upper tract abnormalities and with relapses should receive retreatment for 4 to 6 weeks for presumed prostate infection,[180] as prostate localization is the more likely source of relapsing infections in men.

Several principles should be considered in all patients with recurrent infections:

1. The urine culture becomes negative shortly after the institution of effective chemotherapy.[181] The isolation of any quantitative count of the initial infecting organism while antibiotics are being taken is a failure of therapy. Bacterial persistence with positive urine cultures occurs due to inadequate levels of the antimicrobial agent in the urine, the presence of resistant organisms, or patient noncompliance. Continuing the same antimicrobial regimen, even with a clinical response, is inappropriate if urine cultures remain positive with the same pretherapy isolate and if the patient has been compliant.
2. Relapse is frequently associated with urologic abnormalities. Infected renal cysts, calculi, indwelling devices, prostate infection, and a nonfunctioning kidney allow organisms to persist in sites where effective antimicrobial levels are not achieved.[180,182] Patients with relapses require a careful reevaluation including radiologic and urologic investigation. In the absence of urologic or radiologic abnormalities, many women who have a relapse can be cured with a sufficiently prolonged course of therapy. On the other hand, infection recurs in patients with calculi in the kidneys, prostate infection, or a nonfunctioning kidney, even following prolonged treatment courses of several months or years.
3. Clinical trials of the treatment of urinary infections in men have not generally localized infection to the prostate or kidneys; some may have infections at both sites. Owing to the frequency of complicating urologic abnormalities in men with urinary infection, attempts to define a homogeneous group with renal infections and to determine treatment responses have generally been unsuccessful. Treatment should be undertaken only if recurring symptoms or complicating disease suggest these men are at risk of morbidity from infection. A very prolonged course of therapy with TMP/SMX or a fluoroquinolone for 4 to 12 weeks should be prescribed to eradicate a persisting but curable renal or prostate focus. Even with prolonged fluoroquinolone treatment, however, a cure is obtained in 70% or less of men with chronic prostate infection.[180]
4. Antimicrobial concentrations in renal tissue and urine may be markedly diminished in patients with impaired renal function caused by acute or chronic parenchymal renal disease or obstruction. In patients with unilateral renal impairment, the antimicrobial concentration of some agents may be inadequate to inhibit bacterial growth or sterilize urine originating from the diseased kidney.[183] The contralateral normal or hypertrophied kidney may be excreting the antibacterial agent effectively, so the drug does not accumulate in the serum. Excretion of the antimicrobial agent in the urine from the healthy kidney may be adequate to sterilize the bladder urine and make it appear that the bacteriologic outcome is satisfactory despite persistent or continuing bacterial multiplication in the diseased kidney.
5. Patients with frequent reinfections have altered bacterial flora, reflecting the impact of repeated courses of antibacterial agents on the fecal reservoir.[163] Sulfonamides, penicillins, cephalosporins, and fluoroquinolones eradicate susceptible gram-negative organisms within the intestinal tract, which may be replaced by resistant Enterobacteriaceae or Pseudomonas spp. Broad-spectrum antimicrobial agents preferentially excreted in the bile have a greater impact on the fecal flora than do agents preferentially excreted in the urinary tract. The "next infection," if it occurs within a few months, often will be caused by an organism that is resistant to the therapeutic regimen previously prescribed. With frequent reinfections, particularly in patients with devices such as ureteric stents or an indwelling catheter, the pathogens become progressively resistant to antimicrobial therapy.
6. The treatment of asymptomatic bacteriuria should be avoided except for bacteriuria in pregnancy or prior to an invasive urologic procedure likely to be associated with trauma to the genitourinary mucosa.[3] Following from this, posttherapy urine cultures should only be obtained if there is a symptomatic recurrence.
7. Patients with long-term indwelling suprapubic or urethral catheters are always bacteriuric. Although transient suppression may occasionally yield a negative urine culture, bacteriologic failure is predictable. These patients should only be treated for symptomatic episodes, as efforts to prevent infection with continuous suppressive antibacterial regimens select multiply resistant organisms and have not been shown to prevent morbidity.[184]

8. The successful treatment of struvite stones requires the complete eradication of all stone material. Antimicrobial therapy is an adjunct to maintain sterile urine while a complete stone dissolution is achieved. Advances in the endourologic treatment of infected renal calculi make it possible for most patients with renal stones to be treated with complete removal of all calculous material. The necessary duration of antimicrobial therapy following lithotripsy, however, is controversial.

THE PREVENTION OF PYELONEPHRITIS

Some women with recurrent acute uncomplicated urinary infections may present as recurrent pyelonephritis, although this pattern is uncommon. Subsequent infections in these women can be effectively prevented by chemoprophylactic regimens. The most important intervention to prevent infections in patients with complicated urinary infections is to correct or optimize management of the underlying abnormality that is promoting infection. Recurrent symptomatic infections from a renal or prostate focus in selected patients with abnormalities that cannot be corrected may be suppressed indefinitely without "cure" by long-term treatment with suppressive antimicrobial regimens. Immunization has also been explored for the prevention of recurrent urinary infections. Animal studies have reported some success for the prevention of both cystitis and pyelonephritis through vaccination with E. coli antigens, but effectiveness in humans is not yet documented.[17,185]

Antimicrobial Prophylaxis

Prophylaxis of symptomatic acute uncomplicated cystitis or nonobstructive pyelonephritis in women is highly effective (see Chapter 22). Prophylactic antimicrobial therapy is an option for children[186] or women[187] who experience three or more episodes of symptomatic infections, either cystitis or pyelonephritis, within 1 year. Effective and widely used regimens include nitrofurantoin 50 mg monohydrate or 100 mg monohydrate/macrocrystals, TMP/SMX 0.5 tablet, or trimethoprim 100 mg, all taken once daily at bedtime, or postintercourse. TMP/SMX is also effective taken as a 0.5 tablet every second day. Both symptomatic and asymptomatic urinary infections are prevented with current strategies of TMP/SMX prophylaxis in renal transplant recipients.[188]

The need for and the efficacy of antimicrobial prophylaxis for children with vesicoureteral reflux is controversial. Although some guidelines have recommended continuous prophylactic antimicrobials for these patients, there remains considerable controversy whether this approach prevents the development of new or progressive renal scars, or renal impairment.[186,189,190] In an open randomized trial of Swedish boys and girls with reflux, prophylactic antimicrobial therapy significantly decreased subsequent febrile urinary infection, for girls only, during 2 years of follow-up.[191] Additional prospective, randomized clinical trials to answer the question of whether long-term prophylactic antimicrobial therapy prevents renal scarring and preserves renal function for children with vesicoureteral reflux compared with an optimal management of symptomatic episodes alone are ongoing.[190]

Prevention in Pregnancy

The prevention of acute pyelonephritis in pregnant women should be a part of the antenatal care of all patients.[91] The prevalence of asymptomatic bacteriuria during pregnancy has varied from 2% to 7%, with an incidence of acquiring bacteriuria about 1%—similar to the incidence of new infections in age matched women who are not pregnant.[91] In the absence of a screening and treatment program, acute pyelonephritis occurs in 20 to 30 per 1,000 pregnant women. With an intervention program for the treatment of asymptomatic bacteriuria, acute pyelonephritis is reduced to 3 to 5 per 1,000 pregnant women.[91,92] Pregnant women should be screened for bacteriuria once at 12 to 16 weeks' gestation, and those with positive cultures should be treated. Repeated screening cultures later in the pregnancy are not recommended for asymptomatic women whose initial culture is negative. Pregnant women who have had bacteriuria or symptomatic urinary infections should be followed with urine cultures throughout pregnancy, usually every 4 weeks. Continuous low-dose prophylaxis until 6 weeks after the delivery is recommended for patients with recurrent infections.

The choice of a regimen for the treatment of asymptomatic bacteriuria or for the prophylaxis of symptomatic or asymptomatic infections in a pregnancy must address the potential adverse effects for the fetus.[92] Although TMP/SMX is generally considered safe during pregnancy, concerns about a potential teratogenic effect from the trimethoprim component limits its use, especially during the first trimester. Penicillins and cephalosporins are safe in pregnancy; nitrofurantoin is safe, but is avoided at term because of the potential hemolysis of fetal hemoglobin. Ampicillin or a cephalosporin may be used if the organism is known to be susceptible. Cephalexin may also be used for prophylaxis, at 250 mg per day, and nitrofurantoin may be used for either treatment or prophylaxis. Fluoroquinolones are contraindicated because of the potential harmful effects on fetal cartilage development.

Prevention of Catheter-Associated Upper Tract Infections

Catheter-associated infections are the most common hospital-acquired infection.[184,192,193] Prophylactic antimicrobial therapy is not recommended because of the predictable emergence of infections with organisms with increased resistance.[184] The most important interventions to prevent these infections are to limit use of an indwelling urethral catheter or, if a catheter is necessary, to minimize the duration of catheterization. In addition, catheter insertion using sterile techniques and appropriate catheter maintenance, such as

maintaining a closed drainage system, are necessary. Infection control programs must ensure that prevention practices are current, and should monitor adherence to appropriate practice and patient infection rates.

The Prevention of Infection in Patients with Neurogenic Bladders

Bacteriuria is an anticipated complication following neurologic injury or disease complicated by a neurogenic bladder. Prophylactic antimicrobials are not recommended in spinal cord–injured patients managed with intermittent catheterization.[194] Although TMP/SMX, trimethoprim, or nitrofurantoin prophylaxis may prevent infections in the acute or early injury phase, prophylaxis is not effective in preventing symptomatic infections in the long term, and the induction of resistant bacteria in subsequent infections outweighs any short-term benefits. Maintenance of a low-pressure voiding system is essential to prevent complications of urinary infection.[104]

Continuous Suppression

Continuous long-term suppression may be considered for highly selected patients with recurrent symptomatic relapses despite optimal antimicrobial therapy. Such patients include those with renal calculi or obstructive lesions that cannot be corrected, infections in a nonfunctioning kidney, and men with chronic bacterial prostatitis.

There is relatively little evidence addressing optimal approaches to suppressive therapy. Sheehan and colleagues[195] compared 12 to 24 weeks of norfloxacin therapy for complicated recurrent urinary infections in a prospective, randomized, and blinded study. The longer antimicrobial course served as prophylaxis, suppressive, or curative therapy for different patients and, overall, led to fewer failures or reinfections from 12 to 24 weeks compared to placebo. Chinn and associates[196] demonstrated that antibacterial suppression is effective in patients with renal calculi in whom stones cannot be fully removed. No patients had further loss of renal function during a cumulative 77 years of continuous observation despite the presence of stones and partial obstruction. Renal calculi increased in size in only 4 of the 22 patients during the period of antibacterial suppression, and 4 of the 6 patients with impaired renal function had a decrease in serum creatinine levels while receiving suppressive therapy.

The antimicrobial dosage required for the maintenance of suppressive therapy is not well studied but generally, after an initial 2 to 4 weeks at full therapeutic doses, one-half the treatment dose is continued. In stable patients without a recurrence of bacteriuria, the dose may sometimes be reduced further. Patients on suppressive regimens should be reviewed periodically to ensure compliance and to monitor renal function. "Breakthrough" symptomatic infections occur occasionally. If the initial infecting organism has reappeared, then susceptibility testing will determine whether resistance has developed or if there is a suboptimal dose of medication. New infections may occur with reinfections with a new pathogen, and organisms isolated from a reinfection will usually be resistant to the antimicrobial used for the suppressive therapy. If this occurs, the patient should receive a 7- to 10-day course of an appropriate alternate antimicrobial to eradicate the new pathogen, without discontinuing the antimicrobial being taken for suppressive therapy. No guidelines have been developed to address the duration for which suppressive therapy is continued. If the initial indications for continuous suppressive therapy persist, the antimicrobial therapy may be continued indefinitely.

VIRAL INFECTIONS OF THE KIDNEY

Viruses causing systemic diseases are frequently isolated from the urine. Utz,[197] in 1974, described 16 viruses that were reported to have been isolated from the urine. The number is likely substantially greater now given the many new viruses described and the more sensitive diagnostic techniques. However, viruria commonly occurs during viremic infections as a manifestation of acute generalized diseases with limited, if any, involvement of the kidneys. Many viruses multiply in the tubular epithelium and are excreted in the urine as exfoliated infected cells. In only a few instances are there acute inflammatory changes in the renal tissue or in symptoms of clinical renal illness.

Clinical disease with parvovirus B19, cytomegalovirus, or adenovirus, usually following viral reactivation, occurs in some immunocompromised patients including renal transplant recipients, hematopoietic stem-cell transplant recipients, and occasionally, HIV patients. Hemorrhagic cystitis is the more common clinical presentation, but nephropathy is well described.[198,199] Viral infections of the kidney following a renal transplant are discussed more fully in another chapter.

The hemorrhagic fever viruses frequently cause renal impairment and are important health problems in many parts of the world.[200] Viral hemorrhagic fever with renal syndrome, which occurs in Korea, Scandinavia, the Soviet Far East, and the Balkans, is caused by members of the Bunyaviridae genera. The prototype agent is the Hantaan virus, originally isolated in Korea in 1978. Rodents are the reservoirs for these agents, and transmission to humans occurs by respiratory aerosols with no intermediary vector. Secondary cases have not been described in humans. High fever, myalgias, severe headaches, and a petechial rash characterize the illness. Thrombocytopenia is common. Hypotension and oliguria develop on about the fifth day of the fever. A pathologic examination discloses widespread capillary damage with extravascular leakage of plasma and red cells. Acute oliguric renal failure with massive proteinuria is a frequent complication. Renal biopsy specimens show extensive necrosis of the tubular epithelium with anatomically normal glomeruli except for the presence of extravasated red cells and protein-rich fluid. The overall mortality can be markedly reduced by supportive therapy, including dialysis, and in recent series has been 5% or less.

Rubella, varicella zoster, measles, and cytomegalovirus are commonly isolated during clinical illnesses with these viruses, but renal disease attributed to these agents has not been recognized.[197] Mumps frequently produce a transient renal impairment with a reduction in glomerular filtration together with significant proteinuria and hematuria. These abnormalities disappear within 1 month of resolution of the illness. Rare fatal cases with mumps interstitial nephritis have been reported.[201] Histologic studies suggest that viral multiplication in renal tubular cells induces these changes. Coxsackie B virus has also been associated with mild renal impairment. Infectious mononucleosis may have renal manifestations; hematuria and proteinuria occur in 11% and 18% of patients, respectively.[202] Acute renal failure owing to interstitial nephritis with few glomerular changes has also been described in isolated case reports.

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