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CHAPTER 175

Urinary tract infection in the adult: overview

Neil Sheerin

Introduction

Infection of the urinary tract is one of the commonest human infections. It can vary in severity from asymptomatic colonization, through self-limiting but distressing lower tract infection, to life-threatening sepsis. Any site in the urinary tract can be affected. The site of infection determines the pattern of symptoms, but this is also influenced by the age at presentation. The age at presentation and the nature of symptoms will not only suggest a clinical diagnosis, but also guide investigation and treatment. Section 7 addresses the different presentations of infections of the lower and upper urinary tracts, with a chapter specifically discussing infection in childhood (Chapter 180). There are also two chapters dedicated to the important topic of schistosomal infection, which has a significant impact on health in many countries (Chapters 181 and 182).

Definitions

There are several definitions applied to urinary tract infection (UTI). The first and most important is based on the site of infection which determines the symptoms reported by the patient. Infections of the lower tract, including cystitis, prostatitis, and urethritis, each have a distinct symptom complex suggesting the clinical diagnosis (see Chapter 176). Infections of the upper tract, most commonly pyelonephritis, tend to be more severe and symptoms may occur with or without symptoms of lower tract infection (see Chapter 177). Bacterial colonization of the urinary tract may also occur without symptoms (asymptomatic bacteriuria).

Infection at any site can also be classified depending on whether infection develops in a normal urinary tract (uncomplicated UTI) or whether there is an underlying anatomical or physiological abnormality (complicated UTI; see Chapter 178). Anatomical or physiological abnormalities not only predispose to the acquisition of infection but also predict treatment failure and risk of recurrence. In addition, in complicated UTI, treatment of the underlying abnormality, when possible, is key to a successful outcome and longer duration of antimicrobial therapy may also be needed. Uncomplicated UTI is a diagnosis of exclusion requiring imaging and physiological studies to rule out an abnormality predisposing to infection. However, the majority of UTIs, particularly those occurring in otherwise healthy young women, are uncomplicated. In this situation further investigation is rarely indicated and it is reasonable to assume that infection is uncomplicated, reserving further investigation for those patients in whom an abnormality is suspected.

Infections can be single events, but in many patients (up to 50% of women) infection can recur. Recurrent infection can have a huge impact on quality of life. Although recurrence may suggest that these infections are complicated, in the majority of patients with recurrent infection no predisposing factor can be identified. Nevertheless, these patients are often extensively investigated because of the misery caused by recurrent infection.

Diagnosis

The diagnosis of UTI depends on the clinical scenario and is discussed in detail in each individual chapter. However, there are some general principles that apply to different types of infection. Clinical assessment of the patient, based more on reported symptoms than clinical signs, is key to diagnosis. The presence of a classical set of symptoms, for example, those associated with cystitis, has a high specificity and sensitivity without further testing. However, in other situations, for example, in young children and those patients with cognitive impairment, this is less useful.

Testing of the urine is fundamental in the diagnosis of UTI. This usually involves collection of a mid-stream urine (MSU) sample. This may not always be possible. Young children, patients who cannot cooperate, or those who are catheterized require different collection techniques and interpretation of results. These issues are discussed in more detail in relevant chapter sections. The tests performed on the urine sample are the topic of much debate. Near patient testing with stick tests for bacteria (nitrites) and leucocytes (leucocyte esterase) are used commonly and increase the sensitivity and specificity of diagnosis compared to diagnosis made on the basis of clinical assessment alone. In some low-risk circumstances, for example, cystitis in primary care, this is now the only test used, replacing further laboratory-based techniques. This significantly reduces the number of urine samples processed by microbiology laboratories with associated cost savings. However, with increasing antibiotic resistance in uropathogenic bacteria, this may lead to more treatment failures due to incorrect choice of antibiotics.

Microscopy of urine to look for bacteria and host cells has now been replaced in many laboratories by more automated techniques based on flow cytometry. When infection is suggested, these samples are cultured to further quantify the number of bacteria, identify the pathogen, and determine antibiotic resistance. Although urine culture is an important diagnostic test, it is important to note that a negative culture does not exclude, nor a positive culture confirm, significant infection and results must be considered in clinical context.

The number of bacteria present in a MSU sample that would suggest infection was defined by seminal reports in the 1950s and 1960s as $> 10^5$ colony forming units per millilitre. This number is still widely used to indicate infection and it provides a balance between sensitivity and specificity to detect significant infection. A lower threshold will increase sensitivity but reduce specificity, which may be appropriate when the implications of missing infection are greater or if the urine sample is collected by other methods, for example, suprapubic aspiration. These diagnostic considerations are considered in depth in subsequent chapters in Section 7.

CHAPTER 176

Infection of the lower urinary tract

Ased Ali and Rob Pickard

Host defence and bacterial virulence

Ascending infection

The ascending route is the commonest mode of infection of the urinary tract with most bacteria originating from the individual's own lower bowel and subsequently colonizing the periurethral tissue before ascending through the urethra and into the bladder. Colonization of the periurethral mucosa with bowel flora is particularly problematic in females where the shorter urethra provides a convenient conduit for invading pathogens and rapid entry to the lower urinary tract. Even small variations in perineal anatomy in females can increase susceptibility, Hooton and colleagues demonstrated increased risk of female urinary tract infection (UTI) where anal to urethral distance was < 4.5 cm (Hooton et al., 1999). These anatomical risks can be further increased by the influence of external agents such as spermicides, faecal contamination of the perineum, and the use of urethral catheters.

The most common pathogens are resident facultative anaerobes and Gram-negative bacteria from the bowel and vaginal flora. The risk of symptomatic urinary infection with these organisms increases once they have colonized the periurethral tissues. A cohort study in young women found that the incidence of periurethral colonization with *Escherichia coli* increased from a baseline of 46% to a peak of 90% during the 14 days before the onset of UTI symptoms (Czaja et al., 2009). Furthermore, women with recurrent UTI show a greater tendency towards persistent colonization of the vaginal mucosa with pathogenic strains. It is therefore possible that the patients are being re-infected by their own enteric flora (Russo et al., 1995; Stapleton and Stamm, 1997), and this suggestion is supported by the finding that two-thirds of women with recurrent cystitis have the same uropathogenic *E. coli* (UPEC) strains isolated despite appropriate antibiotic treatment. It is still unclear why some women have increased susceptibility to vaginal colonization and are more prone to recurrent infection with uropathogens (Stamey and Kaufman, 1975; Brumfitt et al., 1987). It has been postulated that this may be partly genetically determined (Svanborg and Godaly, 1997; Finer and Landau, 2004; Hawn et al., 2009; Yin et al., 2010).

In terms of the bacteria themselves, it has been shown that UPEC strains have various mechanisms of avoiding both innate and adaptive immune defences. These mechanisms include the ability to downregulate key intracellular signalling pathways involved in inducing the immune system (Billips et al., 2008; Yadav et al., 2010) as well as the ability to inhibit activation of complement (Johnson, 2003).

The process of bladder colonization and infection begins with the binding of UPEC to host epithelium which is facilitated by various surface bacterial adhesins. The best characterized of these are fimbriae proteins (also known as pilli) which project from the bacterial surface (Hultgren et al., 1993; Dodson et al., 2001; Mulvey, 2002). Type 1 fimbriae express the fimbrial adhesion, FimH at the tip of the bacterial pilli which binds mannose allowing bacterial adhesion to mannosylated residues on proteins that line the luminal surface of bladder epithelial cells and also facilitating subsequent invasion of these cells (Mulvey et al., 2001; Hung et al., 2002; Mulvey, 2002). Type 2 or P fimbriae mediate adherence to uroepithelial cells by binding to glycolipids, in particular the Gal(α1 to 4)Gal disaccharide on the apical surface of renal epithelial cells. This mechanism can be also be used to bind to glomeruli, and endothelia as infection ascends (Nowicki et al., 1986). Given these characteristics it is not surprising that *E. coli* that express P fimbriae account for the majority of ascending urinary tract infections in women with normal urinary tracts (Kallenius et al., 1981).

Following binding to and entry of UPEC into superficial bladder epithelial cells, an intricate sequence of events takes place. However, current experimental evidence has been primarily documented in the mouse model and translation to patients remains speculative (Sivick and Mobley, 2010). Within murine bladder epithelium, UPEC are internalized by epithelial cells and undergo rapid division to form small clusters and establish intracellular bacterial communities (IBCs) which are able to avoid immune surveillance, and to some extent antibiotic action. A series of multiple bacterial phenotypic switches are also observed which culminate in the formation of specialized communities which provide continued protection from environmental changes and insults. These sites confer resistance to host immunity by concealing the bacteria inside a matrix which is also relatively impenetrable to antibiotics (Donlan and Costerton, 2002). Bacteria can then detach from their intracellular niche, rupture the cell, and re-enter the bladder lumen, ready to rebind to epithelium and form further IBCs and a continuing reservoir of infection. At certain stages during this cycle the host may be asymptomatic and despite antibiotic therapy, the bacteria may persist in a quiescent state for many months following the original infection.

Haematogenous infection

Haematogenous infection of the urinary tract is uncommon in normal individuals. However, patients with primary foci of infection elsewhere in the body involving *Staphylococcus aureus, Candida*

spp., *Salmonella* spp., and *Mycobacterium tuberculosis* can cause secondary infection in the kidney. The risk of such infection is enhanced when urine drainage from the kidney is obstructed (Smellie et al., 1975).

Lymphatic route of infection

Infection via the lymphatic route is rare but can be caused by direct invasion of bacteria from adjacent organs in patients with retroperitoneal sepsis and suppuration. The lymphatic route is not thought to play a significant role in the majority of UTIs.

Asymptomatic bacteriuria

Bacteriuria denotes the presence of bacteria in the urine, which may be symptomatic or asymptomatic. Asymptomatic bacteriuria is a microbiological diagnosis based on the number of bacteria isolated in urine from a patient who does not have any of the usual symptoms or signs attributed to local or systemic urinary tract infection. While in healthy individuals, the presence or absence of symptoms is relatively clear, in people with an indwelling urinary catheter, those with neurogenic bladder dysfunction, and those with cognitive impairment, it is frequently more difficult to determine whether an infection is truly asymptomatic. It is also worth noting that other coexisting factors, such as stones, can also induce cystitis in patients with asymptomatic bacteriuria and therefore the presence or absence of pyuria does not differentiate symptomatic from asymptomatic patients (Milo et al., 2005).

The prevalence of bacteriuria increases with age, and is also greater in both women and neuropathic patients. It is virtually ubiquitous in patients with long-term catheters. Bacteriuria is also significantly greater among diabetic women; however, diabetes does not appear to significantly increase the prevalence of bacteriuria among men (Foxman, 2002). Table 176.1 shows the prevalence in key selected populations (Nicolle et al., 2005).

Table 176.1 Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults

Population	Prevalence, %
Healthy, premenopausal women	1.0–5.0
Pregnant women	1.9–9.5
Postmenopausal women aged 50–70 years	2.8–8.6
Diabetic patients	
Women	9.0–27
Men	0.7–11
Elderly persons in the community[a]	
Women	10.8–16
Men	3.6–19
Elderly persons in a long-term care facility	
Women	25–50
Men	15–40
Patients with spinal cord injuries	
Intermittent catheter use	23–89
Sphincterotomy and condom catheter in place	57
Patients undergoing haemodialysis	28
Patients with indwelling catheter use	
Short term	9–23
Long term	100

[a] Age, ≥ 70 years.

From Nicolle et al. (2005).

Aetiology

Escherichia coli is the most common isolate among patients with asymptomatic bacteriuria although this is less commonly the case than in acute simple cystitis (Bengtsson et al., 1998; Hooton et al., 2000). Isolates also express fewer virulence characteristics than those isolated from women with symptomatic infection (Svanborg and Godaly, 1997). Other Enterobacteriaceae (e.g., *Klebsiella pneumoniae*) and Gram-positive uropathogens, including group B streptococci, *Enterococcus*, and coagulase-negative staphylococci are also common. This spectrum is similar in men (Mims et al., 1990; Nicolle, 1997). People living in care or nursing homes and those with a long-term indwelling urinary catheter often show a polymicrobial bacteriuria with a higher prevalence of *Pseudomonas aeruginosa, Proteus* spp., *Providencia stuartii, Morganella morganii*, and multiresistant organisms are commonly isolated (Warren et al., 1982; Mims et al., 1990).

Diagnosis

Seminal work by Kass in 1962 showed that when asymptomatic women were evaluated using multiple voided specimens, bacteriuria documented in an initial voided urine specimen was only confirmed in a second voided specimen in 80% of cases. If two successive voided specimens had similar positive culture results, then the rate of a subsequent positive result rose to 96% (Kass, 1962). Consequently, in asymptomatic women, the Infectious Diseases Society of America defines bacteriuria as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts ≥ 10^5 cfu/mL. In men with asymptomatic bacteriuria, a single voided urine specimen with ≥ 10^5 cfu/mL of an Enterobacteriaceae was reproducible in 98% of cases when the culture was repeated within 1 week (Gleckman et al., 1979) and therefore only a single sample is required for diagnosis. The same level of ≥ 10^5 cfu/mL is set for patients with an indwelling catheter; however, for a urine specimen collected by a single-use in and out catheter, a lower count of ≥ 10^2 cfu/mL is accepted as diagnostic.

Treatment

The treatment of asymptomatic bacteriuria is dependent on the type of patient affected and the risk of complications from the bacteriuria (Mims et al., 1990). In most adults, there is no evidence that asymptomatic bacteriuria is harmful and although the risk of subsequent symptomatic infection is higher than in people without bacteriuria, this is not modified by antibiotic treatment. Most guidelines including those from the British Infection Association, European Association of Urology, and the US Centers for Disease Control therefore recommend that asymptomatic bacteriuria should not be treated with antibiotics. Exceptions are pregnant women due to the risk of fetal growth retardation (Smaill and Vazquez, 2007) and in

those undergoing instrumentation of the urinary tract due to the higher risk of systemic sepsis (Mims et al., 1990).

Cystitis and recurrent infection

Acute uncomplicated cystitis

Acute uncomplicated cystitis is most commonly seen in healthy women who typically will not have any of the factors that are considered to indicate 'complicated UTI' and which are known to increase the risk of complications or of treatment failure. The frequency of simple symptomatic infective cystitis is around 0.5–0.7 episodes per woman per year (Hooton et al., 1996). Around 10% of women report having had an episode of UTI each year and > 50% of all women have at least one episode in their lifetime (Foxman, 2002). While cystitis does occur in younger girls, the incidence increases significantly with the onset of menstruation and sexual activity with a second peak in incidence around the time of the menopause. Men experience cystitis much less commonly (Krieger et al., 1993). Risk factors for cystitis are outlined in Box 176.1.

Aetiology

The organisms that cause cystitis are perhaps surprisingly limited to a small number of bacterial species which include *Escherichia coli*, isolated in around 75–90% of cases (Ronald, 2002), and *Staphylococcus saprophyticus*, a skin commensal, isolated in around 5–10% of cases (Jordan et al., 1980). Other Enterobacteriacea such as *Proteus* spp. and *Klebsiella* spp. are also occasionally isolated (Naber et al., 2008).

Clinical diagnosis

Overview

The diagnosis of cystitis can be made in the community with acceptable diagnostic accuracy on the basis of a combination of pain on voiding (dysuria), altered appearance of urine, and a positive result using nitrite and leucocyte antigen test reagents strips ('dipstick') (Stamm and Hooton, 1993).

Symptoms

The symptoms that individuals with cystitis report vary, typically including dysuria, frequency, urge, and suprapubic pain. Haematuria or foul-smelling urine may also be present but vaginal discharge is usually not. Where a combination of these symptoms is present, the probability of infection can be as high as 90% (Bent et al., 2002). However, when taking the history, it is still worth bearing in mind other differentials such as vaginitis, urethritis, or minor urethral injury.

In vaginitis, the patient characteristically has gradual onset of dysuria associated with vaginal irritation. There is often a history of smelly vaginal discharge and the patient's sexual history may include multiple or new sexual partners. Other urinary symptoms such as frequency, urge, visible haematuria, and suprapubic pain are not typically present. Like vaginitis, patients with urethritis also exhibit a less sudden onset of symptoms with dysuria, and urethral discharge, often with a relevant sexual history. Urinary frequency and urge may be present but are less pronounced than in cystitis. Urethral injury associated with trauma, sex, or chemical irritants can also cause dysuria but the history and lack of vaginal or urethral discharge will usually suggest this diagnosis.

Since cystitis is a superficial infection of the bladder epithelium, systemic symptoms of infection such as fever, chills, and rigors are not usually present. Many sufferers have few findings on examination but suprapubic tenderness on deep palpation may be found. Loin tenderness would be highly suggestive of upper tract involvement. In women, physical examination should also assess for vaginal discharge and the possibility of sexually transmitted infection.

Laboratory diagnosis

Near-patient testing by reagent test strip ('dipstick') urinalysis is the cornerstone of a presumptive diagnosis of acute cystitis. Testing for bacteria (nitrites) or pyuria (leucocyte esterase) using such methods has largely supplanted microscopy and urine-culture analysis, although urinalysis is less sensitive than microscopy. Dipstick testing is most accurate if there is clinical suspicion of cystitis when the presence of either nitrite or leucocyte esterase has a sensitivity of 75% and specificity of 82% (Hurlbut and Littenberg, 1991). However, in up to 25% of women the diagnosis will remain uncertain. It is important to note that a negative result on a dipstick test does not reliably rule out an infection where the pre-test clinical history is highly suggestive. Similarly, a positive result in the absence of symptoms does not necessarily indicate a need for treatment. In such cases a culture should still be obtained for diagnosis. Laboratory diagnosis is now frequently performed by initial screening of urine samples in a flow cytometer. This can give automated counts for white blood cells (WBCs), red blood cells, and bacteria. Subsequent culture is only routinely performed if a threshold bacterial count (typically 10^4 organisms/mL) is reached. Older studies comparing pyuria with visible bacteriuria on microscopy show that the former has greater sensitivity (95% vs 40–70%) but the latter has greater specificity (85–90% vs 70%) for diagnosis of UTI (Fihn, 2003).

Urine culture is the 'gold standard' test and remains very useful for ecological studies particularly focused on resistant patterns in the community and hospitals. However, the interpretation of the findings on culture of a 'clean-catch', mid-stream specimen of urine (MSU) depends on the definition of a positive culture. The original criterion put forward by Kass (1956, 1962) specified 10^5 cfu/mL of uropathogenic bacteria in urine. This gives high specificity but sensitivity is lower at around 50%. Lowering the threshold to 10^2 cfu/mL in cases of young women with symptoms of cystitis raises the sensitivity to 95%, with a specificity of 85% (Stamm et al., 1982). Nonetheless, *routine* urine cultures are frequently unnecessary for diagnosis and treatment planning and particularly in a primary

Box 176.1 Risk factors for uncomplicated cystitis

- Sexual activity—increased inoculation
- Urinary incontinence—increased inoculation
- Faecal incontinence or constipation—increased inoculation
- Spermicide—increased binding
- Oestrogen depletion—increased binding
- Antimicrobial agents—decreased commensal 'healthy' flora
- Inadequate fluid uptake (dehydration)—decreased urine flow
- Diabetes—enhanced medium for growth.

care or outpatient situation. There is an economic argument for treating simple cystitis without sending an initial culture because treatment is usually started on an empirical basis from local guidelines and is often completed before the culture result is reported by the laboratory. Use of initial culture in this situation has been shown to increase costs by 40% but decrease the duration of symptoms by only 10% (Carlson and Mulley, 1985).

Consequently, it is recommended that most patients with consistent symptoms and a positive dipstick test be treated without urine culture results except where there are factors suggesting upper tract involvement or complicated infection. Cultures are also valuable in identifying unusual or resistant organisms in women whose symptoms either do not resolve or recur within 2–4 weeks after the completion of treatment and for ecological surveillance of causative organisms and antibiotic resistance patterns (Stamm, 1986).

Treatment

It is generally recommended that simple cystitis is treated with antibiotic therapy as successful resolution of symptoms is significantly more likely in adult non-pregnant women when treated with antibiotics compared with placebo (Falagas et al., 2009). The choice of antibiotic therapy should always be guided by local microbiological advice concerning resistance patterns. Other factors to consider are listed in Table 176.2.

According to these principles and the susceptibility patterns, trimethoprim 200 mg twice daily and nitrofurantoin 100 mg twice daily are typically used in the United Kingdom as first-line agents because they are narrow-spectrum antibiotics that cover the most prevalent pathogens and, in the case of both trimethoprim and nitrofurantoin, are preferentially excreted in the urine (Christiaens et al., 2002; van Merode et al., 2005). A third possibility is co-amoxiclav (in most communities resistance to amoxicillin is higher than 30%). Evidence from trial data indicates that a 3-day course is sufficient for women (Lutters and Vogt, 2002; Milo et al., 2005) but no such evidence exists for men, where expert opinion suggests a 7-day course should be used. In the United Kingdom, broad-spectrum antibiotics (e.g. pivmecillinam, quinolones, and cephalosporins) are usually avoided as first-line agents where narrow-spectrum antibiotics are effective, due to the increased risk of *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and extended-spectrum beta-lactamase activity (ESBL) in *E. coli*. However, these are all possibilities as second-line treatment. In other parts of Europe, fosfomycin, trometamol, and pivmecillinam are used as first-line agents but this is largely due to high community rates of trimethoprim resistance in *E. coli*.

Table 176.2 Factors influencing a decision to treat symptomatic cystitis

Pathogen related	Pathogen identity
	Sensitivities of pathogen
Therapy related	Efficacy
	Tolerability
	Route of administration
	Adverse effects
	Guidelines
Healthcare related	Cost of therapy
	Availability of therapy

Routine repeat urinalysis or cultures in patients who are asymptomatic following treatment is not necessary (Nicolle et al., 2005). Where symptoms have not resolved by the end of treatment, and where symptoms resolve but recur within 2 weeks, urine samples should be sent for culture and sensitivity as it is likely that the organism is resistant to the original agent used. Use of an alternative agent for 7 days is then advisable.

Recurrent cystitis

Cystitis is generally regarded as having recurred if a second symptomatic infection follows clinical resolution of an earlier infection, although there is not a universally accepted definition. A practical working categorization is the occurrence of at least two episodes of acute uncomplicated cystitis within a 6-month period, or at least three episodes in a 12-month period (Schooff and Hill, 2005).

Recurrent cystitis is very common among young healthy women and is rarely associated with any anatomical or functional abnormality of the urogenital tract. In the 1970s, Mabeck found that almost one-half of the women whose initial uncomplicated UTIs resolved spontaneously developed a recurrent UTI within the first year (Mabeck, 1972). In a Finnish study of women aged 17–82 years who had *E. coli* cystitis, there was an overall recurrence rate of 44% within 1 year with rates of 53% in women older than 55 years and 36% in younger women (Ikaheimo et al., 1996). It should be noted that to date no large population-based studies have been performed to determine what proportion of women with cystitis develop a pattern of repeated frequent recurrences over longer periods.

Aetiology

Recurrent cystitis occurs in one of two situations:

- Bacterial persistence, that is, infecting bacteria re-emerge from a reservoir within the urinary tract
- Re-infection, that is, new infection from bacteria outside the urinary tract (bowel or skin flora).

Bacterial persistence is typically characterized by infection with the same organism recurring at very short intervals. In contrast, re-infections usually occur at more varied, longer intervals which can be up to several months and may not necessarily be caused by the same organism. It is important to distinguish between these two categories since identification and removal of reservoirs of infection, if present, will resolve the problem. Re-infection is a more complex situation where a single remediable abnormality is much less likely to be found. In men, recurrent UTI is less common and more likely to be associated with underlying abnormality such as bladder outlet obstruction.

Bacterial persistence

Diagnosis

Once acute cystitis has resolved and there is no further microbiological evidence of bacteriuria, it is possible under certain circumstances for the organism to 'hide' within a part of the urinary tract which was exposed to lower concentrations of antimicrobial chemotherapy. The specific abnormalities that can result in this situation are outlined in Table 176.3.

Urinary culture is useful in the detection of *Proteus mirabilis*, the commonest organism linked with the presence of infection

Table 176.3 Urinary tract abnormalities causing bacterial persistence

Anywhere in urinary tract	Stones
	Foreign bodies
Renal	Infected atrophic kidney
	Medullary sponge kidney
	Papillary necrosis
	Infected renal calyceal cyst
Ureter	Ureteral duplication
	Ectopic ureter
	Non-refluxing, infected ureteral stump
Bladder	Infected urachal cysts
	Perivesical/pelvic abscess
Prostate	Chronic bacterial prostatitis
Urethra	Urethral diverticula

stones (although most patients with *P. mirabilis* cystitis do not go on to form infection stones). *P. mirabilis* can cause significant alkalinization of the urine with precipitation of calcium, magnesium, ammonium, and phosphate salts and the subsequent formation of branched struvite (triple phosphate) renal stones. This has serious consequences as bacteria can persist inside struvite stones even when the urine shows no growth. Consequently, struvite infection stones are the major cause of bacterial persistence in women.

Many of the other abnormalities can be identified by a combination of imaging and endoscopic evaluation of the urinary tract. Although conventional intravenous urography may still be used, computed tomography (CT) of the kidneys, ureters, and bladder (KUB) (non-contrast) and CT urography (late phase contrast-enhanced) and cystoscopy provide the most sensitive investigation (particularly as struvite stones are often relatively radiolucent). Retrograde urography, and ureteroscopy are also useful in some situations. Many of these abnormalities also contribute to 'complicated' UTI which will be discussed in a subsequent section.

Treatment

Where a reservoir for persistent infection is identified, the standard treatment is to remove the foreign body or correct the anatomical abnormality. Most of the abnormalities listed in Table 176.3 will require surgical intervention to facilitate removal and eradication of the source of bacterial persistence. For struvite infection stones, complete removal of the calculus by either percutaneous nephrolithotomy, ureteroscopic lithotripsy, extracorporeal shockwave lithotripsy, or rarely open removal is needed for bacteriological cure and to prevent renal damage due to obstruction (Silverman and Stamey, 1983). However, management with continuous antibiotic prophylaxis and acidification of the urine provides some symptomatic relief and may slow deterioration in renal function. Chronic bacterial prostatitis is usually treated initially with penetrative long-course antibiotic therapies but transurethral resection may be helpful in some cases (Barnes et al., 1982).

Where the reservoir of infection cannot be removed, long-term, low-dose antibiotic treatment may be the only option to supress bacterial growth and prevent symptoms. Agents typically recommended for this use are nitrofurantoin and trimethoprim. Other drugs such as cephalexin, and the fluoroquinolones are avoided where possible due to higher risk of ecological bacterial change.

Re-infection

Diagnosis

Recurrent infections occurring at longer intervals or involving different species/type of bacteria are the hallmarks of re-infection and the diagnosis is therefore typically made on the basis of history, examination, and urine culture. This pattern is more commonly seen in females of all ages and is usually secondary to infection by ascending bowel flora particularly coliforms. Though the ascending route is by far the most common route, fistulas (enterovesical or vesicovaginal) or other structural abnormalities are important possibilities to consider particularly where other risk factors are present such as diverticulitis, and previous surgery or radiotherapy. In men, re-infection is more frequently associated with structural or functional abnormality impeding bladder emptying.

As in the case of bacterial persistence, it is important to identify and correct urinary tract structural and functional abnormalities where they exist. Any abnormality which either reduces the formation of urine or disrupts flow through the urinary tract can increase the risk of re-infection and limit the effectiveness of antibiotic therapy. Imaging typically by ultrasound is useful to demonstrate the anatomy of the urinary tract and indicate the emptying ability of kidneys, ureter, and bladder. Cystoscopy should also be performed if symptoms are suggestive of persistent mucosal irritation (stones or cancer), obstruction (urethral stricture), bladder dysfunction (diverticula), or fistula.

Treatment

Initial management should be directed towards identifying and correcting any of the reversible risk factors outlined in Table 176.3. Consequently, in patients with diabetes, glycaemic control should be optimized. In women using spermicides, a diaphragm, or depot hormonal contraception, alternative forms of birth control should be explored. Where an indwelling catheter or intermittent catheterization is used, catheter management should be reviewed. In postmenopausal women, the local effects of reduced oestrogen should be examined and local replacement considered. In elderly patients, perineal hygiene, general hydration, and both faecal and urinary incontinence should be managed. General advice in terms of increased fluid intake, use of sanitary towels instead of tampons, post-coital micturition, and avoiding the use of soaps in the vaginal area is also often given, though evidence of benefit is weak (Remis et al., 1987; Strom et al., 1987; Foxman and Chi, 1990).

When an infection occurs it should be treated with a full course of an appropriate antibiotic (as in the case of acute uncomplicated cystitis). After the resolution of an acute episode, there are several evidence-based antibiotic strategies which may be employed to prevent recurrences: long-term prophylaxis, post-coital prophylaxis, and patient-initiated therapy as well as some alternate, non-antibiotic based strategies with weaker evidence of effectiveness.

Antibiotic strategies

Low-dose continuous prophylaxis

Long term prophylaxis usually requires a single daily dose of antibiotic (typically taken at bedtime). The success of prophylaxis is

dependent on the ability of an antimicrobial agent to eliminate pathogenic bacteria from the urogenital tract prior to symptomatic infection and without causing the development of significant resistance or change to the ecology of bowel or vaginal commensal flora. Evidence of efficacy exists for the following antimicrobials: trimethoprim, trimethoprim/sulphamethoxazole, nitrofurantoin, and norfloxacin (Nicolle and Ronald, 1987; Nicolle et al., 1989). It should be noted that the use of fluoroquinolones for this purpose is discouraged by most guidelines.

Long-term prophylaxis typically involves continuing the daily antibiotics for 6–12 months, although this can be extended to several years. It is possible that breaks of 1–2 months every 6 months or the use of alternating agents may reduce the risk of changing resistance patterns although good evidence of effectiveness is lacking. If symptomatic re-infection occurs during prophylactic treatment, then urine should be sent for culture and full therapeutic dosage of another antimicrobial should be used for treatment. Prophylaxis may then be resumed once the infection has resolved provided the culture results do not show the presence of resistance to the prophylactic agent. Long-term prophylaxis is effective at preventing recurrences in 95% of patients whilst they are on prophylaxis. Unfortunately, once prophylaxis is discontinued, around 50% of patients will have a further UTI within 3 months (Nicolle, 2002).

As an alternative to the conventional antibiotics described earlier, good evidence for the use of methenamine hippurate also exists. Methenamine decomposes at an acid pH to formaldehyde and ammonia, and the formaldehyde is bactericidal. Urinary acidity can be ensured by co-administering vitamin C (ascorbic acid) or ammonium chloride. Methenamine is particularly useful for long-term prophylaxis as bacteria do not develop resistance to formaldehyde. However, it should not be used in the presence of renal insufficiency.

Patient-initiated intermittent therapy

Patient-initiated intermittent or self-start therapy is a useful alternative to long-term prophylaxis. The key aim is to empower the patient to initiate a 3-day course of empirical antibiotic treatment at the first onset of their symptoms or at an 'early warning sign' which is consistent with development of previous episodes of cystitis (Schaeffer and Stuppy, 1999; Gupta et al., 2001). As an adjunct, the patient can be given reagent strips and instructed to also occasionally submit a urine sample for culture when symptoms of infection occur with a subsequent culture a week after treatment to check for efficacy and resistance patterns.

As the antimicrobial agent selected for patient-initiated therapy will be largely used on an empirical basis, it should have a reasonably broad spectrum of activity and achieve high urinary levels to minimize development of resistance while having as little effect as possible on the bowel flora. Nitrofurantoin and trimethoprim are recommended in the UK whilst trimethoprim-sulphamethoxazole is also available in other countries. Agents such as tetracycline, amoxicillin, cephalexin, and fluoroquinolones in full doses should be avoided because they can give rise to resistant bacteria and ecological bacterial change (Wong et al., 1985). Overall, there is much to commend patient-initiated therapy both from a bacterial point of view as the use of a full-dose course is less likely to result in resistant strains and from a patient point of view where it is gives patients with less frequent infections the ability to play an active role in their diagnosis and management.

Post-intercourse prophylaxis

In women where sexual intercourse has been identified as a 'triggering event' in the history, post-intercourse prophylaxis is a useful option (Nicolle, 2002). Taking a reduced dose of an antimicrobial agent such as nitrofurantoin 50 mg or trimethoprim 100 mg immediately after voiding after intercourse can be very effective at reducing the rate of re-infection (Pfau et al., 1983). Furthermore, studies have shown the efficacy to be comparable to daily prophylaxis with the advantage of fewer side effects as on average only a third of the total dosage of antibiotic is used (Melekos et al., 1997).

Oestrogen therapy

Postmenopausal women are recognized as a group more prone to frequent re-infections (Raz and Stamm, 1993). While in some cases, pelvic organ prolapse contributes to residual urine after voiding, in others, the lack of oestrogen causes marked changes in the vaginal commensal microflora and vaginal pH which leads to reduced *Lactobacilli* spp. and increased colonization by *E. coli* (Melekos et al., 1997). Oestrogen replacement therapy is believed to partially restore the normal vaginal environment which allows re-colonization with lactobacilli, reduces uropathogenic bacterial colonization, and hence occurrence of UTI. However, the mechanism of action is not typical of a classical endocrine effect. Local oestrogen reduces UTI occurrence whilst systemic therapy does not (Perrotta et al., 2008). The vaginal response is also rapid in onset but short-lived, lasting only for the duration of the therapy. The beneficial effects of local oestrogen therapy in recurrent UTI are also seen in younger women using the oral contraceptive without evidence of oestrogen deficiency (Pinggera et al., 2005). Despite the unclear mechanism, the use of vaginal oestrogen in postmenopausal women is supported by evidence from a meta-analysis performed as part of a Cochrane systematic review and there may also be a role in premenopausal women.

Other strategies

For women with a persistent post-void residual urine (> 100 mL) and evidence of reduced urethra calibre, a single dilation of the urethra under a general anaesthetic to improve bladder emptying may be appropriate. There is no evidence, however, that repeated urethral dilation is beneficial in the routine management of women with recurrent UTI.

Cranberry extract has been a popular preventive method for many years. It is believed to work partly by acidifying the urine, and partly by reducing bacterial adhesion and bacteriuria. Cranberry extract contains proanthocyanidins which are believed to either competitively inhibit the *E. coli* fimbrial subunit from binding to the uroepithelial cells, or prevent the expression of normal fimbrial subunits (Patel and Daniels, 2000). In 1994, Avorn et al. studied 153 women and showed that 300 mL/day of Cranberry juice reduces bacteriuria and pyuria by 42% and persistent bacteriuria and pyuria by 72% (Avorn et al., 1994). However, the proportion of cranberry extract in commercial juices and tablets is highly variable therefore effects are unpredictable. Furthermore, subsequent randomized controlled trials of cranberry products have not shown benefit and a Cochrane systematic review has shown no evidence that they are effective for management of UTI (Jepson et al., 2000).

There is currently no evidence that behavioural factors such as frequency of voiding, timing of voiding, wiping patterns, use of hot baths, or type of undergarments, play any significant role

in recurrent infection. There is therefore no rationale for giving women specific instructions regarding these issues.

Prostatitis and urethritis

Prostatitis

Although inflammation of the prostate gland has been recognized for around two centuries (it was first described by Legneau in 1815), it remains primarily a clinical syndrome with symptoms suggestive of either inflammation or infection localized to the prostate. Bacterial prostatitis is typically described as either acute or chronic according to the duration of symptoms, > 3 months indicating chronic disease. Abacterial prostatitis (a subcategory of chronic pelvic pain syndrome) has no definite evidence of being related to a past of continuing infection. Asymptomatic inflammatory prostatitis refers to the histological presence of inflammatory change in prostatic biopsies.

The classification system suggested by the National Institute of Diabetes and Digestive and Kidney Diseases of the US National Institutes of Health is the most widely used by both European and American clinicians (Krieger et al., 1999) (Table 176.4). This section will focus only on acute and chronic bacterial prostatitis (type I and II respectively) as there is no evidence that the other forms are directly caused by active infection.

Aetiology

Acute bacterial prostatitis typically consists of a generalized infection of the prostate gland which is associated with severe symptoms of both UTI and systemic sepsis. In contrast, chronic bacterial prostatitis is typically associated with recurrent UTI and cystitis due to persistence or re-infection of uropathogenic bacteria within the prostate gland and is generally associated with less severe local symptoms.

In common with cystitis, the most frequent cause of bacterial prostatitis is the Enterobacteriaceae family of Gram-negative bacteria. These originate from the affected individual's gastrointestinal flora and up to 80% of infections are caused by strains of *E. coli* (Weidner et al., 1991). *Pseudomonas aeruginosa, Serratia* spp., *Klebsiella* spp., and *Enterobacter* spp. are other Gram-negative bacteria which have been identified in a further 10–15% of cases (Meares and Stamey, 1968; Krieger et al., 1999). Gram-positive *Enterococci* are believed to account for 5–10% of documented prostate infections (Bergman, 1994). The role of other Gram-positive organisms, such as coagulase-negative staphylococci, which are also commensal organisms in the anterior urethra, is controversial. While there is evidence suggesting that coagulase-negative staphylococci may be involved in the pathogenesis of chronic prostatitis, it still unclear whether the bacteria were actually causing the inflammation and symptoms or simply colonizing the prostate (Krieger et al., 2002). Nonetheless, eradication of Gram-positive bacteria in men with symptoms gives similar clinical results to treatment of men in whom Gram-negative prostatic uropathogens have been localized.

Other bacteria which have implicated include *Corynebacterium* spp., *Chlamydia trachomatis*, and *Ureaplasma urealyticum*. Evidence for a causative role for these bacteria is unclear with studies reporting conflicting findings and tending to suffer from methodological problems such as lack of appropriate controls and accounting for urethral contamination.

As in the case of cystitis and pyelonephritis, virulence factors play a key aetiological role in the pathophysiology of bacterial prostatitis (Johnson et al., 2005). The same bacterial pilli (P-fimbriae) which facilitate binding to urothelial receptors and ascent up the urinary tract, also play a role in establishing progressive infection of the prostatic ducts and acini (Andreu et al., 1997). The presence of *E. coli* with type 1 fimbriae (mannose-sensitive fimbriae), often associated with cystitis, have also been seen in prostatitis. A further pathogenic mechanism is the ability to form biofilms which allows bacteria to persist in the prostate gland even after the urinary infection has been treated with antibiotics (Nickel et al., 1994).

As well as virulence of pathogens, any discussion of aetiology would be incomplete without also mentioning factors affecting host defence. A number of risk factors have been identified which facilitate bacterial colonization and infection of the prostate these include:

- intraprostatic ductal reflux (Kirby et al., 1982)
- phimosis (Van Howe, 1998)
- unprotected penetrative anal intercourse
- indwelling urethral catheters and condom catheter drainage
- transurethral surgery, especially in men who have untreated, infected urine.

Secretory dysfunction of the prostate is also commonly associated with bacterial prostatitis with alterations to the sugars, salts, enzymes, and pH all identified. It is possible that these alterations in fluid composition may adversely impact the normal antibacterial nature of prostatic secretion fluid (Fair et al., 1976); pH changes may also hamper the penetration of antimicrobial drugs into the prostatic tissue (Fair and Cordonnier, 1978).

Clinical diagnosis

Bacterial prostatitis is categorized as either acute or chronic with an arbitrary threshold of 3 months. While acute bacterial prostatitis is rare, it is nonetheless a very significant lower UTI as it is frequently associated with systemic sepsis. Acute bacterial prostatitis is characterized by the following triad of symptoms:

- Acute onset of pain—typically severe and localized to the perineum, rectum, and scrotum. There may be associated pain or discomfort in the penis, bladder, or lower back (Table 176.5).
- Lower urinary tract symptoms—urinary frequency, urgency, and dysuria are common. Voiding symptoms include hesitancy, poor stream, strangury, and frequently urinary retention.

Table 176.4 Classification of prostatitis

Type	Name and description
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic abacterial prostatitis—chronic pelvic pain syndrome (CPPS) A. Inflammatory CPPS B. Non-inflammatory CPPS
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

Table 176.5 Localization of pain in prostatitis

Site of pain	Percentage of patients
Prostate/perineum	46%
Scrotum and testes	39%
Penis	6%
Urinary bladder	6%
Lower back	2%

- Systemic febrile illness—fever, chills, malaise, nausea, and leading to generalized sepsis with hypotension typical of secondary bloodstream infection.

The combination and severity of symptoms in acute bacterial prostatitis will vary depending on the nature of the infection and the patient. Approximately 5% of cases progress to chronic bacterial prostatitis. While symptomatically similar, the hallmark of chronic bacterial prostatitis is a history of recurrent culture-positive UTIs. Between 25% and 43% of patients diagnosed with chronic bacterial prostatitis have recurrent UTIs (Wright et al., 1994). Due to its recurrent nature, it is particularly desirable to isolate the aetiological organism from the prostatic fluid/urine, in particular to differentiate the condition from chronic abacterial prostatitis.

On clinical examination, the prostate is frequently normal on palpation. However, in acute bacterial prostatitis, the prostate may be swollen with tenderness elicited on digital rectal examination. Sometimes a prostatic abscess may be palpable or seen on transrectal ultrasound imaging. The primary aim of the examination is to exclude other pathologies of the urogenital tract and anorectum. An absence of clinical findings on examination does not exclude prostatitis.

Laboratory diagnosis

The principal laboratory investigation in patients presenting with acute bacterial prostatitis is a urine culture and is often the only laboratory evaluation of the lower urinary tract required. Vigorous prostatic massage prior to urine culture is advocated by some as the expressed prostatic secretions may improve the sensitivity of culture, however, this is likely to be very painful and may also exacerbate the clinical situation and is therefore not routinely recommended. A MSU specimen will typically reveal significant numbers of white cells and bacteria microscopically. Culture frequently demonstrates uropathogens or occasionally other bacteria. Blood cultures are useful if there are systemic symptoms or signs and when positive, may show the same organism.

For chronic bacterial prostatitis, the mainstay of laboratory diagnosis is the quantitative bacteriological localization cultures and microscopy of urine collected after prostate massage.

The role of imaging and biopsies is limited. Perineal prostatic biopsies have been used to help in the detection of difficult-to-culture microorganisms, but such an invasive technique is rarely clinically justified. Transrectal ultrasound without biopsy may useful if an intraprostatic abscess is suspected and may also reveal dilatation in the seminal vesicles or prostatic calcification but generally the technique has no routine diagnostic role in acute or chronic prostatitis.

Prostate-specific antigen (PSA) levels rise in both symptomatic and asymptomatic bacterial prostatitis (Carver et al., 2003) as well as during the majority of UTIs. Levels do not usually rise in abacterial prostatitis. If a patient has elevated PSA and histological evidence of prostatic inflammation, serum PSA is expected to normalize following antibiotic treatment for 4 weeks in about 50% of patients (Bozeman et al., 2002). There is little to be gained in using PSA as a screening tool for localized prostate cancer in men with bacterial prostatitis or UTI and a delay of at least 3 months should be allowed before it can be assumed that a stable level of PSA has been reached.

Treatment

Antibiotics

Acute bacterial prostatitis can be a severe infection with both painful local symptoms and generalized systemic sepsis. While in mild cases a fluoroquinolone given orally for 10 days is usually sufficient (Schaeffer, 1999), in more severe cases intravenous administration of antibiotics is recommended. Typical choices consist of broad-spectrum penicillin, a third-generation cephalosporin, or a fluoroquinolone. Where there is systemic sepsis an aminoglycoside may also be included. Once there is clinical improvement and usually apyrexia for 24 hours, treatment can be 'stepped down' to oral medication which should continue for 4 weeks.

Chronic bacterial prostatitis can be treated with a number of different antibiotics; those advocated principally include fluoroquinolones, trimethoprim (or trimethoprim-sulfamethoxazole), tetracyclines, and macrolides (Bjerklund Johansen et al., 1998). Fluoroquinolones are the most commonly used as they have good bioavailability and penetration of the prostate with good activity against Gram-negative pathogens, including *Pseudomonas aeruginosa*. Some fluoroquinolones are also effective against Gram-positive and atypical pathogens, such as *Chlamydia trachomatis* and *Mycoplasma*. Trimethoprim is also a good, inexpensive alternative with the only significant disadvantage being no activity against *Pseudomonas*, some enterococci, and some Enterobacteriaceae. Tetracyclines are useful against *Chlamydia* and *Mycoplasma* but less effective against some of the more common pathogens such as *E. coli*, some Enterobacteriaceae, enterococci, staphylococci, and *Pseudomonas*. In chronic bacterial prostatitis, antibiotics should be trialled at high dose for 2 weeks in the first instance. If cultures are positive or the patient reports positive symptomatic relief then the treatment should continue for 4–6 weeks (Wagenlehner and Naber, 2003).

Surgical intervention

Acute urinary retention is common with acute prostatitis; temporary catheter drainage of the bladder is therefore required. Both urethral and suprapubic drainage are valid options, while a suprapubic catheter has advantages in terms of not traversing through the prostate and is likely to be more comfortable for the patient, this has to be weighed against the potential risks of sepsis and bowel injury during the placement of such a catheter. In the rare instances where a prostatic abscess is present, direct drainage of the abscess has an important role. This can be achieved through either the transperineal or transrectal route or by transurethral resection of the prostate.

Urethritis

Aetiology

There are principally two types of urethritis, gonorrhoeal urethritis and non-specific urethritis (also known as non-gonococcal urethritis). The former is caused by *Neisseria gonorrhoeae* and the

latter most commonly by *Chlamydia trachomatis*—both are sexually transmitted with increased risk in those with a history of multiple sexual partners. Other less frequent causes of non-specific urethritis (Borchardt et al., 1995; Busolo et al., 1997; Evans et al., 1998) include:

- *Mycoplasma genitalium*
- *Ureaplasma urealyticum*
- *Trichomonas* spp.
- UPEC
- adenoviruses
- herpes simplex
- Reiter syndrome.

The frequency of the different species varies between patient populations and clinical evidence of *Mycoplasma* or *Ureaplasma* infection may be confounded by asymptomatic colonization of the urogenital tract.

The main causative agents, *N. gonorrhoeae* and *C. trachomatis,* will usually penetrate the epithelium and cause pyogenic infection. Both chlamydiae and gonococci can then spread further through the urogenital tract to cause epididymitis in men or cervicitis, endometritis, and salpingitis in women. *Mycoplasma genitalium* can also cause cervicitis and pelvic inflammatory disease in women (Haggerty, 2008).

Clinical diagnosis

A diagnosis of urethritis is difficult to make on clinical grounds alone. Symptoms include mucopurulent or purulent discharge, dysuria, orchialgia, and urethral/glans pruritus. However, many infections of the urethra are asymptomatic and women often exhibit no discharge. In males, the examination should focus on the distal urethra which can be inspected for redness and discharge by holding the meatus open. Examination of the penis and testicles should look for swelling and tenderness, a digital rectal examination may also reveal evidence of prostatic tenderness. In females, a vaginal examination should be performed looking for discharge and checking for cervical excitation pain. In both males and females, a standard set of microbiological swabs should be taken at the beginning of the examination. For females this would routinely consist of a high vaginal swab and in males this consists of a urethral swab. Rectal and/or oropharyngeal tests should also be considered when patients are symptomatic at these sites and as indicated by sexual activity.

Laboratory diagnosis

The traditional method of laboratory diagnosis is a Gram stain of a urethral discharge or a urethral smear. This is the preferred rapid diagnostic test for evaluating urethritis as it is sensitive and specific both for identifying urethritis and the presence or absence of gonococcal infection. Pyogenic urethritis can be diagnosed if slide shows more than five WBCs per high power field (× 1000) and then subsequently gonococci located intracellularly as Gram-negative diplococci.

Conventional urinalysis is a less useful test in patients with urethritis, however, in patients with gonococcal urethritis, > 10 WBCs per high power field (× 400) in the first voiding urine specimen suggests infection; but > 30% of patients with non-specific urethritis do not have WBCs in their urine. *Trichomonas* spp., can usually be identified microscopically. Modern pathogen detection techniques use PCR amplification systems to increase sensitivity so that the first voiding urine specimen can be taken instead of a urethral smear.

Treatment

As sensitivity patterns are changing and in particular, fluoroquinolone-resistant *N. gonorrhoeae* has become more prevalent (particularly in the United States), it is essential that the choice of antibiotic therapy should always be guided by local or national microbiological advice which is usually available as written guidance.

The British Association for Sexual Health and HIV (BASHH) recommends ceftriaxone 500 mg intramuscularly as a single dose with azithromycin 1 g oral as a single dose for first-line treatment of uncomplicated anogenital infection in adults. Other options for first-line treatment include a single dose of cefixime 400 mg orally or ceftriaxone 1 g intramuscularly (Workowski and Berman, 2002). Quinolones taken as a single dose are an alternative but resistance is > 25% in the United Kingdom and use is contraindicated in adolescents (< 18 years) and pregnant women.

For non-specific (non-gonococcal) urethritis, azithromycin 1 g orally or doxycycline 100 mg twice daily for 7 days are good first-line regimens. Second-line alternatives include 7-day oral courses of erythromycin or quinolones such as ofloxacin and levofloxacin. It is usually advocated that even in cases of gonococcal urethritis, treatment for *Chlamydia* should also be initiated as the two sexually transmitted diseases (STDs) commonly coexist.

As for all STDs, contact tracing and treatment of sexual partners is very important. Patients should also be advised to accept testing for other STDs, including syphilis and HIV. It is generally recommended that patients abstain from sexual activity for a week after the initiation of treatment and only resume if symptoms have resolved and partners have been treated.

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CHAPTER 177

Upper urinary tract infection

Mark Harber

Pyelonephritis

Epidemiology of acute pyelonephritis

The incidence of acute pyelonephritis in women has been estimated at 3 per 1000 person-years (Scholes et al., 2005). Host risk factors for pyelonephritis are very similar to those of lower urinary tract infection (UTI), namely recent UTI, female sex, recent sexual intercourse, the use of a diaphragm and spermicides, oestrogen deficiency, increasing age, pregnancy, renal transplantation, impaired voiding, diabetes (95% of those patients with emphysematous pyelonephritis), obesity, stones, congenital urological abnormalities, neuropathy affecting the bladder, and recent catheterization or urological intervention. Emphysematous pyelonephritis also has a very strong female predominance and a peak incidence in the sixth decade (which may reflect the increasing prevalence of diabetes) (Pontin and Barnes, 2009). Emphysematous pyelonephritis is still rare but as with xanthogranulomatous pyelonephritis it seems likely to become an increasingly significant problem with the increasing prevalence of elderly diabetics.

Pathogenesis

The vast majority of pyelonephritis is secondary to ascending infection and this is reflected in the fact that > 85% of cases of pyelonephritis are due to Gram-negative bacilli, with serological studies confirming that the majority are from the patient's own faecal flora. The medulla of the kidney appears much more susceptible to infection than the cortex. It requires 10,000 times fewer organisms to establish infection in the medulla than the cortex, one explanation of which is the poor targeting and functioning of neutrophils in an acidic and hypoxic environment (Sobel and Kaye, 1984).

The organisms responsible for acute uncomplicated pyelonephritis are similar to those causing lower UTI with *Escherichia coli* predominating, although virulence factors may differ significantly from strains causing lower UTI. *Proteus, Pseudomonas, Klebsiella, Staphylococcus, Enterococcus*, and *Enterobacter* species are other important bacterial pathogens. Similar organisms are the causal agents in emphysematous pyelonephritis but *Clostridium septicum* and *Bacteroides fragilis* have also been reported. Rarely, pyelonephritis is secondary to fungal (especially *Candida* or *Aspergillus* spp.) or viral infection (BK virus, cytomegalovirus, herpes simplex virus, and adenovirus) predominantly in the immunocompromised.

Haematogenous infection does occur and the kidneys are frequently infected in settings of systemic bacteraemia, particularly with *Staphylococcus aureus* (bacteraemia or endocarditis) or fungal infections such as *Candida* spp. There is experimental evidence to suggest that bacteria are much more likely to evade host defences and seed damaged or obstructed kidneys compared to normal kidneys following haematological spread, presumably due to a failure of bacterial clearance. It is relatively uncommon to develop renal infection following Gram-negative bacteraemia in the context of normal kidneys (Measley and Levison, 1991). The identification of a virulent Gram-positive or fungal infection in the kidney should provoke a search for a distinct haematological source and exclusion of endocarditis.

In acute pyelonephritis, the kidney is enlarged (either focally or diffusely). There may be papillary necrosis, most typically in predisposed individuals (those with diabetes, sickle cell disease, or analgesic nephropathy). Localized bacterial infection may form an acute lobar nephronia (Fig. 177.1), intrarenal abscess, or perinephric abscess. Microscopically the hallmarks of acute pyelonephritis are wedge-shaped areas of intense inflammation, patchy and sharply demarcated with polymorphs in and around the tubules (Fig. 177.2) with relative sparing of the glomeruli, ultimately with suppurative necrosis or abscess formation.

Chronic pyelonephritis tends to have similar aetiological factors but is frequently associated with a failure of adequate resolution secondary to an abnormal urinary tract (particularly reflux in children), recurrent infection, impaired immunity, or inadequately treated infections.

Bacterial virulence factors in pyelonephritis

As with lower UTIs, the bulk of pyelonephritis is due to *Escherichia coli*. Only a few serotypes are responsible for the majority of these infections, exhibiting genetically distinct O, H, and K antigens. Interestingly, *E. coli* isolates from pyelonephritis have better adherence than cystitis isolates and the presence of mannose-resistant P fimbriae is found in > 90% of acute pyelonephritis isolates (Wullt et al., 2001) and the papGAP (class II) genotype strongly associates with pyelonephritis (Tseng et al., 2002; Johnson et al., 2005). Furthermore, while type 1 fimbriae expression is almost universal in cystitis it is less common in pyelonephritis strains possibly because P fimbriae downregulate type 1 as an adaptive mechanism (Holden et al., 2006). Another fimbrial adhesion, the Dr adhesin, binds to the Dr blood group component of decay-accelerating factor to facilitate invasion and has been associated with chronic and pregnancy-associated pyelonephritis (Goluszko et al., 2001; Nowicki et al., 2001; Das et al., 2005).

Clinical features

Acute pyelonephritis classically presents with fever, chills, costovertebral pain or tenderness, and lower urinary tract symptoms in the form of dysuria, frequency, and positive urine dipstick. However,

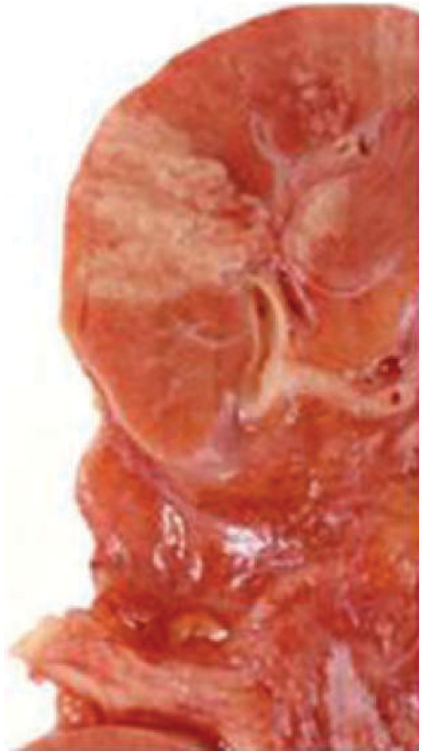

Fig. 177.1 Macroscopic appearance of localized pyelonephritis.

clinical presentation can vary greatly from almost asymptomatic to fulminant septic shock and a high index of suspicion is required, especially in the context of unexplained sepsis or renal dysfunction. This is particularly the case in the elderly who appear more prone to bacteraemia (Gleckman et al., 1982) and along with diabetics and the immunocompromised are more likely to present with non-specific signs and symptoms.

Blood cultures are positive in only 10–25% of cases but mid-stream urine (MSU) culture is positive in 95% of cases (Rubin et al., 1992) and consequently a urine culture should always be attempted before treatment is commenced. However, urine cultures may be negative in patients who are on or have recently finished antibiotics and it is important to remember that there may be an absence of pyuria in neutropenic patients, leading to the false assumption

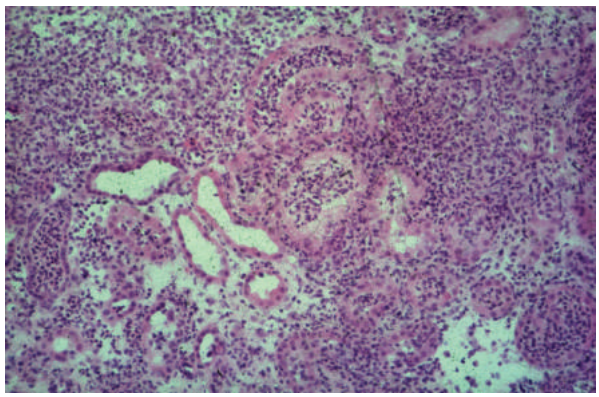

Fig. 177.2 Histology of acute infection.

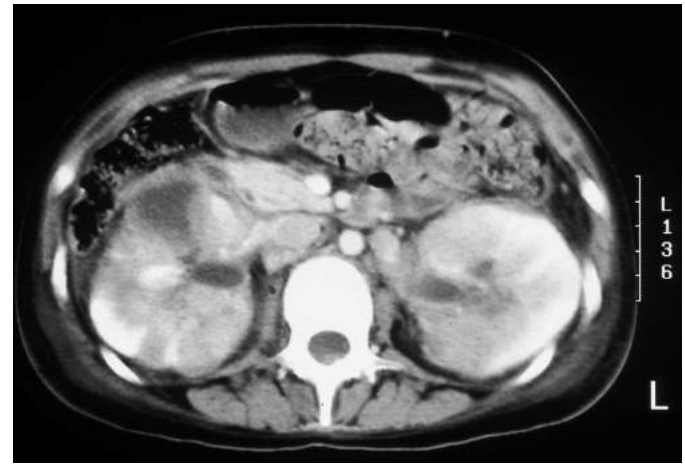

Fig. 177.3 CT scan of pyelonephritis.

that growth in the MSU is merely a contaminant. Although a rare finding, demonstration of a white blood cell cast on phase contrast microscopy can be invaluable in making an early diagnosis, particularly in the absence of a positive culture (Rubin et al., 1992).

A plain X-ray may show calcification and gross emphysematous pyelonephritis but is fairly insensitive and should be combined or replaced with an ultrasound (US) scan as initial imaging (McNicholas et al., 1991). A US scan may show an enlarged kidney (Johnson et al., 1992), rarely a nephronia or abscess, but is most critical in excluding a pyonephrosis (an infected, obstructed system) or emphysematous pyelonephritis, both of which are medical emergencies.

Contrast-enhanced computed tomography (CT) of the kidney, ureter, and bladder (KUB) is the most sensitive imaging technique (Fig. 177.3) (Sandler et al., 2000) and is particularly useful for demonstrating enlargement, focal infections, and perinephric stranding, excluding emphysematous pyelonephritis (Fig. 177.4), and is exquisitely sensitive for detecting stones. Magnetic resonance imaging (MRI) currently appears to hold no diagnostic advantage over CT except for the avoidance of potentially toxic contrast in patients at risk of contrast nephropathy. Occasionally a gallium, white blood cell scan or positron emission tomography (PET) scan may identify pyelonephritis or nephronia in a patient with pyrexia of unknown origin (PUO) (Fig. 177.5).

Following an episode of presumed pyelonephritis, US scanning or CT may show cortical scarring or localized thinning but dimercaptosuccinic acid (DMSA) scanning is the most sensitive method for detecting scarring (Fig. 177.6) (Lavocat et al., 1997). It requires reasonable kidney function and should not be performed in the acute phase of pyelonephritis (it is normal to delay for at least 3 months) to avoid false-positive results due to reduced uptake in areas of recent inflammation.

In acute pyelonephritis, deterioration in renal function is variable and probably dependent on the degree of shock, how extensive or localized the pyelonephritis is, and whether there is any concomitant obstruction. Infection can directly impact on renal function and over 40 years ago Kaye and Rocha demonstrated urinary concentration deficits early in experimental pyelonephritis which reversed with treatment and prostaglandin inhibitors (Kaye and Rocha, 1970).

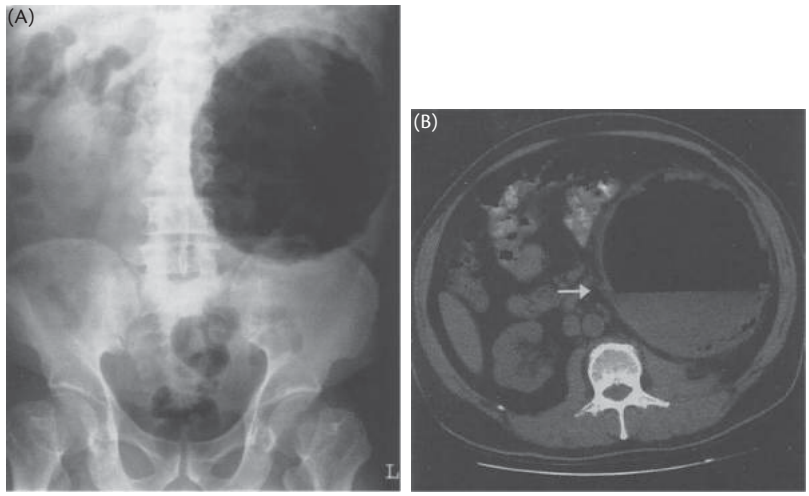

Fig. 177.4 Abdominal X ray and CT scan of emphysematous pyelonephritis.

Pregnancy

Pyelonephritis is said to be the most common severe medical complication of pregnancy with 1–2% of pregnant women being admitted for pyelonephritis in one retrospective study (Hill et al., 2005). The spectrum of organisms is similar to pyelonephritis in other settings (*Escherichia coli* in 70–85%) but with increasing numbers of Gram-positive organisms towards the end of gestation. Eighty to 90% of pyelonephritis occurs in the last two trimesters and more commonly on the right (50%; 25% on the left and 25% bilateral) (Hill et al., 2005; Archabald et al., 2009). Progesterone-induced dilatation of the ureters and renal pelves with decreased ureteral peristalsis and impaired drainage secondary to gravid uterus are all thought to contribute (Patterson and Andriole, 1997). Importantly, < 1% of those patients *without* bacteriuria in early gestation go on to develop pyelonephritis in the pregnancy compared to 20–40% of those *with* untreated bacteriuria early in pregnancy, emphasizing the importance of screening and treating asymptomatic bacteriuria in this setting (Gratacos et al., 1994).

Transplantation

In one study, the rate of acute pyelonephritis in transplants was 18.7%, mostly occurring in women and mostly within the first year

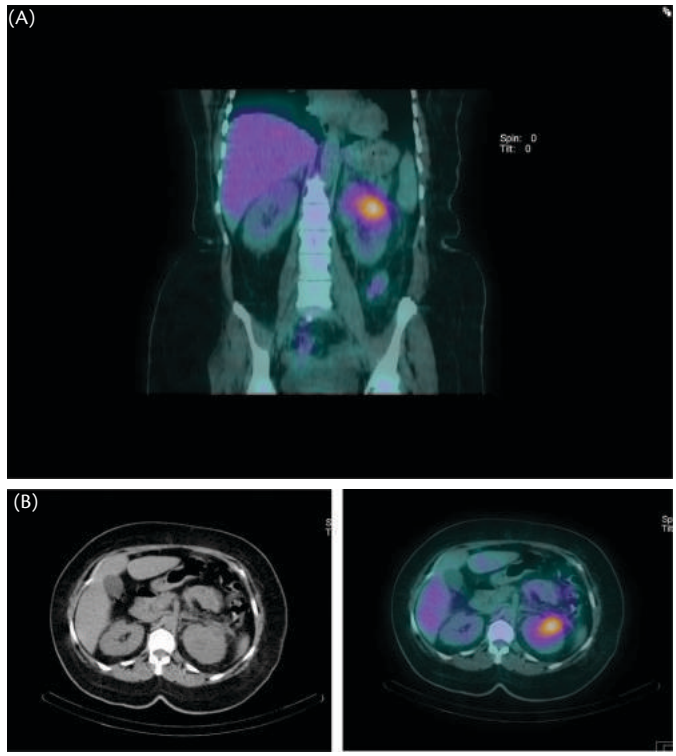

Fig. 177.5 Gallium SPECT CT imaging in pyelonephritis. Coronal (A) and transverse (B) images are shown.

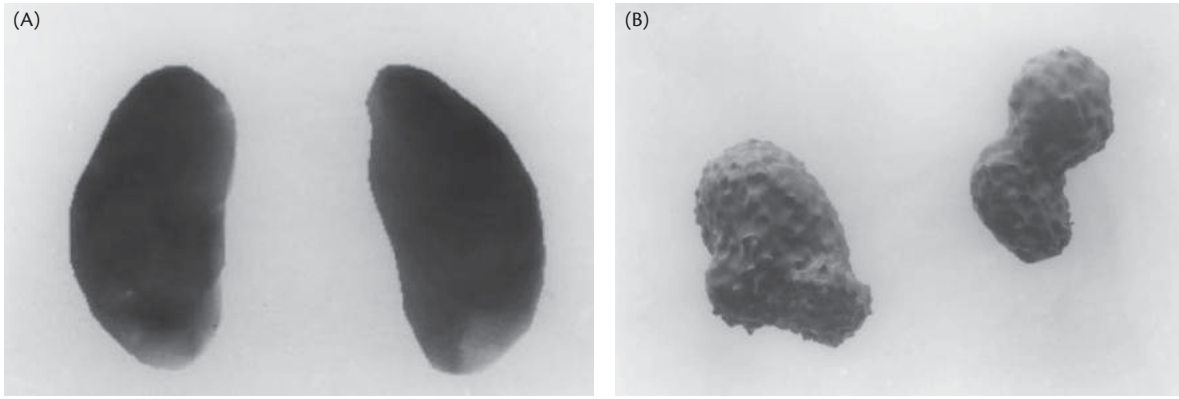

Fig. 177.6 DMSA of focal scar. (A) Normal. (B) Multiple scars.

(Pelle et al., 2007). The high incidence of transplant pyelonephritis is related to several factors including a very high incidence of lower UTI (see Chapter 179), manipulation of the urinary tract (universally with a urinary catheter and commonly with a ureteric stent), a high incidence of diabetes, and free reflux into the graft. The latter permits infection of the graft with less virulent strains that would not normally be capable of ascending to the kidney and causing pyelonephritis as well as promoting incomplete emptying with micturition. Deceased donors may bring hospital-acquired UTIs at the time of transplant and acquisition of multiresistant organisms is increasingly a feature of transplant tourism which should encourage surveillance cultures and isolation. Transplant pyelonephritis is not always obvious and distinguishing between an uncomplicated lower UTI and an infected kidney in an immunocompromised patient may be difficult, but has important implications for patient management.

Unusual presentations of pyelonephritis

Pyonephrosis and emphysematous pyelonephritis

Pyonephrosis occurs when there is infection in an obstructed upper urinary tract. It is a medical emergency and associated with a high morbidity and mortality. It is for this reason that ultrasound examination is recommended within 12 hours for any patient presenting with acute kidney injury, sepsis, and the possibility of an obstructed system. Obstruction is usually secondary to stones but can be secondary to any cause such as sloughed papillae, pelvoureteral junction obstruction, or malignancy. Pyonephrosis is more common in middle-aged women and diabetics.

Emphysematous pyelonephritis is a severe form of upper UTI with the presence of gas in the kidney and/or the surrounding tissues. Most (90–95%) cases occur in diabetics (Huang and Tseng, 2000; Pontin and Barnes, 2009) and it is associated with a rapid course, septicaemia, and high mortality (Schultz and Klorfein, 1962; Somani et al., 2008). The presence of gas-forming bacteria, impaired tissue perfusion (e.g. diabetic vasculopathy), and high levels of glucose predispose to emphysematous pyelonephritis and explain the marked preponderance of diabetics in this condition (Huang and Tseng, 2000) as well as asymptomatic bacteriuria being significantly more common in diabetics (Stapleton, 2002). Emphysematous pyelonephritis can be bilateral (5–8%) and is associated with obstruction in up to a third of cases (Stein et al., 1996).

The treatment of emphysematous pyelonephritis and pyonephrosis is described in more detail below but in essence, for both conditions, rapid diagnosis, culture, appropriate parenteral antibiotics, and percutaneous drainage are essential and urgent.

Xanthogranulomatous pyelonephritis

This condition is a rare, chronic form of pyelonephritis resulting in destruction of renal tissue and infiltration of lipid-laden macrophages (histiocytes), multinucleate giant cells, as well as neutrophils, plasma cells, and lymphocytes (Fig. 177.7). It has been reported at all ages, including neonates (Youngson and Gray, 1990) and children (Gupta et al., 2010), but the peak incidence is in the sixth decade. As with all pyelonephritis it is much more common in women and diabetics but has also been associated with obesity, chronic interstitial cystitis, rheumatoid arthritis, hepatitis C, and cirrhosis (Li and Parwani, 2011). Xanthogranulomatous pyelonephritis represents only 0.6% of chronic pyelonephritis but 19% of nephrectomies for chronic pyelonephritis. Xanthogranulomatous pyelonephritis is usefully divided into focal (15.4%) and diffuse (involving the entire kidney) (84.6%) (Loffroy et al., 2007); this classification determines treatment and prediction of prognosis. The precise aetiology is unclear but obstruction appears to be an almost universal prerequisite (usually secondary to a stone) along with chronic infection, although rare cases detected prenatally suggest that infection may not always be critical. *Escherichia coli* and *Proteus* are causative organisms in 59–95% of cases, the latter organism probably reflecting the strong association with stone disease. There is little data on virulence but the fact that xanthogranulomatous pyelonephritis is usually a subacute condition suggests that infection of an obstructed system with low-virulence organisms may predispose to xanthogranulomatous pyelonephritis whereas a virulent organism is more likely to result in a fulminant or emphysematous pyelonephritis.

Clinically, xanthogranulomatous pyelonephritis may present with malaise, fevers, weight loss, lower urinary tract symptoms, and loin pain although the latter is by no means universal. A renal mass may be palpable, pyuria is present in 57%, anaemia, an acute phase response, and raised alkaline phosphatase are very common

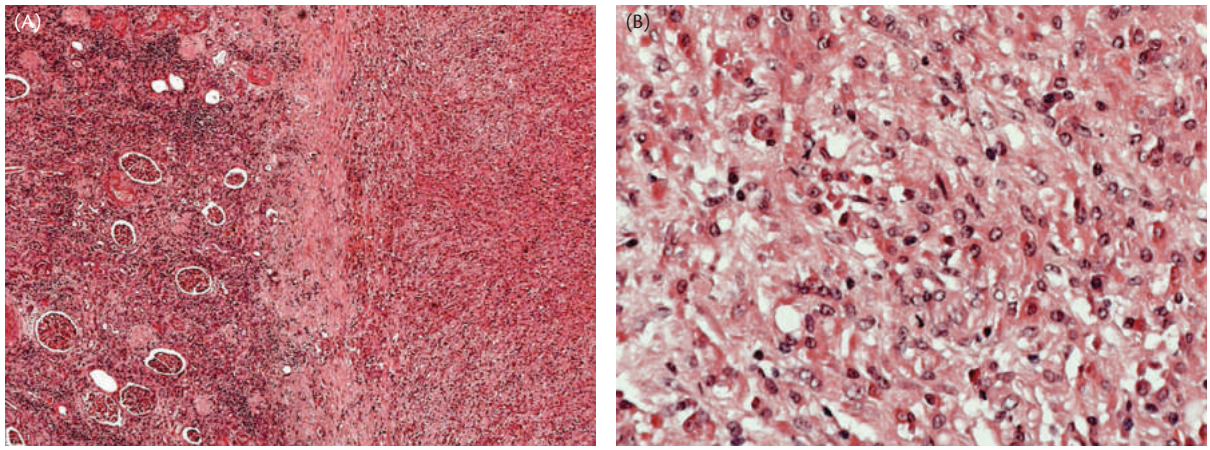

Fig. 177.7 Histology of xanthogranulomatous pyelonephritis. (A) Low power. (B) High power.

findings and a polyclonal increase in immunoglobulin G may point towards an infective rather than malignant origin.

The non-specific but progressive nature of the presentation often raises renal cell carcinoma, tuberculosis, and renal abscess as primary diagnoses and explains very low preoperative diagnosis rates in adults ranging from 22% to 46%.

Imaging is critical and a recent review of CT images demonstrated hydronephrosis in 90.9%, stones (often staghorn calculi) in 72.7%, pyonephrosis in 45.5%, and non-functioning kidney in 36.4%. Although contrast CT is probably the most sensitive modality for initial assessment, MRI may be helpful in differentiating renal cell carcinoma from xanthogranulomatous pyelonephritis if there is a sufficiently high burden of lipid-laden macrophages. Although renal cell carcinoma is an important differential, percutaneous biopsy is rarely performed and can be misleading; however, if there is a high index of suspicion, biopsy with immunohistochemistry may help diagnose xanthogranulomatous pyelonephritis and spare nephrectomy in patients with focal disease.

Treatment for diffuse xanthogranulomatous pyelonephritis is supportive and nephrectomy; there is no literature on medical salvage of a kidney with diffuse xanthogranulomatous pyelonephritis. However, there are cases of cure and renal preservation in patients with focal xanthogranulomatous pyelonephritis including in renal transplant grafts (Jones et al., 1989; Elkhammas et al., 1994). Nutritional support, removal of obstruction/calculus, appropriate prolonged antibiotics, and follow-up imaging are all important in this setting.

Malakoplakia

Malakoplakia is a rare granulomatous condition, secondary to impaired lysosomal clearance of intracellular bacteria by macrophages associated with reduced intracellular cyclic guanosine monophosphate activity. The failure to clear intracellular bacteria results in the pathognomonic Michaelis–Gumann bodies. Malakoplakia classically involves the urinary tract (typically bladder) but has been described causing upper and lower respiratory tract disease, and skin, ovarian, and thyroid disease. Bladder involvement is predominant with soft plaques and thickening of the bladder surface and may result in ureteric obstruction. Renal involvement does occur, can be bilateral, and results in diffuse involvement of the kidney and loss of function (Sheerin et al., 2003). Causative organisms are from the same spectrum associated with uncomplicated UTI, predominantly *Escherichia coli*. A history of recurrent UTI is common, and malakoplakia is four times more common in women and immunocompromised patients. Patients often present with chronic bladder irritation, fevers, haematuria, and non-specific constitutional symptoms as well as recurrent UTIs (Dobyan et al., 1993). Renal involvement may mimic malignancy or tuberculosis and CT scanning will often show diffuse enlargement or focal lesions but there are no diagnostic features to differentiate malakoplakia from other renal diseases.

Treatment should involve antibiotics (often a prolonged course) with good penetration into macrophages, typically quinolones and trimethoprim-sulfamethazoxole, but nephrectomy may be required for a diffusely involved, poorly functioning kidney.

Cyst and abscess infections

Infected renal cysts

In practical terms, the majority of patients suffering from infected renal cysts have adult polycystic kidney disease (APKD) and present with combinations of macroscopic haematuria, flank pain, lower UTI recurring after treatment, or PUO. The diagnosis is often empirical as differentiating active acute infection in a cyst from chronic changes or an acute bleed in APKD is difficult, even with contrast CT. Occasionally, aspiration of the cyst may yield useful microbiological results and should be considered in patients with restricted antibiotic choices or recurrent infections.

Renal abscess

Renal abscesses can be the result of haematogenous spread or as a rare complication of upper UTI particularly in the setting of renal stones or diabetes. Classically it may present as loin pain, fever, rigors, and tenderness in the costovertebral angle, but may simply manifest as a PUO and a raised acute phase response. A renal abscess may not be associated with a positive urine culture or may arise following inadequate treatment of pyelonephritis and should always be considered in a patient with pyelonephritis not responding rapidly to treatment. As with other renal infections, CT scanning is the imaging of choice but US is helpful if aspiration

or sequential imaging is required. Most renal abscesses respond to appropriate parental antibiotics without the need for percutaneous drainage but the bigger the abscess, the less likely conservative management will be effective without percutaneous or sometimes surgical drainage.

Perinephric abscess

This is most commonly as a result of extending renal infection/abscess but can be the result of a blood-borne bacteraemia and this differential is important in determining and treating the underlying cause. The causative organisms are the usual pathogens for UTI but with *Staphylococcus aureus* being relatively more common (and if cultured should provoke investigation for a haematological origin). The abscess is usually localized within Gerota's fascia but can extend to almost any proximate tissue including the psoas muscle, pelvis, diaphragm, and pleural space. The presence of pyuria or a positive MSU sample is very likely if the abscess is the result of an ascending infection and the patient is not on antibiotics, but less likely if the abscess of haematological origin.

The combination of percutaneous drainage and parenteral antimicrobial therapy is highly successful, and the treatment of choice unless percutaneous drainage is technically not possible. Surgical intervention should be considered if percutaneous drainage has failed and there is not significant improvement in the patient's condition.

Treatment and outcome of upper urinary tract infection

Treatment

The majority of uncomplicated pyelonephritis is treated in the community with only a fraction of patients requiring hospital admission. In one study of 242 non-pregnant women with acute pyelonephritis, only 7% required admission (Scholes et al., 2005). In uncomplicated pyelonephritis, clinical response to treatment should occur within 48–72 hours and patients treated in the community should be reassessed early to ensure that they are responding to treatment, and following cessation of treatment to ensure the infection has completely resolved. The immunocompromised, those with abnormal anatomy, unable to take medicine orally or be compliant, pregnant, or those showing signs of systemic sepsis should be referred to hospital.

The Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases have recently revised guidelines on the treatment of uncomplicated pyelonephritis in healthy premenopausal women (Gupta et al., 2011). Oral ciprofloxacin 1 g daily (single or divided dose) for 7 days (with or without an initial dose of 400 mg of intravenous (IV) ciprofloxacin) or levofloxacin 750 mg daily for 5 days is appropriate for community treatment when the prevalence of quinolone resistance is < 10%. When resistance is > 10%, an initial IV dose of aminoglycoside or 1 g of ceftriaxone should be added.

Alternatively, trimethoprim-sulfamethoxazole double strength 960mg twice a day for 14 days is very effective if the organism is sensitive. However, in one study this had inferior microbiological cure 89% versus 99% with ciprofloxacin and clinical cure 83% versus 96% for ciprofloxacin (Talan et al., 2000) and because of high rates of resistance trimethoprim-sulfamethoxazole is not recommend as empirical treatment. Oral beta-lactams are less effective in pyelonephritis and use for < 2 weeks is associated with treatment failure (Warren et al., 1999). They are associated with unacceptable levels of resistance in many populations and if used, patients should be given an initial IV dose of aminoglycoside or ceftriaxone and probably in combination with clavulanate or using a cephalosporin.

Hospitalized patients, especially if unwell or suspected Gram-negative bacteraemia, should have IV therapy which will be determined by local guidance and resistance patterns but should cover all potential organisms. Once an organism is identified, treatment can be de-escalated on the basis of resistance profile. If the patient is not showing a response within 48 hours an alternative antibiotic should be commenced in close liaison with microbiology support. Although 5–7 days of fluoroquinolone is appropriate for uncomplicated pyelonephritis, the duration of treatment for a more serious infection is not clear but treatment for 2 weeks is usually recommended (Hooton, 2003) and a longer course may be required in those with abnormal anatomy, stones, perirenal/perinephric abscess, or a recent relapse.

Infectious cysts in polycystic kidneys need to be treated with antibiotics that have good penetration into cysts. Fluoroquinolones and trimethoprim-sulfamethoxazole have good penetration with the caveat that trimethoprim is less effective with poor glomerular filtration rate, and beta-lactams have poor penetration.

The treatment of emphysematous pyelonephritis differs in the degree of urgency and that immediate nephrectomy historically had been the treatment of choice (Dutta et al., 2007; Wang et al., 2007). The mortality of this condition has improved from 78% in the late 1970s to 13.5% (Somani et al., 2008). This may be the result of earlier diagnosis with increasing use of CT scanning and lesser degrees of emphysematous pyelonephritis being identified earlier. It is clear that the majority of patients can be treated successfully with supportive management and percutaneous drainage (with a large drain ≥ 14 Fr). A meta-analysis of outcomes showed that medical management alone was associated with an increased mortality (Odds ratio 2.85) but that medical management with percutaneous drainage had the lowest mortality at 13.5% (superior to emergency nephrectomy) (Somani et al., 2008). Emphysematous pyelonephritis is often the dramatic climax to chronic subclinical UTI and as such, many patients may have received courses of antibiotics with serious risk of resistance to standard antibiotics (Soo Park et al., 2006). The choice between surgical nephrectomy and percutaneous drainage (reviewed by Pontin and Barnes, 2009) depends on the clinical scenario and stability of the patient but even if the kidney is non-functioning, percutaneous drainage and medical resuscitation may stabilize the patient before surgical relief of obstruction or nephrectomy.

The treatment of perirenal and intrarenal abscesses follows similar principles of resuscitation and broad-spectrum antibiotics following multiple cultures with percutaneous or surgical drainage (and culture) of large abscesses. As with emphysematous pyelonephritis, it is important to have close liaison between microbiology, radiology, and surgical teams.

In pregnancy, screening and elimination of asymptomatic bacteriuria is of prime importance to reduce risk of subsequent pyelonephritis. Treatment needs to be modified as fluoroquinolones (and tetracyclines) are contraindicated in pregnancy and sulphonamides should be avoided in the third trimester due to the risk of grey baby syndrome. Aggressive treatment of pyelonephritis is important and

third-generation cephalosporins given intravenously are a reasonable first-line choice assuming no previous resistance in antenatal testing.

In transplantation, similar treatment strategies apply: screening for and early treatment of lower urinary tract sepsis. Where possible, removal of catheter and stent, assuming free drainage, and aggressive treatment with IV antibiotics and hydration is vital. There is no good data on the duration of treatment for transplant pyelonephritis but it is common to treat for a minimum of 2 weeks. Due to the high risk of conversion of simple lower UTI to pyelonephritis it is important to address any underlying cause for recurrent UTI (see Chapter 176) and there is usually a low threshold for using low-impact prophylactic antibiotics.

Consequences of pyelonephritis

Papillary necrosis can occur as a complication of pyelonephritis most commonly associated with diabetes (50%) but is also a well-recognized complication of sickle cell disease, non-steroidal anti-inflammatory abuse, and obstruction. The abnormal anatomy of papillary necrosis of whatever cause almost certainly predisposes to complicated infection, especially if the sloughed papilla causes obstruction.

Renal scarring was said to be a cause of hypertension. Although this can happen, in practice, patients with a history of chronic pyelonephritis are often salt wasting, relatively polyuric, and normotensive when compared to other causes of chronic kidney disease (CKD).

Chronic pyelonephritis clearly does result in renal impairment which can be step-wise and often undiagnosed in the setting of CKD. In transplantation, acute pyelonephritis has been shown to be an independent risk factor for persistent renal function decline (Pelle et al., 2007); acute pyelonephritis in pregnancy has very significant fetal and maternal risks.

Pyelonephritis is stated as the primary cause of end-stage renal failure in 11% of patients in the United Kingdom (UK Renal Registry https://www.renalreg.org/wp-content/uploads/2014/12/02-Chap-02.pdf). However, the genuine impact of recurrent upper tract sepsis on renal function is clouded by the fact that many of these patients suffer from dysplastic kidneys, reflux nephropathy, or other congenital abnormalities of the urinary tract that predispose to renal impairment. Nonetheless it is likely that some patients, particularly diabetics, progress to end-stage renal failure more rapidly due to undiagnosed chronic pyelonephritis.

Summary

The majority of pyelonephritis is uncomplicated and relatively straightforward to treat. However, the increasing prevalence of resistant organisms, patients with diabetes, and other co-morbidities provides a serious challenge to the clinician. It seems very likely that chronic, emphysematous, and xanthogranulomatous pyelonephritis will be an increasing cause of CKD especially in those with co-morbidity. A high index of suspicion, early imaging (ideally CT scanning), early (microbiology-guided) treatment, and follow-up to ensure complete cure are critical in the management of patients with complicated pyelonephritis.

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CHAPTER 178

Complicated urinary tract infection

Ased Ali and Rob Pickard

Introduction

There are multiple ways in which urinary tract infection (UTI) can be defined related to the different perspectives of patients, clinicians, microbiologists, and public health specialists. For patients, UIT can cover a spectrum of symptoms from bad-smelling urine to full-blown pyelonephritis with significant loin pain, fever, and systemic symptoms. The microbiological definition was provided as a result of seminal work by Kass (1956, 1957), setting a threshold of at least 10^5 colony-forming units (cfu)/mL of the same bacterial species. Clinicians will typically take note of microbiological findings but will also consider symptomatic status and will, to some extent, define UTI by the need for antibiotic treatment. The British Infection Association actually does not recommend routine urine culture in adult women with suspected UTI and currently lists six symptoms as indicative of UTI: dysuria, frequency, suprapubic tenderness, urgency, polyuria, and haematuria. It recommends empirical antibiotic treatment either in the presence of one severe symptom or three or more mild symptoms (provided that no vaginal discharge is present). Culture is only indicated where there are fewer than two symptoms present. There is greater consensus in relation to complicated UTI, which is typically defined as 'a urinary infection occurring in a patient with a structural or functional abnormality of the genitourinary tract' (Nicolle and AMMI Canada Guidelines Committee, 2005). A complicated UTI is typically diagnosed on the basis of a positive urine culture in conjunction with one of the clinical features in Table 178.1 (Nicolle and AMMI Canada Guidelines Committee, 2005; Grabe et al., 2012).

While pregnancy can have functional and immunological effects, UTI during pregnancy is not normally considered to be 'complicated' but does require specific consideration. People affected by complicated UTI have widely differing underlying abnormalities but can be broadly categorized into two groups: those in whom the 'complicating' factors can be eliminated by treatment and those in whom the factors cannot be eliminated. Examples of the former group include removable stones or short-term catheters, examples of the latter group include those with neurological bladder dysfunction or long-term permanent indwelling catheters.

Aetiology

A wider spectrum of causative organisms are associated with complicated UTI, but as in simple cystitis, Enterobacteriaceae predominate, with *Escherichia coli* still the most common organism isolated (Frankenschmidt et al., 1997). *E. coli* strains isolated from patients with complicated UTI have been noted to have a lower prevalence of virulence characteristics than strains isolated from patients with acute uncomplicated cystitis—this finding is consistent with the host abnormality being at the heart of pathogenesis rather than bacterial virulence (Nicolle, 2007). However, despite the lower expression of virulence factors, the bacteria isolated from patients with complicated UTI are more likely to be antibiotic resistant than those isolated in uncomplicated infection. This is most likely due to repeated antimicrobial treatment in patients with recurrent infection prior to addressing the underlying abnormality and the healthcare-acquired origin of many complicated infections (Wright et al., 1999).

Other Gram-negative organisms frequently isolated include *Proteus mirabilis, Providencia stuartii*, and *Morganella morganii* and *Pseudomonas* spp., which are particularly common in patients with indwelling catheters. The most commonly isolated Gram-positive organisms are enterococci and coagulase-negative staphylococci, both of which are more commonly seen in asymptomatic patients (Tambyah and Maki, 2000). *Candida* spp. are also frequently isolated. Elderly patients (Tenney and Warren, 1988) and those with indwelling catheters (Nicolle, 1997) frequently have a mixed culture bacteriuria, with the latter also exhibiting biofilm formation.

Clinical diagnosis

The clinical presentation of complicated UTI is frequently the same as for uncomplicated UTI with a spectrum of symptoms such as dysuria, urgency, frequency, flank or suprapubic pain, and fever, but it may also present with no localizing symptoms. In those with neurological disease, reduced lower urinary tract sensation, or elderly patients with indwelling catheters, symptoms can be particularly difficult to identify because of atypical presentations (Cardenas and Hooton, 1995). For example, patients with spinal cord injuries may complain of increased bladder and leg spasms or autonomic dysreflexia (Trop and Bennett, 1991). In patients with more generalized neurological pathology such as multiple sclerosis, symptoms may be more non-specific such as increased fatigue, deterioration in neurological function, or increasing urinary incontinence. Such symptoms may be consistently exhibited by individual patients during episodes of UTI such that they can reliably indicate infection. Patients with complicated UTI may report cloudy or foul-smelling urine which can be distressing. Whether

Table 178.1 Risk factors for complicated urinary tract infection

Urological instrumentation	Intermittent catheterization
	Indwelling device, e.g. catheter or stent
Urinary obstruction	Urethral stricture
	Bladder outlet obstruction commonly related to prostatic enlargement
	Urethral diverticula
	Upper tract obstruction
	Urinary tract calculi
	Tumour
Voiding dysfunction	Persistent post-void residual urine of > 300 mL
	Dysfunctional voiding associated with vesicoureteric reflux
	Cystocele
	Neurological bladder dysfunction
Urinary tract modification	Renal transplant
	Urinary diversion
	Bladder replacement or reconstruction using bowel segments
Other	Urothelial trauma
	Renal failure

this is defined as a symptomatic UTI or as asymptomatic bacteriuria is unclear (Nicolle, 1994). Fever without local symptoms is a more reliable indicator of infection but lacks specificity.

In addition to urological abnormalities other co-morbidities such as diabetes are frequently present as additional risk factors and may be implicated in the causation of the underlying urinary tract abnormality.

Laboratory diagnosis

Due to the wide variety of organisms involved in complicated UTI as well as the increased prevalence of resistant strains and mixed populations, a urine culture taken prior to the commencement of treatment is highly recommended. As well as confirming the infection, this sample will also help identify the bacteria involved, their antibiotic susceptibilities, and potentially their virulence factors.

Depending on individual national and local reference thresholds which may differ for men and women, significant bacteriuria in a complicated UTI may be defined by counts of $\geq 10^5$ cfu/mL or $\geq 10^4$ cfu/mL, in a mid-stream urine sample (Grabe et al., 2012). If an 'in and out' catheter urine sample is taken, $\geq 10^4$ cfu/mL can be considered relevant. For an asymptomatic patient, two consecutive urine cultures (at least 24 hours apart) yielding $\geq 10^5$ cfu/mL or $\geq 10^4$ cfu/mL of the same microorganism are required.

Although a positive urine culture is useful in confirming infection, it should be remembered that it is not an essential part of the clinical diagnosis of symptomatic urinary infection. In populations with a high prevalence of asymptomatic bacteriuria such as the elderly and those living in institutions or those with indwelling urological devices such as urethral catheters or ureteric stents, a positive urine culture has a low positive predictive value for symptomatic infection (Orr et al., 1996; Nicolle and AMMI Canada Guidelines Committee, 2005). A urine sample with no significant growth on culture is an important finding in terms of excluding urinary infection although the method of collection, prior use of antibiotics, and previous response of antibiotic treatment all have to be considered.

Pyuria (identified by urinalysis or a leucocyte esterase dipstick test) is also present in many patients with asymptomatic bacteriuria and like positive culture is consistent with, but not diagnostic of, infection. Similarly, the absence of pyuria has a high negative predictive value and a urinalysis without pyuria makes urinary infection using microbiologically based definitions less likely.

Treatment

The treatment of complicated UTI should be tailored to the severity of disease judged by the history and clinical signs, and the results of investigation such as renal function tests and imaging. There is no evidence to support the use of antimicrobial therapy in the absence of symptoms apart from prior to interventions such as urinary drainage or stone removal (Nicolle and AMMI Canada Guidelines Committee, 2005). Clinical trials have shown no benefit in the treatment of asymptomatic bacteriuria in people with diabetes, long-term indwelling catheters, elderly residents of nursing homes, or spinal injury patients managed with intermittent self-catheterization (Nicolle and AMMI Canada Guidelines Committee, 2005). The use of antimicrobial therapy in these situations may cause harm in terms of increasing the risk of colonization with resistant organisms and altering the individual's and community's bacterial ecology.

Choice of agent for empirical treatment of a symptomatic complicated UTI is made difficult by the wide spectrum of possible pathogens and increased likelihood of resistance. Local knowledge of potential pathogens and antibiotic resistance patterns is vital, and if possible, it is prudent to delay antimicrobial therapy until culture and sensitivity results are available to enable targeted therapy against the known pathogen. An assessment of the severity of the underlying urological abnormality and its effect on renal function will also inform the prognosis and decision on treatment. However, where the clinical status of the patient necessitates that early empirical therapy is initiated, the antimicrobial choice should be reassessed once culture results become available (typically 2–3 days).

While there are a number of clinical trials of treatment in complicated urinary infection, small sample size, variability in cohorts, and exclusion of patients with resistant strains has made it difficult to translate findings into practical guidance for management. It is very important to seek local microbiological guidance and local or national antibiotic policies should provide guidance. For symptomatic infection without immediate threat to life or health then fluoroquinolones such as ciprofloxacin are effective. This class of antibiotic has a wide spectrum of bactericidal activity that covers most of the likely pathogens, and they reach high concentrations in both urogenital tissues and urine. In addition, most patients with symptomatic infection can be treated effectively with oral therapy as high plasma concentrations can be attained (Mombelli et al., 1999). Unfortunately, widespread and perhaps indiscriminate use of fluoroquinolones is leading to rapidly increasing bacterial resistance and is also implicated in bacterial ecological change and public health concern about the emergence of highly resistant strains of *Escherichia coli*. Its use is therefore being increasingly restricted in countries with active public health systems such as the

United Kingdom. The main alternative agent for complicated UTI, co-trimoxazole (trimethoprim/sulfamethoxazole), is also not used in some countries due to concerns regarding toxicity.

The other alternatives are therefore second-generation cephalosporins such as cephalexin and drugs that can counter beta-lactamase activity such as amoxicillin/clavulanic acid (co-amoxiclav). For people presenting with life- or health-threatening infection and those with marked systemic symptoms, parenteral therapy should be used with the co-administration of gentamicin when appropriate. With all parenteral drugs the agent and dosage should be adjusted according to culture results and clinical response and step-down to oral therapy should take place as soon as possible.

Successful first-line antimicrobial therapy will usually ameliorate symptoms rapidly, with substantial clinical improvement in 2–3 days. However, where initial therapy has failed or in clinically severe infections, alternative broader-spectrum antibiotics with anti-pseudomonal activity should be considered. Options include fluoroquinolones (if not used for initial therapy), ureidopenicllins with a beta-lactamase inhibitor, for example, piperacillin and tazobactam (Naber et al., 2002), a group 3b cephalosporin, for example, ceftazidime (Cox, 1993), or a carbapenem. An aminoglycoside may also be included. The use of an intravenous anti-pseudomonal agent is particularly recommended in the treatment of hospital patients with severe UTI due to the increased risk of urosepsis (Carson and Naber, 2004).

The optimal duration of treatment for acute symptomatic episodes in complicated UTI has not been systematically studied. However, for general guidance, it is recommended that treatment be continued for 7 days in cases where symptoms are primarily restricted to the lower urinary tract and 14 days in cases with fever, bacteraemia, or organ impairment (Nicolle and AMMI Canada Guidelines Committee, 2005). However, where the clinical situation dictates, a course may be prolonged for up to 21 days (Grabe et al., 2012). In cases where resolution is taking longer than expected, it is worthwhile reassessing the patient to exclude (a) urinary obstruction or abscess (which may require drainage), and (b) the presence of resistant strains.

Due to the increased risk of resistant bacteria in complicated UTI coupled with the increased risk of recurrence (Nicolle, 1997), it is recommended that urine cultures are obtained after the end of antimicrobial therapy and compared with pre-treatment cultures to confirm eradication and check for any remaining resistant strains (Grabe et al., 2012).

Long-term treatment

Where the underlying genitourinary abnormality cannot be corrected and patients suffer with frequent, recurrent, symptomatic infection, it is reasonable to consider the careful and well-monitored use of long-term suppressive antimicrobial therapy. Typically patients with long-term ureteric stents, non-removable stones, or immunosuppression such as for renal transplantation may be considered for this type of management. There is evidence showing the efficacy for norfloxacin, a quinolone, in this regard although the concerns regarding adverse personal and community effects should be considered (Sheehan et al., 1988).

In contrast to the above situation, there is no evidence to support the use of antibiotics to prevent infection or treat asymptomatic bacteriuria during long-term or short-term catheterization as it promotes the emergence of resistant strains (Warren et al., 1982; Yoshikawa et al., 1996). Symptomatic UTI associated with an indwelling catheter should be treated firstly by replacement with a fresh catheter and secondly with a 7-day course of a narrow-spectrum antibiotic, based on culture and sensitivity results.

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CHAPTER 179

Urinary tract infection in a patient with a kidney transplant

Mark Harber

Definition

There is variation in reporting of post-transplant urinary tract infection (UTI) that is partly dependent on definition: UTIs post transplant can include asymptomatic bacteriuria, pyuria, acute cystitis, pyelonephritis, and septicaemia and to some extent the incidence depends on the vigour of surveillance and culture. In the presence of pyuria it is important to exclude bacterial contamination but it is necessary to note that pyuria may be absent if the patient is neutropenic. In addition, standard culture techniques are not ideally suited to fastidious organisms (which may be responsible for disease in the immunocompromised). Patients frequently receive concomitant antibiotics and immunosuppression tends to suppress clinical symptoms and signs of urosepsis. Consequently both upper and lower UTIs post transplant are probably significantly under-reported.

Epidemiology

With the above in mind, the reported incidence of post-transplant UTI varies substantially from 6% to 86% (Schmaldienst et al., 2002), but most studies report evidence of UTI, symptomatic or otherwise, at rates > 50% of patients. In one representative study, 74% of transplant recipients developed a UTI within the first year, of which 81.9% were in the first 3 months (Pelle et al., 2007). Prospectively screening *asymptomatic* transplant patients, Fiorante and co-workers detected bacteriuria in 51% (Fiorante et al., 2010). Thus whatever the true incidence, compared to the general population there is clearly a huge excess among transplant recipients (Foxman, 2002). This vastly increased risk relates to recipient, donor, surgical, and immunological factors, very few of which are modifiable (Box 179.1).

Aetiology and pathology

The vast majority of UTIs post transplant result from ascending infection. *Escherichia coli* remains the commonest uropathogen responsible for transplant UTIs, however the proportion is significantly less (55–70%) compared to non-transplant patients (80–95%) (Dantas et al., 2006). The difference is made up with an increasing proportion of Gram-positive as well as less virulent and atypical organisms. In some cases there may be evidence of polymicrobial infections, perhaps dominated by a more prosaic organism (Domann et al., 2003).

The urinary tract is protected from ascending infection in a variety of ways including the physiochemical antibacterial effects of urine (acidic and hyperosmolar), urine flow, and complete voiding. Urine also contains inhibitors of bacterial adhesion and growth (lactoferrin, low-molecular-weight oligosaccharides, mucopolysaccharides, and Tamm–Horsfall protein). Uroepithelial defence mechanisms include antibacterial peptides and FimH-mediated exfoliation of infected superficial epithelial cells. Finally, the innate immune system is important in combating urosepsis via neutrophils and pro-inflammatory cytokines. The role of acquired immunity is likely to be much less significant, especially for lower UTIs. Therefore, the evidence implicating one immunosuppressive agent over another or even the total exposure in predisposing to UTIs is weak. However, in transplantation many of the above natural defences against ascending infection will be impaired, especially in the setting of delayed or poor graft function. Furthermore, urinary tract manipulation with urinary catheters and ureteric stents is universal, and this coupled with reflux to the transplant kidney in up to 85% of patients and a high prevalence of abnormal urinary tract anatomy all impair complete voiding (Fig. 179.1) and breach natural defences.

Clinical presentation

UTIs may present classically with lower urinary tract symptoms, fever, pain, and tenderness over the graft and constitutional symptoms. They may also present with fulminant and life-threatening sepsis particularly in the first weeks after a transplant. However, as many as 50% of patients have asymptomatic bacteriuria (Fiorante et al., 2010) and immunosuppression (especially steroids) may subdue the normal clinical response and it is relatively common for patients, even with transplant pyelonephritis, to be entirely asymptomatic. Infection may result in unexplained graft dysfunction, anaemia, or persistent acute phase response.

Investigations

As infections can be clinically covert it is important to maintain active surveillance and have a high index of suspicion. An ultrasound is helpful to exclude an obstructed system and critical in assessing bladder emptying. In the setting of acute pyelonephritis (APN) or urosepsis failing to settle, computed tomography scanning may demonstrate stones, perinephric stranding, or a focal infection and a gallium scan may show uptake in native or

Box 179.1 Reported risk factors for urinary tract infection post transplant

- Female
- Elderly
- Urological cause for end-stage renal disease
- Urinary tract infections pre transplant
- Diabetes
- Long period on haemodialysis prior to transplant
- Impaired bladder drainage or prostatic hypertrophy
- Infected perfusion fluid or graft
- Deceased donor
- Adult polycystic kidney disease (native kidneys *in situ*)
- Delayed graft function
- Acute rejection
- Chronic viral infection
- Immunosuppression
- Reflux to transplant
- Ureteric stent
- Indwelling catheter
- Surgical manipulation of the graft.

transplant kidneys as the source of sepsis (Fig. 179.2). Occasionally the diagnosis of APN is made incidentally on transplant biopsy with histological evidence of ascending infection.

Consequences of post-transplant urinary tract infection

Although the commonest post-transplant infection, reporting bias has made it difficult to identify the genuine impact of lower and upper UTIs post transplant. In terms of acute complications there is relatively little data on hospitalization but general experience is that this is common and septicaemia is quoted as a complication in up to 7% of post-transplant UTIs. Septicaemia from UTI is potentially fatal at any stage but is associated with a mortality of 11% when occurring early post transplant (within the first month) (Saemann and Horl, 2008). Recurrence is common and of those experiencing a UTI, approximately 40% go on to have a second UTI.

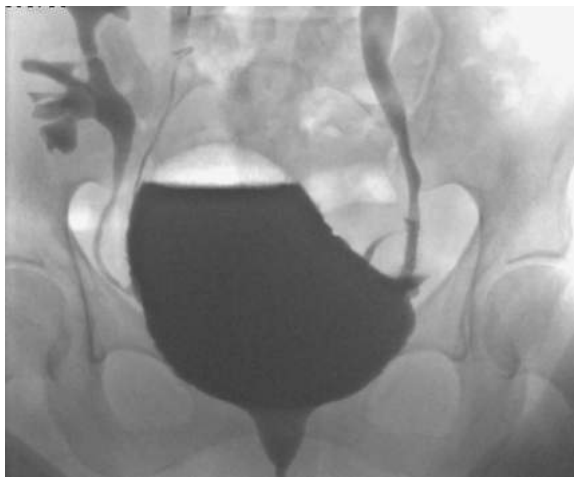

Fig. 179.1 Micturating cystourethrogram in transplant patient with recurrent transplant pyelonephritis demonstrating reflux to transplant and native ureters.

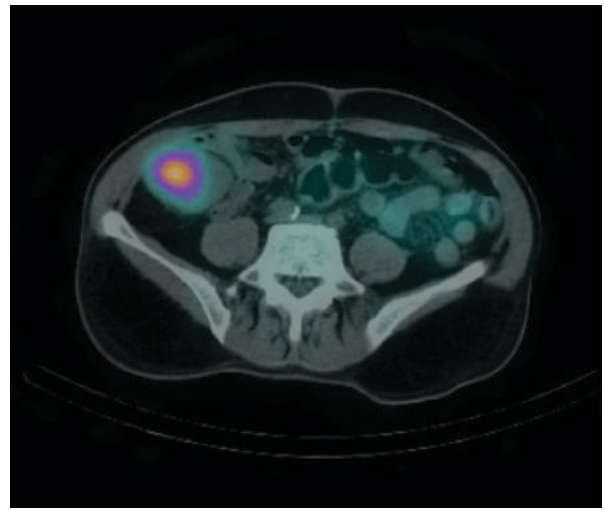

Fig. 179.2 Gallium CT demonstrating pyelonephritis in a transplant kidney.

Importantly, 7–40% of patients with lower UTIs are said to go on to develop APN of the transplant. The risk factors for graft involvement of an UTI include (a) female sex, (b) recurrent UTIs, and (c) rejection. The link with rejection is intriguing and may represent an increased burden of immunosuppression (especially steroids) with UTI following treated rejection or the increase in pro-inflammatory cytokines in a UTI provoking an alloimmune response. Once developed, APN is an independent risk factor for reduced graft function, rejection, and graft loss (Kamath et al., 2006; Pelle et al., 2007; Saemann and Horl, 2008; El-Zoghby et al., 2009) and not surprisingly is usually associated with acute deterioration in graft function.

The consequences of seemingly uncomplicated UTI or asymptomatic bacteriuria on long-term graft survival or function are less clear and late UTIs were traditionally thought of as largely benign. However, patients with asymptomatic bacteriuria have significantly higher APN rates (12–26 per 100 patient-years compared to 1.07 if no asymptomatic bacteriuria) and in some studies it is associated with increased creatinine and impaired function (Ciszek et al., 2006). Dupont and colleagues demonstrated that late UTIs are associated with scarring of the transplant (Dupont et al., 2007) and in a large retrospective registry study of nearly 29,000 patients, UTIs after 6 months associated with worse long-term patient survival (Abbott et al., 2004). A retrospective analysis of 189 patients demonstrated that 50% had asymptomatic bacteriuria. Treatment of these patients while asymptomatic resulted in a reduced rate of APN (7.6 vs 12–26 per 100 patient-years) compared to historical controls but with no difference in creatinine clearance at 3 years (Fiorante et al., 2010).

Treatment and prophylaxis

The role of prophylactic antibiotics post transplant is complicated by the almost universal use of trimethoprim-sulfamethoxazole as prophylaxis against *Pneumocystis jirovecii* and very high rates of resistance to antibiotics in the post-transplant setting, often exceeding 50% for ciprofloxacin, Augmentin®, and approaching 100% for trimethoprim-sulfamethoxazole. Despite this, several studies have shown benefit of trimethoprim-sulfamethoxazole in reducing the rate of UTI post transplant and current KDIGO guidelines recommend trimethoprim-sulfamethoxazole as UTI prophylaxis (Kasiske et al., 2010). In one study, 250 mg once daily of ciprofloxacin for 6 months significantly reduced the rate of UTI compared to trimethoprim-sulfamethoxazole from 48% to 15% (Moysés Neto et al., 1997). A recent meta-analysis of six trials of antibiotic prophylaxis totalling 545 patients demonstrated a 60% reduction in bacteriuria and an 87% reduction in bacteraemia (Green et al., 2011).

There are no randomized controlled trials providing guidance for the treatment of post-transplant UTI and most practice has been based on dogma. In the past, it had been advocated that early lower UTIs in the transplant recipient should be treated for 4 weeks, more recent advice has suggested 10–14 days with 5 days for UTIs occurring later (Saemann and Horl, 2008). In practical terms many clinicians treat a lower UTI or asymptomatic bacteriuria for 5–7 days and APN for 14 days (initially with intravenous therapy).

It is clearly critical to exclude obstruction acutely and to have close liaison with microbiology regarding local resistance profiles to ensure the appropriate antibiotic is given intravenously to an acutely unwell patient. It seems prudent to also ensure high fluid intake, good diabetic control, and rapid removal of urinary catheter or ureteric stent if present (with culture). It is important to ensure that appropriate antibiotics have already started at the time of stent removal. If the patient fails to respond rapidly, has highly resistant organisms, or has a rapid relapse with the same organism then significantly prolonging the course of antibiotics is prudent. In this setting, good imaging of the bladder, transplant, and native kidneys to exclude stones, obstruction, or a localized collection is mandatory.

In short, there are currently no clear data that long-term prophylaxis in the first year of transplant alters graft or patient survival but there is now emerging evidence that prophylaxis against UTI in the early transplant period significantly reduces bacteriuria and septicaemia. The implication from this is that prophylaxis is probably a good thing in the first weeks or months of a transplant. However the optimum duration of prophylaxis is far from clear; resistance rates to common antibiotics are already extremely high in this setting, and very few studies assess the incidence of C*lostridium difficile* or allergy with long-term antibiotics. For established patients with late recurrent UTIs, the situation may be slightly different in that there is anecdotal evidence that single-dose night-time prophylaxis is helpful as is a single post-coital dose in those women who have a close association between intercourse and subsequent UTI.

Summary

There is a dramatically high incidence of UTIs post transplant ranging from asymptomatic bacteriuria to fulminant sepsis. Furthermore there is increasing evidence that early and late UTIs can have significant adverse consequences for the transplant and recipient. Relatively few of the risk factors are modifiable but reducing catheter time, culture of perfusion fluid, and early removal of ureteric stent (especially if infection present) all seem sensible. Prophylactic antibiotics reduce the rate of UTIs post transplant but resistant rates are very high, the optimum duration unknown, and determining the risk:benefit ratio of additional antibiotics in combination with *Pneumocystis jirovecii* prophylaxis with trimethoprim-sulfamethoxazole is a challenge for the transplant physician.

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CHAPTER 180

Urinary tract infection in infancy and childhood

Heather Lambert

Impact and long-term sequelae of childhood urinary tract infection

Epidemiology

Urinary tract infection (UTI) is common in childhood occurring in between 2% and 8% of children. Incidence of UTI varies with age, gender, and race (Shaikh et al., 2008). In boys, the highest incidence is in infancy and reducing thereafter. Reported rates in Sweden (Jakobsson et al., 1999) and in northern England (Coulthard et al., 1997) are similar. It is generally accepted that rates are higher than those reported in earlier epidemiological studies from the 1970s and 1980s (Hellström et al., 1991; Marild and Jodal, 1998). It is not known whether this represents a true rise in incidence or difference in rates of ascertainment. There is considerable geographic variation in reported incidence of UTI, some of this may be due to rates of ascertainment as in areas with a centre of interest rates appear to be higher.

Large numbers of children with UTI are seen in the community by general practitioners and primary care physicians but there is frequently a delay in treatment and not all are referred for further investigation (Vernon et al., 1997). There are considerable problems in the diagnosis of UTI especially in younger patients, including a lack of awareness, non-specific symptoms, and difficulties in collecting and analysing specimens. UTI may be recurrent; about a third of girls have a further UTI within a year. The recurrence rate in boys is much lower.

Long-term sequelae

UTI is usually uncomplicated but does constitute a considerable burden of acute illness because it is so common. In addition it may sometimes be associated with significant long-term sequelae related to reflux nephropathy. This may cause hypertension, proteinuria, pregnancy-related complications, and, in a very small proportion, renal failure.

Reflux nephropathy is the term describing either reflux-associated dysplasia or acquired renal scarring, or a combination of these. Scarring, once present, is irreversible and if severe may lead to chronic renal failure (CRF). This may present years or decades later. Reflux nephropathy is probably the most important aetiological factor in the development of hypertension in children and young adults. However, it is difficult to quantify the long-term risk of CRF or hypertension resulting from an individual episode of UTI in childhood. In a meta-analysis in 2010, the risk of renal scarring after an initial UTI in childhood was estimated to be 15%; about 50% in children having acute pyelonephritis and those with vesicoureteric reflux (VUR) being more likely to develop acute pyelonephritis and permanent scarring compared to those without VUR, and those with higher grade VUR more than those with lower grades (Shaikh et al., 2010). However, there is not good evidence of the extent of long-term risk associated with minor degrees of scarring. One major problem is timescale. Adults presenting with reflux nephropathy may not have access to details of medical problems in their early childhood, many decades ago. In addition, many will not have had UTI in early childhood correctly diagnosed or appropriately investigated. Children with reflux nephropathy may not present in renal failure or with hypertension until very many years later, making prospective studies difficult to perform. Many existing studies are of small numbers or are retrospective. Ideally, cohorts of children need following prospectively for 40 or 50 years to determine more accurate estimates of adverse outcomes in adulthood.

The terms renal scarring, reflux nephropathy, and chronic pyelonephritis are often used loosely and, sometimes, interchangeably which leads to confusion. Focal renal scarring is usually associated with previous UTI, and is usually inferred from investigation findings, for example, the photon deficient areas on a radioisotope dimercaptosuccinic acid (DMSA) scan or the appearance of an ultrasound (US) or intravenous urogram. Reflux nephropathy refers to a spectrum of renal diseases associated with VUR which include renal scarring, dysplasia of various degrees, and some *in utero* renal damage. It is often difficult to distinguish between antenatal and postnatal reflux nephropathy as the two frequently coexist. Pyelonephritis is perhaps strictly a histological diagnosis but is often used to describe a clinical pattern.

Hypertension

Several retrospective and prospective studies link the development of hypertension with renal scarring (Goonasekera and Dillon, 1998; Jacobson et al., 1989). There is very good evidence that there is a substantially increased risk, which is worse for those with more severe and bilateral scarring (Smellie et al., 1998). The size and duration of risk for any individual or for those with less severe scarring is difficult to enumerate. The data depend on the population studied as one small population-based follow-up study 16–26 years after childhood UTI found no difference in blood pressure (BP) between those with or without renal scarring (Wennerström et al., 2000a). What appears to be a small or scarred kidney on imaging may actually represent a number of different or combined

underlying pathologies, for example, dysplasia or hypoplasia. Not all of these may be associated with a greater risk of hypertension but in cases of doubt, regular long-term monitoring of BP is required. It is currently recommended that children with scars have their BP monitored on at least a yearly basis for life in order to detect pre-symptomatic hypertension.

Renal failure

The published incidence of end-stage renal failure (ESRF) secondary to renal scarring varies. Pyelonephritic renal scarring was reported to be the primary renal diagnosis in 39% of children undergoing renal transplantation in Ireland from 1980 to 1990 (Thomas et al., 1992). In Australia and New Zealand from 1971 to 1998 reflux nephropathy was the primary diagnosis in 13% of patients entering the dialysis and transplantation programme between the ages of 5 and 44 years, with no clear trend of change during the study period (Craig et al., 2000). In one part of France pyelonephritis with reflux accounted for 12% of CRF (Deleau et al., 1994). In a cohort of siblings recruited for a VUR genetics study those with bilateral scarring had lower glomerular filtration rate (GFR) than those with unilateral or no reflux nephropathy (Lambert et al., 2011). In a follow-up study of 127 individuals with childhood VUR for an average of 37 years, 83% of those with bilateral scarring had reduced GFR (Landes-Vasama et al., 2006). In North America, 5.3% of transplant patients and 3.5% of dialysis patients are reported as having a diagnosis of reflux nephropathy (North American Pediatric Renal Trials and Collaborative Studies, 2007), but North American and European registries do not code specifically for renal scarring. Thus it is difficult to distinguish between those reaching renal failure due to scarring of normal kidneys (i.e. possibly preventable reflux nephropathy) and those in whom the underlying diagnosis is reflux-associated dysplasia. Nor is it possible to discern the role of UTI in deterioration of renal function in those with dysplasia (who also have a high incidence of VUR putting them at risk of possible damage from UTI).

The real risk of ESRF is not known, in a recent review the risk of ESRF following a first UTI was estimated to be between 1 in 154 and 1 in 200,000 (Round et al., 2012). Hopefully prospective studies will clarify issues. The most compelling data come from Sweden where the reported incidence of ESRF in childhood caused by non-obstructive reflux nephropathy has reduced from 6% in the years 1978–1985 to zero in the years 1986–1994 and it was suggested that increased awareness and improved diagnosis of UTI in young children was important (Esbjorner et al., 1997; Jakobsson et al., 1999).

Pregnancy-related complications

Pregnant women have an increased risk of cystitis and UTI if they had a UTI and VUR in childhood. However, ureteric re-implantation in childhood does not necessarily protect against symptomatic UTI in pregnancy and may be associated with increased risk (Mansfield et al., 1995). There is controversy about the role of UTI in pregnancy and risk of pre-term delivery or poor fetal outcome (Davison, 2001). The risk of hypertension (Martinell et al., 1990) and pre-eclampsia (McGladdery et al., 1992) is higher in women with renal scarring. Scarring, rather than continued presence of VUR, is related to morbidity in pregnancy (Hollowell, 2008). Fetal and maternal outcome are worse if the mother has severe renal impairment or established hypertension prior to the pregnancy (Lindheimer et al., 2001).

Challenges

Is renal scarring preventable? Most children who are going to acquire renal scars already have them at the time they are investigated for the first time following UTI. However, there is evidence showing that scarring can be potentially prevented by rapid treatment in susceptible children. Fig. 180.1 shows DMSA 1 performed after the first episode of UTI and DMSA 2 after later UTIs. The major clinical factor between how these episodes of UTI were treated was that the first episode was treated within 1 day but mean time to treat for subsequent episodes was 7 days (Coulthard et al., 2009a). Thus if long-term outcome is to be improved, there are many challenges. There is general agreement that rapid diagnosis and treatment of acute UTI in susceptible individuals is very important.

Controversy exists about how best to achieve that—some propose identification of those at high risk of sustaining renal damage while others propose more rapid treatment of young children with suspected UTI (National Institute for Health and Clinical Excellence (NICE), 2007; American Academy of Pediatrics (AAP), 2011; Prasad and Cheng, 2012). Increased awareness amongst healthcare professionals and the public of the importance of UTI is needed. The evidence for association of scarring with delay in treatment is largely from clinical series (Winter et al., 1983; Smellie et al., 1994; Hiraoka et al., 2003; Coulthard et al., 2009), but this

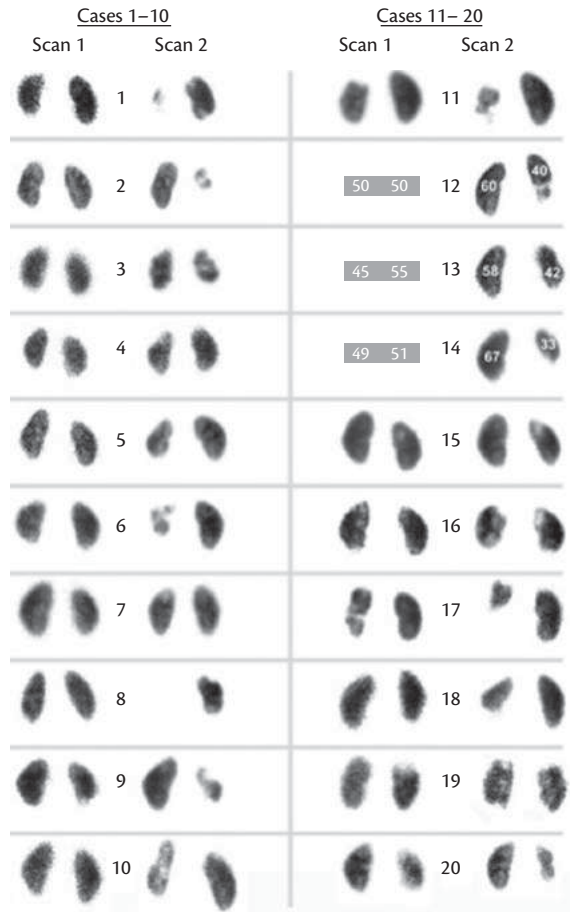

Fig. 180.1 DMSA appearances after first UTI and repeat scan after further UTIs demonstrating progression of renal scarring.
From Coulthard (2009a).

is supported by animal studies (Miller and Phillips, 1981; Ransley and Risdon, 1981; Slotki and Asscher, 1982). Secondary analysis of data from an Italian study designed to compare different antibiotic regimens (IRIS 1 and 2), proposed that in children with evidence of pyelonephritis, the degree of permanent renal scarring was not related to the number of days (1–5) of reported fever before treatment commenced (Hewitt et al., 2008). However that conclusion appears to be based on analysis only of children with acute DMSA changes and re-analysis including those with normal acute DMSA suggests a possible opposite interpretation. Other clinical series indicate that fever and clinical illness are not clearly related to finding of scarring (Coulthard et al., 2010). Prospective audit indicates scarring rates may be reduced by a programme of education, awareness, and active rapid management of UTI (Coulthard et al., 2014a). We would recommend that until better evidence materializes, UTI in the young, particularly acute pyelonephritis, should be treated very promptly (within about 3 days from start of symptoms).

Clinical presentation

Clinical features of UTI in childhood are often different to those found in adults and are frequently non-specific. Without a high index of suspicion many UTIs especially in the very young will be missed. *Classical* symptoms of lower UTI (dysuria, frequency, and incontinence) and upper UTI (fever, systemic upset, loin pain, and renal tenderness) are frequently not seen in paediatric practice. Attempts to distinguish between upper and lower UTI on clinical grounds or laboratory grounds are unreliable except by acute DMSA scan (see 'Investigations') and clinical history is not closely related to findings on imaging (Coulthard et al., 2009b). UTI can occasionally produce life-threatening illness, especially in very young infants, who may present severely unwell with shock or septicaemia. Boys and girls are equally affected in infancy but after that the ratio of girls to boys progressively rises (Fig. 180.2). After puberty the incidence of UTI is low in both sexes, but rises in females who are sexually active.

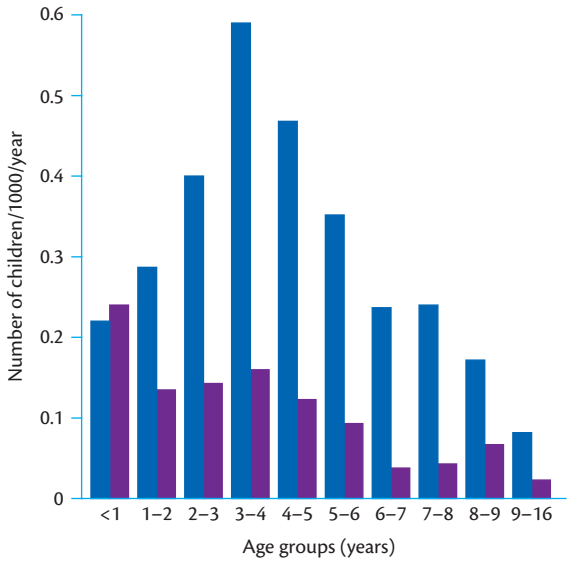

Fig. 180.2 Graph of UTI incidence by age; girls (blue)/boys (purple) (Newcastle data).

Pre-school children

In general terms, the younger the child the more diverse and less specific are the symptoms and signs, for example, poor feeding, vomiting, irritability, abdominal pain, failure to thrive, lethargy, or restlessness. Evaluation of unwell or febrile young children should include examination of urine. Five per cent of febrile children < 2 years old presenting to an emergency department were found to have a UTI (Hoberman et al., 1993). There may be a history of smelly urine or of crying on micturition; an altered pattern of micturition and wetting may recur. Dysuria, urgency, frequency, or hesitancy may occur even in young children but is difficult to recognize in children who are still wearing nappies and who have limited means of communication. Fever is frequently but not always present.

Older children

Older children may have more typical signs and symptoms localizing to the urinary tract including dysuria, frequency, urgency, hesitation, and enuresis. Some may have loin pain but absence of loin pain does not exclude upper urinary tract involvement. Generalized symptoms are common, including fever, lethargy, anorexia, abdominal pain, nausea, and vomiting.

Not all children with dysuria have a UTI. Dysuria may be associated with localized skin conditions such as candidiasis, vulvitis, or excoriation secondary to thread worms or other irritation; with passing concentrated 'strong' urine because of fever and mild dehydration; and with haematuria, for example, from glomerulonephritis.

Recurrent infections

About one-third of girls will have a further UTI within a year and some go on to have repeated infections. Recurrent infections may be associated with an underlying urinary tract abnormality or renal scarring, but in practice a significant number of girls with non-scarred and non-refluxing urinary tracts have recurrent symptomatic UTIs. This may cause considerable distress, anxiety and frustration to the child and family. There is some evidence that UTI is more common in children with constipation and a history should be sought (Shopfner, 1968; Blethyn et al., 1995). UTI may be associated with dysfunctional voiding and bladder instability (Koff et al., 1998). The outcome for those patients may be worse. UTI may be more frequent in girls suffering sexual abuse and this diagnosis should not be overlooked during assessment. Teenage girls may be sexually active and this may be a contributing factor in a recent onset of recurrent UTI. Boys seldom get recurrent UTI in the absence of urinary tract abnormalities (Wennerström et al., 2000a).

The risk of UTI in uncircumcised boys under the age of 1 year is reported to be increased between 3 and 15 times compared to those who are circumcised (Schoen et al., 2000; Wiswell, 2000). However, that increased risk, when countered against the risks of circumcision, is not considered sufficient to recommend it as a routine preventative measure (AAP, 1999a; Singh-Grewal et al., 2005), though it may be an effective intervention in infants with severe VUR and recurrent UTIs.

Assessment

Clinical history and appropriate examination are important, including examination of the urine. Details should be sought of

family history of urinary infection, VUR, renal disease or hypertension; antenatal and perinatal history; and drinking, voiding pattern, and bowel habits. Examination should include measurement of BP, abdominal palpation for masses (bladder, kidney), inspection of external genitalia and lower back, and assessment of lower limb sensation and reflexes. When UTI is recurrent, it is particularly important that bladder and bowel habits are evaluated.

Some centres attempt to distinguish between upper and lower UTI. Indicators such as temperature, C-reactive protein, and loin pain have been used but are unreliable. Whilst those with classical pyelonephritis may have an increased risk of scarring there is no convincing evidence of the opposite. Renal scarring may occur in association with minimal symptoms (Coulthard et al., 2009b).

Antibacterial defence mechanisms

Neonates, with immature immune systems, are particularly susceptible to *Escherichia coli* infection and may present with septicaemia. Colonization of the newborn gut with bacteria including *E. coli* is thought to start rapidly. It is possible that this is influenced by factors such as bottle or breast feeding, location of delivery, maternity unit procedures, and use of antibiotics. It is not known whether these influence later development of UTI though UTI may be caused by bacteria from the child's own gut (Jantunen et al., 2000).

After the first year of life there is a marked sex difference in incidence of UTI, with girls being far more susceptible. The short female urethra is thought to provide easy access to the bladder for bacteria. Repeated voiding, encouraged by increasing fluid intake, and complete emptying of the bladder helps remove bacteria. Children with VUR, bladder outlet obstruction, constipation, neuropathic bladder, and dysfunctional voiding may have significant residual urine in the bladder limiting the ability to reduce bacterial colonization by simple washout. Infection may affect normal ureteric peristalsis and thus reflux and upper renal tract emptying.

The bladder epithelium may have some antibacterial activity. Many uropathogenic *E. coli* strains have surface structures called type 1 pili that can facilitate both attachment to and invasion of bladder mucosal cells. There are numerous defence mechanisms which may be provoked in response, including cytokine production, inflammation, and exfoliation of superficial bladder cells which are removed in the flow of urine. Studies in animals have shown some strains of *E. coli* may form a persistent quiescent bacterial reservoir in deeper layers of the bladder mucosa, despite sterilization of the urine with antibiotics, which could theoretically lead to recurrent infection (Mulvey et al., 2000).

Making the diagnosis of urinary tract infection in children

Urine collection and testing

Unfortunately, it is common for some children to receive an antibiotic for a presumed UTI without a urine sample being either collected or tested (Jadresic et al., 1993; van der Voort et al., 1997; Vernon et al., 1997). Once this has happened, it is not possible to reach a certain diagnosis, and the decision about subsequent management is very difficult. The practical issues regarding urine collection are addressed below.

Collecting urine samples from children

Background

The best method for a particular child will depend on the clinical setting, and the child's age. Every method produces some contaminated samples. Unfortunately, young children whose urine is most difficult to collect are at the greatest risk of scarring.

Collecting urine in infants

- *Clean catch* Clean catch collection has a low contamination rate but collection failure is frequent.
- *Pads* Urine collection pads are inexpensive, modified sanitary towels without antiseptics or absorbent gel which are placed inside the nappy and removed as soon as wet to reduce contamination (Vernon et al., 1994; MacFarlane et al., 1999). The urine is aspirated from the wet fibres using a syringe. The white cell count is lower in pad-collected urines, but urine white cell count is not particularly helpful in confirming diagnosis of UTI in infants
- *Sterile adhesive bags* These bags are stuck to the skin around the genitalia, but produce redness and soreness on removal. They are more expensive than pads and have similar contamination rate.
- *Suprapubic aspiration (SPA)* The bladder is aspirated with a syringe and needle after thorough skin cleaning. This is easier in infants than older children because their bladders extend into the abdomen even when only partially full (Pryles et al., 1959; Nelson and Peters, 1965). Localization is helped by use of US. SPA urines have less contamination than voided ones (Wettergren et al., 1985; Hansson et al., 1998). However, up to 16% of SPA samples yield just one species of organism at very low colony counts (Nelson and Peters, 1965) which would be considered evidence of contamination in voided urine. Inadvertent contamination of SPA urine can occur from skin or bowel flora (Weathers and Wenzl, 1969). SPA is particularly valuable in ill infants to avoid delay starting antibiotic treatment.
- *Urethral catheterization* Like SPA this is very useful in an ill child for speed prior to starting antibiotics, for example, as part of an infection screen in a septic infant, and is considered less invasive and painful than SPA in young infants (Kozer et al., 2006).
- *Collecting urine in toddlers* Toddlers can be encouraged to void into a potty washed in hot water and detergent which removes bacteria and biofilm (Rees et al., 1996) or into a sterile tray in the potty.
- *Collecting urine in older children* Older children can usually void directly into a sterile collection bottle after washing the genitalia. Disposable plastic funnels make this easier in girls. Ideally a mid-stream sample is collected which may be impractical in younger children, but cleanly caught complete samples have relatively little contamination. The glans should be washed in those boys whose foreskin retracts easily. In girls, bacterial contamination may occur from the labia, or from urine flowing into the vagina before being collected, and this can be minimized by voiding with legs and labia parted.

The 2011 American Academy of Pediatrics guideline (AAP, 2011) suggests that UTI in under 2 year olds should be diagnosed only with SPA or catheter specimens. There will undoubtedly be considerable difference of opinions about this advice. Whilst there are arguments to support this recommendation to

reduce false positives from contaminated urine specimens, both are invasive methods, useful for rapid diagnosis in the sick infant in hospital but unsuited to primary care. The main disadvantage of using non-invasive collection methods is the greater risk of obtaining contaminated samples, but this problem is minimized if fresh urine can be screened by phase-contrast microscopy or Gram stain and microscopy, and a repeat sample collected immediately if necessary.

Testing urines for UTIs in children

General principles

The diagnosis of a UTI in childhood is universally defined as the culture of > 10^5 colonies/mL of a single bacterial species from urine, but additional factors such as urinary white cells are deemed important by some authors. A rapid near-patient diagnostic test would allow children to be confidently treated without delay (using a 'best guess' antibiotic, adjusted later according to the bacterial sensitivities on culture), or for treatment to be safely withheld (Coulthard et al., 2010a). Rapid treatment allows children to recover rapidly from acute symptoms. Delayed treatment may increase the risk of scarring, but starting treatment on clinical suspicion risks overuse of antibiotics. The younger the child, the greater the risk of severe illness and of scarring, and therefore the stronger the argument is for immediate treatment.

Bacteria in UTI

Organisms that cause UTI

About 85% of urine samples from boys and girls with a first UTI grow *Escherichia coli* on culture (Jodal, 1987; Winberg et al., 1974). *Klebsiella, Proteus*, and *Streptococcus faecalis* are responsible for most of the rest. Children with abnormal urinary tracts are much more likely to have UTI due to less virulent organisms such as *Pseudomonas* or *Staphylococcus aureus*. These bacteria often contribute to the flora which may cause contamination from the genitalia and skin. Suspicions that bacteria that cause urine infections derive from the child's own bowel have been confirmed by genetic 'fingerprinting' of the bacteria (Jantunen et al., 2000).

Proteus species metabolize urea to produce ammonia, and the increased urinary pH tends to make calcium and magnesium phosphate salts precipitate, and thereby produces a risk of stone formation, especially if there is mucus and cellular debris from the inflammatory process. A thick sludge is initially created taking up the shape of the drainage tract, and further chemical precipitation may make it more solid. Thus stag-horn-shaped calculi develop in the pelvicalyceal system, and date-stone-shaped calculi in the ureter.

Bacterial numbers in a UTI

Kass provided the now universally accepted diagnostic criterion of a UTI in the middle of the last century, though he was aware that it was a compromise, and not an ideal definition (Kass, 1956).

Use of the traditional inoculation technique for urine culture, with a wire-loop of urine being applied to the agar of a petri dish, limits the concentration of colony forming units (cfu) that can be counted; 10^5 bacteria per ml produce confluent colonies, so no more can be counted without pre-dilution. Kass recognized that most infected urines had a bacterial count in the order of 10^9 cfu/mL, and whilst < 10^5 bacterial colonies/mL are generally regarded as indicating contamination, setting the threshold as low as 10^5 per mL for diagnosis of UTI increases the false-positive rate.

Kass reported apparent positive culture rates among asymptomatic adult outpatients of 4% in men and 6% in women. Similar false-positive rates have been reported in infants, 8% (Liaw et al., 2000) in children, 6.6% (Vickers et al., 1991) in neonates (Nelson and Peters, 1965; Hardy et al., 1976), infants (Hardy et al., 1976; Shannon et al., 1969), and older children (Shannon et al., 1969) who did not have urine infections (confirmed by sterile SPAs). The use of >10^6 threshold for diagnosis of UTI would considerably reduce the number of false-positive results (Coulthard et al., 2010b).

Laboratory culture for bacteria

Culture has an inherent delay and in practice, several days may elapse between a doctor seeing a child, receiving the laboratory report, and starting treatment. This is a problem, since delay in treatment is associated with increased risk of scarring in susceptible individuals. To minimize the overgrowth of contaminating organisms, refrigeration provides effective storage for 72 hours (Watson and Duerden, 1977), but is not always convenient. Collection bottles containing boric acid are widely used, but may produce false-negative results if underfilled (Watson and Duerden, 1977; Jewkes et al., 1990).

Bacterial culture on dipslides

Dipslides, which have a miniature agar-covered culture plate attached to the inside of the lid of a sterile bottle, are useful for urine culture in the community.

Microscopy of urine for bacteria

Bacteria in fresh undiluted urine are readily identified by Gram staining, or more easily, for near-patient testing, by phase contrast microscopy (Vickers et al., 1991), when they appear as clearly defined black organisms against a light background (Fig. 180.3).

The phase contrast microscope can be a convenient tool if kept in the clinical area (e.g. outpatients, ward, day-unit) and is dedicated for use with urine only. We use ×400 magnification and a slide with two counting chambers, each 0.1 mm deep, and with a grid etched on a lightly mirrored surface. This provides a clear point of focus when inspecting a sterile urine which itself has no features to see. Reliable diagnosis depends on training and maintaining practice and experience facilitated by using a double viewing head or monitor attached.

Uninfected urine has no organisms to see. Infected urine usually has many rods visible per high-power field. We advise inspecting about five fields (about 0.02 μL of urine) and completely clear urine can be discarded without being cultured, thus saving money.

When an infected urine is examined by phase contrast microscopy there will typically be tens, hundreds, or thousands of identical rods per high-power field, equivalent to bacterial counts of between 10^6 and 10^9/mL (all reported identically as > 10^5/mL on culture). Occasionally UTIs are caused by *Streptococcus faecalis* which are easily recognized as chains of cocci (not to be confused with phosphate crystals with which are a similar size, often moving due to Brownian motion, and seen individually or in clumps, but not chains). Rarely, a UTI is diagnosed by phase contrast but the culture is negative; typically this is because standard culture fails if the organism is anaerobic. Antibiotics can be commenced on positive urine microscopy but adjusted according to subsequent culture and sensitivity testing.

Microscopy is probably most useful for screening out contaminated specimens. As it is performed near the patient a repeat specimen can immediately be requested for samples with uncertain

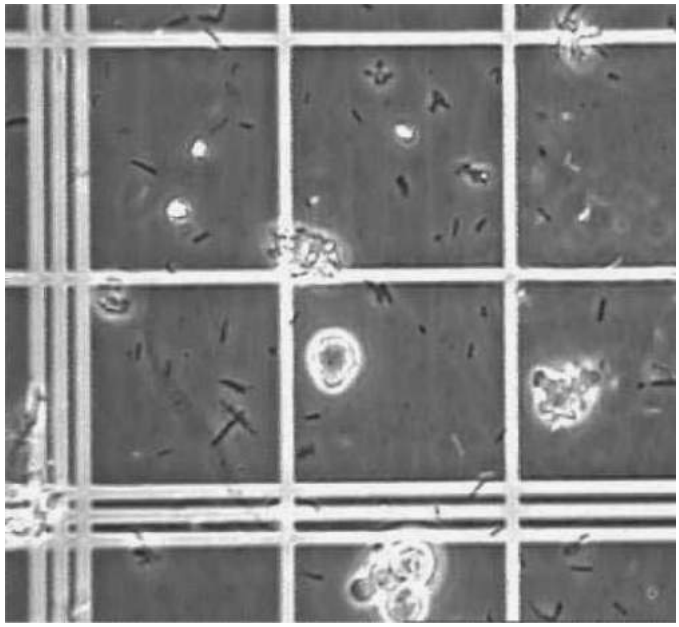

Fig. 180.3 Phase contrast microscopy of urine at ×400, showing myriad rods of similar length against the counting grid. Note the presence of some white blood cells.

results (few bacteria are seen, or rods and cocci are present together, or there is amorphous debris, cotton strands, etc.) (Vickers et al., 1991). By using microscopy a confident diagnosis can be made at the time of presentation, if necessary by voiding two or more specimens, thus reducing the use of invasive methods such as SPA or urethral catheterization as proposed by AAP (AAP, 2011) except in the most urgent cases.

Phase contrast is also useful for examining other elements in the urine. White cells can be seen in detail. Red cell morphology is clear, and can be used to differentiate glomerular from lower tract bleeding. The content of casts is clearly visible. Many older girls have vaginal epithelial cells in the urine, and occasionally long rods which are anaerobic vaginal lactobacilli. Children with metabolic stones may have identifiable crystals. Phosphate crystals are common in normal concentrated urine.

Urinary stick tests

Nitrite stick tests

Most uropathogens produce nitrite as a result of metabolism, and given sufficient concentration of bacteria in urine for a sufficient period of time, this can be detected with a test -strip. The specificity nears 100% (AAP, 1999b, 2011). However, it may take hours for the bacteria to produce detectable quantities of nitrite (Powell et al., 1987). Since UTI tends to cause frequency of voiding, it is predictable that the test sensitivity is low (53%, range 15–82%) (AAP, 1999b) especially a problem in the youngest children. There may be other factors influencing nitrite excretion including dietary vitamin C. A negative stick test is unhelpful in reliably excluding a UTI in young children.

Urinary white blood cells in UTI and leucocyte esterase stick test

Typically, children with UTI have an increased number of white blood cells (WBCs) in the urine, but this is not diagnostic (Coulthard et al., 2010a). Some infected urines have few WBCs. This may because few WBCs were voided or because WBCs do not survive intact for very long and therefore are not reported by the laboratory (Vickers et al., 1991). Rarely, a young child with overwhelming infection or who is immunosuppressed may be unable to maintain a urinary WBC response (Kumar et al., 1996). There is a reduction in WBC numbers in urine samples collected by pad (Vernon et al., 1994) In addition there may be an excess of urinary WBC in the absence of UTI infection but in the presence of pyrexia (and presumably leucocytosis) from other causes (Turner and Coulthard, 1995). The interpretation of the presence or absence of urinary WBCs is thus difficult whether detected by microscopy or leucocyte esterase stick test.

Stick testing for protein or blood is unhelpful in making or excluding the diagnosis of UTI. Combining stick testing results improves sensitivity and specificity (AAP, 2011).

Treatment of children with urinary tract infection

The primary treatment goals are twofold: elimination of symptoms associated with an acute UTI together with prevention of renal injury. In animal models there is evidence of scarring of susceptible kidneys occurring if infection lasts more than a few days before treatment (Miller and Phillips, 1981; Ransley and Risdon, 1981; Slotki and Asscher, 1982). Audit of children after first UTI shows children who were treated within 3 days of symptoms starting were one-third as likely to scar as those whose symptoms lasted longer (Coulthard et al., 2014a). From retrospective studies in children there is an association between delayed treatment and increased risk of renal scarring (Smellie et al., 1985, 1994; Dick and Feldman, 1996; Coulthard et al., 2009). Because of this, in practice if UTI is suspected, especially in younger children, a 'best guess' antibiotic should be started whilst awaiting results of the urine culture, and antibiotics altered accordingly. This does, however, present the dilemma of overuse of antibiotics if the urine is eventually found not to be infected. Judicious use of near-patient tests may reduce this problem.

Cephalexin, amoxicillin, trimethoprim, or nitrofurantoin are frequently used, but local microbiology advice is required about local resistance patterns in the paediatric population. Recent antibiotic use, including prophylaxis, should also be taken into account when medication is chosen. Commonly increased intake of fluids is encouraged.

Ill children, particularly infants, who are dehydrated, toxic, or vomiting, require parenteral antibiotics initially. If the clinical condition does not improve within 48 hours a repeat urine specimen should be obtained and further urgent investigation should be considered, for example, renal tract US. Other children can be treated with oral antibiotics from the start but currently there is no conclusive evidence about the ideal length of therapy in children. The AAP 1999 report recommended longer courses of antibiotics (5–10 days) over short courses (1–3 days) (AAP, 1999b; Tran et al., 2001). However, a 2003 Cochrane review found no difference in recurrence of UTI after short (2–4 days) or long (7–14 days) courses (Michael et al., 2003). After the acute course of antibiotics many clinicians check a urine specimen. This is probably more important in complex cases—in uncomplicated UTI the clinical improvement is a useful guide to success of therapy. Some clinicians continue a low

dose of a suitable antibiotic, especially in the very young and those with a high suspicion of underlying abnormality, until investigations are completed, but this is opinion rather than evidence based (Mattoo, 2009).

In children with a normal urinary tract, but recurrent symptomatic UTI, there is some evidence that a long course of antibiotics (6 months) is associated with a reduced frequency of UTI whilst the antibiotics are being taken and for the subsequent 2 years (Smellie, 1978). Rotation of prophylactic antibiotics is sometimes advocated. Cranberry juice may be useful based on anecdotal reports (Jepson et al., 2000). Clinical experience suggests simple measures like increasing fluid intake, regular voiding, and avoiding perineal irritants like bubble-bath may be helpful in prevention of recurrent UTI in some girls.

Constipation, dysfunctional voiding, and bladder instability are associated with recurrent UTI (Koff et al., 1998). Active treatment of constipation may reduce recurrent UTI in patients with normal urinary tracts (Loening-Bauche, 1997). Post-micturition residue and upper tract dilatation has been found to be increased in children with constipation and improved after treatment (Dohil et al., 1994). There is little evidence regarding efficacy of interventions like bladder training, behaviour modification, or anticholinergic drugs but clinical experience suggests these approaches may be effective and they warrant further study.

Treatment of children known to have VUR is addressed in Chapter 355. Children with complex urinary tract problems including those who require intermittent catheterization, frequently have both asymptomatic bacteriuria and symptomatic UTI. Management and treatment will vary depending on the individual circumstances. There is no evidence of benefit from treatment of asymptomatic bacteriuria in girls with normal urinary tracts. They do not therefore require routine screening of urine when well.

Investigation of children with UTI

Though UTI is a common problem there is no established consensus on investigation and management in childhood. The natural history of UTI in childhood is still poorly understood because of a number of factors—most children are managed in primary care and the course runs over many years so establishment of long-term studies or registries is difficult; strategies have changed over the years and in different locations without much real new evidence; and there are inherent problems associated with establishing studies on large numbers of young children.

There are considerable differences of opinion regarding investigation following UTI (Montini et al., 2011; Prasad and Cheng, 2012). The aim is to identify those with an underlying renal tract abnormality or predisposition to UTI such as structural abnormality of urinary tract, urinary tract obstruction, VUR, or abnormal bladder emptying. Those who have sustained damage to their kidneys or who are likely to do so may be identified. This strategy of investigation assumes that at least some renal damage is acquired and therefore preventable.

Unfortunately recent investigation strategies in the United Kingdom and elsewhere have largely identified those who have already scarred their kidneys rather than identifying those at high risk in whom renal damage may be prevented. This has led to a belief by some that renal damage is not preventable. In addition, there is little convincing evidence about effective interventions. Our understanding of the pathophysiology and development of logical hypotheses have been used to formulate a pragmatic approach to investigation of UTI but inevitably practice varies. The dilemma is that if a minimalist approach to investigation after first UTI is adopted then those who are at highest risk of developing acquired renal scarring will not be identified. Services would need to offer very rapid access to diagnosis and treatment to all with acute UTI—something which has hitherto not been achieved in the United Kingdom. One can argue that identifying those at higher risk enables resources to be targeted at that population; however, the downside is that many more children are investigated. Factors which help identify the high-risk population would reduce the imaging of children with normal urinary tracts. In 2007 in the United Kingdom, NICE published a guideline on UTI in childhood (NICE, 2007) which proposed a minimal approach to investigation to reduce the imaging burden. AAP guidelines (AAP, 2011) propose not investigating children aged 2 months to 2 years until after a second UTI and only diagnosing UTI on SPA or catheter specimens. Audit suggests adoption of the NICE imaging strategy would greatly reduce the number of children imaged but at the cost of missing significant urinary tract abnormalities (Coulthard et al., 2014b).

The argument against investigations is that UTI is so common that many children with no urinary tract abnormalities are subjected to invasive investigations without benefit. Ideally investigations would identify children who have underlying abnormalities, are at high risk of renal damage, and thus of long-term sequelae. Some units try to identify those with *upper* versus *lower* UTI. However clinical features and laboratory tests such as C-reactive protein are not closely related to findings on imaging, particularly in younger children.

Risk factors for development of renal scarring include young age (Berg and Johansson, 1983), delay in antibiotic treatment of UTI (Smellie et al., 1985; Coulthard et al., 2009; Oh et al., 2010), recurrent infections (Winter et al., 1983; Wennerström et al., 2000b), VUR (Stokland et al., 1998; Shaikh et al., 2010), and obstruction of the urinary tract. Whilst there is an association between renal scarring and VUR, the relationship is not fully understood and there are conflicting views about the importance of detection and active management of the condition (see Chapter 355). The detection of abnormalities of the urinary tract after UTI is higher the younger the child. Demonstration of urethral anatomy is important in very young boys with UTI. Very young children appear to be at highest risk of sustaining permanent renal damage. Therefore the opportunities for prevention of initial or extending damage are high. However, there is still no general consensus about investigation of these children. Our local practice is to emphasize definitive diagnosis of UTI and investigate children aged < 1 year thoroughly with an US, DMSA, and micturating cystourethrogram (MCUG). Over the age of 1 year we perform an US and DMSA and suggest high index of suspicion for further UTI and reserve MCUG or other investigation for VUR only for those with abnormalities on DMSA or US or who have recurrent infections. Our local strategy of engagement with primary care has reduced the age of referral after first UTI (Coulthard et al., 2014b).

Practicalities of investigation

Infants

Younger children appear to be at higher risk of sustaining renal damage associated with UTI and in the young a UTI is more likely

to be a marker of an underlying urinary tract abnormality such as VUR or obstruction. Currently after a first recognized UTI, about a third of children aged < 1 year will be found to have VUR on MCUG. The non-specific symptoms in this age group may lead to a delay in treatment and diagnosis of UTI, though the severely ill and those with associated febrile convulsion are likely to gain very rapid access to hospital and treatment

Ultrasonography

US is widely available, involves no ionizing radiation, is good for detecting structural abnormalities (e.g. dilated kidneys and ureters, cysts in kidneys), but is very operator and situation dependant. It can be used to detect parenchymal abnormalities but in childhood scars are often small and frequently missed. Colour flow imaging may be useful in detection of VUR. The findings on US cannot easily be reviewed retrospectively from still pictures. US can be performed in the acute phase or subsequently. Severe acute pyelonephritis may cause the kidney to appear 'bright' and/or enlarged on US. These changes may be focal.

DMSA scan

DMSA renal scans are useful for detection of focal parenchymal defects. Differential renal function is provided (though this is proximal tubular function, it corresponds well with GFR). Original data can be easily reviewed for comparison with previous or later studies. The technique can be standardized. The main disadvantages are that an intravenous injection is required and the patient receives a dose of ionizing radiation. The dose is small compared to background radiation. Timing is important: if DMSA is performed at the time of UTI then a large proportion will show some defects (Jakobsson et al., 1992; Rosenberg et al., 1992; Stokland et al., 1996a). However, < 50% of those defects will be still there > 2 months later (Jakobsson et al., 1992; Benador et al., 1994). It is important therefore that the clinician is aware of the timing of the DMSA scan in relation to the acute infection in any individual case. In the piglet model of acute pyelonephritis, DMSA is highly specific and sensitive in diagnosing pathologically proven pyelonephritis (Parkhouse et al., 1989; Rushton et al., 1988). Whilst if permanent scars occur they localize to the site of the acute defect, we do not understand the factors involved in resolution of acute changes versus progression to permanent scarring. DMSA performed to show *permanent* scarring reliably should be done at least 2–3 months after a UTI, though some suggest a longer interval (Jakobsson and Svensson, 1997) (Fig. 180.4)

Detection of scars by DMSA scan versus US

There are several comparisons of DMSA scan and US for detecting scars which report a widely varying degree of concurrence (Roebuck et al., 1999). There is much evidence that there is good agreement for widespread and diffuse scarring but that US misses focal scars (Tasker et al., 1993; Smellie et al., 1995). US is extremely operator and subject dependent. Under research conditions, in experienced hands with time and a cooperative subject, US can detect scars as well as a DMSA scan (Barry et al., 1998), but in routine clinical settings and in younger children it is less good at detection of scars.

Detection of reflux

There is no ideal test for detection of VUR. The contrast MCUG is often described as the gold standard but it has limitations. The main disadvantage is that it requires the insertion of a bladder catheter, and delivers ionizing radiation to the gonads. The test may fail

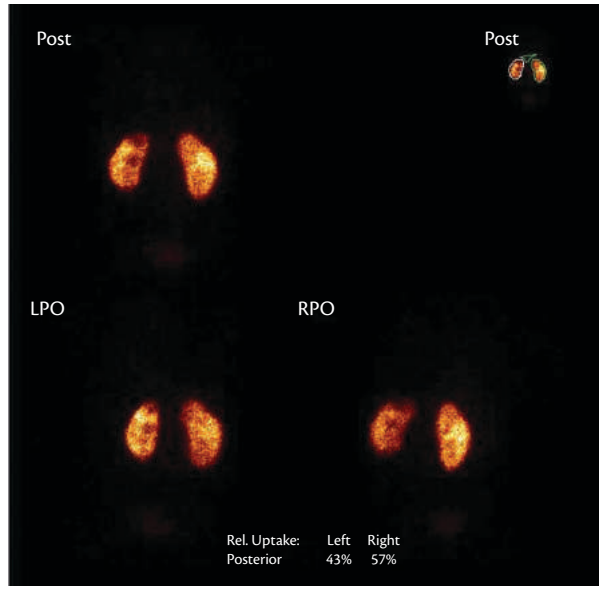

Fig. 180.4 DMSA scan showing unilateral focal scarring.

to demonstrate intermittent VUR and many units advocate filling the bladder twice. It is unphysiological because of the presence of a catheter, and the child is unlikely to be relaxed. The use of general anaesthetic or sedatives for insertion of the catheter is controversial. The main advantage of contrast MCUG is in showing detail of anatomy including bladder, urethra, and ureters, which is important in excluding bladder outflow obstruction in male infants with UTI (Fig. 180.4). Timing and grade of VUR are demonstrated and intrarenal reflux may be seen. Grading is important since the risk of renal scarring and probability of resolution of VUR can be predicted from the grade at the outset (Elder et al., 1997; Austin and Cooper, 2010) and thus may alter management.

MCUG may be performed once the initial infection is treated. There is a suggestion but no good evidence that there is an increased detection of VUR at the time of UTI. Even if this hypothesis was correct then the patient is at risk of VUR at the very time it may be important.

Contrast-enhanced ultrasonography is used in some centres where there is sufficient expertise. This still requires bladder catheterization for introduction of sonicated albumin or saline but avoids a radiation dose. Colour flow Doppler has also been used in experienced hands to demonstrate VUR.

MCUG direct radioisotope study delivers a lower radiation dose than contrast MCUG; prolonged imaging can be performed and therefore this procedure may detect intermittent VUR, but may miss lower grades of VUR (Poli-Merol et al., 1998). It still requires the insertion of a bladder catheter, anatomy and bladder outflow are not demonstrated, and grading of reflux is not possible.

Indirect radioisotope study is appealing because no bladder catheter is required, though an intravenous injection is, and there is a lower radiation dose than contrast MCUG. However, no anatomical information is provided. It requires cooperation and ability to micturate on demand so is only useful for older children (from age 3 or 4 years). Studies show high sensitivity and specificity in selected patients (Gordon et al., 1990) and its use is dependent on attention to good technique.

Fig. 180.5 MCUG showing intrarenal reflux.

Abdominal X-ray

Abdominal X-ray is useful for localization of stones in selective cases (e.g. *Proteus* infection) where there is a suggestive history. In addition, spinal defects may be identified and constipation demonstrated.

Other imaging

Previously commonly employed, there is now little call for intravenous urography having being superseded by computed tomography or magnetic resonance imaging where specific detailed anatomy is required.

One of the problems in investigating older children is judging whether the first *recognized* UTI is actually the first; often it is not. In children presenting with their first diagnosed UTI, the rate of discovery of scars was similar at all ages (Coulthard et al., 1997) but this has changed as children are being referred earlier (Coulthard et al., 2014a). When scarring is first detected it is not possible to determine at what age that scar occurred. There is evidence that the vast majority of novel scarring takes place within the first few years of life, but there is also evidence that scarring can occur at any age (Coulthard et al., 2002). There is also evidence that once a scar is present, progression of that scarring may develop at any age. Progression of scarring is presumed to occur because the conditions of intrarenal reflux and VUR are still present and in the face of infection further renal damage may occur. In addition, scarring itself may distort intrarenal architecture and may make it more likely that adjacent areas of kidney will have intrarenal reflux and be susceptible to scarring in the face of infection.

Whilst it is clear that VUR is a major risk factor for development of renal scarring, many children are found to have a scarred kidney but no evidence of VUR. A number of theories are proposed to explain this. In many cases the child had VUR but has now grown out of it. In a few cases the child has VUR but the test may fail to detect it. The diagnosis may be wrong, the child having dysplasia or hypoplasia rather than acquired scarring. Pyelonephritis and scarring can occur in the absence of demonstrable VUR, for example, when infection is introduced by blood-borne spread or septicaemia. Resolution of reflux with time may be the explanation in many cases when scarring is discovered at initial investigation but the timing of the development of scarring is not known. However, there are sufficient anomalies to require an open mind to be kept about the precise nature of the relationship of VUR and scarring.

Box 180.1 Management plan for a child found to have reflux nephropathy

- Consider whether they have VUR and are at risk of further scarring.
- No consensus about how best to manage—education, awareness, and practical strategies to enable rapid treatment of subsequent UTIs important; some advocate in addition prevention of UTI whilst VUR persists with antibiotic prophylaxis.
- Consider surgical treatment in some situations, for example, if medical management fails; breakthrough infections; non-compliance.
- Initiate long-term (life-time) BP and renal function monitoring especially for severe or bilateral scarring.
- Discuss familial nature of VUR and increased risk in siblings, future siblings, parents, and future offspring.

Working with families

A culture of partnership with families should be encouraged. Information and education of families is important in suspicion and detection of UTI and understanding of medical issues may improve concurrence with treatment. One of the major problems with analysis of outcomes of interventions like long-term antibiotics to prevent UTI is lack of compliance with treatment regimens even when part of a study (Hensle et al., 2007; Rodriguez et al., 2011). However, parents will often be more assiduous with tasks like urine collection than healthcare professionals. Important points about issues such as investigation plans or VUR should be backed up with written information whenever feasible, since it is well recognized that people absorb only a fraction of the information given in a clinic discussion (Box 180.1).

Conclusion

UTI is common and may be associated with renal abnormalities and significant long-term sequelae in a minority of cases. There are many unanswered questions about the precise relationship of VUR, UTI, and scarring and there is debate about the best investigation and management strategies. Since currently in the United Kingdom most children with scarring already have it at the time of first investigation, it is likely that the greatest potential for prevention of renal damage lies in increased awareness, rapid diagnosis, and urgent treatment of very young children with UTI. Children

with a family history of reflux or reflux nephropathy are at high risk of developing UTI and renal scarring. Therefore increased awareness amongst adult physicians and nephrologists is important in education of patients of the risks to their offspring and the potential for preventative action.

Key points

- Childhood UTI is usually uncomplicated but may be associated with significant long-term sequelae in some individuals.
- Increased awareness, early diagnosis, and rapid treatment of childhood UTI is important in preventing renal damage.
- Accurate diagnosis of UTI is vital.
- All urine collecting methods may result in contamination.
- Antibiotics should be started as soon as a suitable urine sample has been collected.
- There is no clear consensus on investigation after a first UTI.
- VUR is a congenital condition with a familial basis associated with renal scarring in an as yet undefined way.

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CHAPTER 181

Schistosomiasis: the parasite and the host

Rashad S. Barsoum

Introduction

Schistosomes are highly conserved worms that seem to have emerged with the existence of man. They were blamed by the pharaohs for causing haematuria in the Royal servants collecting the sacred papyrus leaves from the Nile. The disease, which they called 'bloody urine disease', was well described in the Ebers papyrus (sixteenth century BC), which also referred to its known response to antimony (Ghalioungui, 1963). Material evidence for the identity of 'bloody urine disease' with schistosomiasis was provided by Ruffer (1910) who discovered schistosomal ova in the bladder of a rehydrated Egyptian mummy, over 3000 years old. Ova were subsequently identified in the livers and bladders of other mummies, more recently examined in The Manchester Museum, Department of Egyptology, University of Manchester.

It remained for the German clinician Theodore Bilharz to rediscover *Schistosoma haematobium* in Kasr El-Aini Medical School of Egypt (Bilharz, 1852), hence the alternative name 'bilharziasis'. About 40 years later, the Australian parasitologist, Sonsino, described its life cycle, also while working in Cairo (Sonsino, 1893). Different species of the parasite were subsequently identified in Africa, Latin America, and the Far East, with the most recent being *S. mekongi* discovered in Malaysia in 1974.

In 1994, the World Health Organization initiated the '*Schistosoma* Genome Network' that led to sequencing of the worm's genome. The first sequence for *S. mansoni* was published in 2009, comprising seven pairs of autosomes, and one pair of sex chromosomes (ZW female and ZZ male) (Berriman et al., 2009).

The parasite

Schistosomes are bisexual, flat trematodes with a highly sophisticated genome (Le et al., 2000). Seven species affect man as a definitive host, namely *S. hematobium, mansoni, japonicum, intercalatum, mekongi, mattheei*, and *bovis*. Others are principally diseases of apes, cattle, domestic animals, and certain birds, but they may also infest humans without completion of their life cycles, leading to limited morbidity. The different species are distinguished by their egg morphology, intermediate hosts, antigenicity, and pathogenicity. Whether strain variation also modifies the epidemiology and/or morbidity of the disease in humans awaits further elucidation (Barsoum, 1987).

Life cycle

Infection is acquired through contact with contaminated fresh water in relatively stagnant small rivers and canals. The parasite's infective stage, the cercaria, penetrates the skin and mucous membranes, a process that is completed in about 30 seconds. The cercariae lose their bifid tails and are transformed into 'skin-stage schistosomulae' which stay in the dermis for 1–3 days during which they change their surface structure and antigenicity. They eventually migrate by the regional lymphatics to the bloodstream and ultimately are trapped in the pulmonary capillaries. Some 10–40% of the 'lung-stage schistosomulae' manage to escape from this sieve and find their way to the hepatic sinusoids, where they increase in size and differentiate into males and females. The male is larger, measuring about 15 mm × 2 mm × 3 mm, and has a mammillated surface and two suckers that help to fix it to the venous walls. The longer and more slender female has a smooth surface and two tapered ends, and also has two suckers.

The worms then migrate to their eventual habitat, that is, the mesenteric veins for all human pathogenic schistosomes except *S. haematobium* which resides in the perivesical venous plexus. It has been suggested that the route of migration of the latter species involves retroperitoneal venous communications between the mesenteric, perivesical, and pudendal veins. Pairs live for some 3–8 years, but prolonged survival for up to 30 years has been reported.

The worms live in almost continuous copulation. The female leaves the male's 'gynaecophoric canal' for a few hours every day and travels against the bloodstream to reach the mucosa of the colon, rectum, or lower urinary tract where it lays its eggs, starting 8–10 weeks after infection. The daily production of ova varies from 300 with *S. haematobium* and *S. mansoni* to 3000 with *S. japonicum*. Some ova remain trapped in the submucosa leading to local granulomatous reactions, but the majority are able to find their way to the rectal or bladder lumena 10–12 days after being laid. Exteriorization is facilitated by the spines, which are characteristic of *Schistosoma* eggs. The position of the spine helps to differentiate species, as it is located terminally in *S. haematobium* eggs or laterally in all other species.

The eggs that reach fresh water hatch, releasing miracidia. These are ciliated organisms which can survive for up to 8 hours while searching for the appropriate intermediate host. This is a snail, specific for each species of schistosomes, within which the miracidium

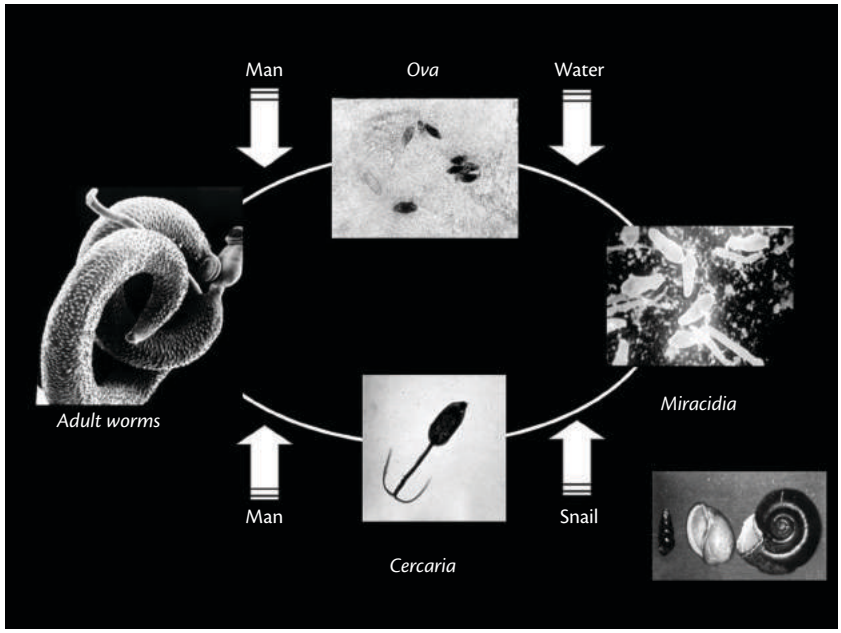

Fig. 181.1 Schistosomal life cycle. Eggs are shed in fresh water where they hatch releasing miracidia that infect species-specific snails where they evolve into cercariae, which infect humans and other definitive hosts.

grows and multiplies, producing large numbers of cercariae. The latter are subsequently shed into the fresh water and remain viable for up to 72 hours searching for their definitive host to complete the life cycle (Fig. 181.1).

Parasitic antigens

Over the past four decades, over 100 schistosomal antigens have been identified, and their role in the host's immune response was outlined in experimental models and infected humans. Most of these antigens have been more recently characterized by genomic and proteomic analysis (Han et al., 2009). It is generally believed that *S. japonicum* is most antigenic to man, followed in descending order by *S. mansoni* and *S. haematobium*. There is also evidence that antigenicity varies with different strains of schistosomes, and that it declines with ageing of the parasite.

Four groups of antigens have been isolated *in vitro*:

- *Tegument-associated antigens* (TAA) are a complex set of proteins and glycoproteins on the surface of cercariae, schistosomulae, and adult worms. Many such antigens have been characterized, sequenced, and prepared by recombinant techniques (van Balkom et al., 2005). They are distinguished according to their sources (e.g. Sm for *S. mansoni*, Sj for *S. japonicum*, etc.) and molecular weights (in kilodaltons). TAAs appear to have a limited role in the pathogenesis of host morbidity, yet they are of crucial importance in immunity to infection and re-infection.
- *Adult worm tissue antigens* include those associated with microsomes, smooth muscle, and other parasitic cells. The adult microsomal antigens (AMA) are specific for the genus *Schistosoma*, with distinct species differences (MAMA, HAMA, and JAMA for *S. mansoni, S. haematobium*, and *S. japonicum* AMAs respectively). Hence they are of particular epidemiological importance as serological markers of active infection (Al-Sherbiny, 1996).
- *Gut-associated antigens* are released by regurgitation of the worm's digestive juices, and constitute the main part of circulating schistosomal antigens *in vivo*. Of six such antigens identified *in vitro*, two are clearly involved in the pathogenesis of immune-complex-mediated lesions, namely a proteoglycan called circulating anodic antigen (CAA) and a glycoprotein called circulating cathodal antigen (CCA) (Deelder et al., 1976).
- *Soluble egg antigens* (Boros and Warren, 1970) are released by diffusion through micropores in the eggshell into the surrounding tissue fluids. Quite a large number have been purified by various techniques and proven to be protein or glycoprotein in nature. Best known are the major serological antigens MSA 1, MSA 2, and MSA 3 (Pelly et al., 1976). Egg antigens are mainly involved in the pathogenesis of local granulomas and may be oncogenic to the bladder mucosa (see Chapter 182).

The host

Schistosomiasis affects people of all ages. Infection is usually acquired during childhood, reaching a peak during the second decade. Significant morbidity occurs two or three decades later.

There is a considerable variation in the susceptibility to infection with schistosomiasis among different animal species. For example, mice and chimpanzees are highly susceptible, while guinea pigs are fairly resistant and rats are poorly permissive. Similarly, the resistance of humans to infection and re-infection is variable according to age, gender, race, and several genetic settings. Children are more susceptible even when compared to adult fishermen who are considerably more exposed to contaminated water, which is attributed to improving immunity with age. Males are more often infected than females, which was formerly believed to be due to higher exposure imposed by social factors, but again this turned out to reflect an immunological advantage of the human female gender.

Genetic influence

Studies during the past three decades have identified several associations between infection susceptibility and subsequent morbidity. Unfortunately, many of these observations were inconsistent and did not provide solid pathogenetic links to the immune response. This has changed over recent years, with genetic studies linking to cytokine profiles at different stages of infection.

Genes and susceptibility to infection

Th2 cytokine expression has been associated with resistance to schistosomal infection in many animal models as well as in humans (Isnard and Chevillard, 2008). The main players are (a) interleukin (IL)-4 and IL-5, which provide a positive feedback loop between the antigen-presenting cells (APCs) and the Th2 cells; and (b) IL-13, which is chemotactic and trophic to eosinophils, and a major promoter of IgE synthesis and release by B lymphocytes (see Chapter 194).

It has been shown that a gene locus called *SM1* located on chromosome 5q31–33, in close proximity to *CSF1R*, upregulates IL-4, -5, -9, and -13 mRNA in Th2 lymphocytes. Interestingly, the same gene locus also regulates other pathways involved in the innate resistance to schistosomal infection including IL-12, interferon, and colony-stimulating factor (see Chapter 194). *SM1* polymorphism has been consistently associated with significant variance in the susceptibility of humans to schistosomal infection.

Another gene, also involved in IL-13 upregulation is *STAT6*, located on chromosome 12q13. Polymorphism of this gene has been associated with variance in the susceptibility to infection. *SM1* and *STAT6* impact is additive (Fig. 181.2), displays gender and familiar clustering, and leads to manyfold change in the incidence of re-infection (Isnard et al., 2008).

Genes and morbidity from schistosomiasis

The genetic impact on morbidity is even more obvious, particularly when it comes to late sequelae such as hepatic fibrosis or glomerulosclerosis. Studies have shown an association between hepatic fibrosis and MCH A1, B5, and B8 in Egypt, and DRB, DPA1, DQA1, DQB1 in China. Recent genomic studies have shown that hepatic fibrosis is largely dependent on a connective tissue growth factor (CTGF) encoded on chromosome 6q23. Two single nucleotide polymorphisms, rs9 402 373 and rs12 526 196, that lie close to *CTGF* are independently associated with severe hepatic fibrosis across different populations infected with either *S. mansoni* or *S. japonicum* (Dessein et al., 2009).

The racial influence on the type of *Schistosoma*-associated glomerulonephritis has been reported from Africa and South America. For example, a study from Brazil has shown that black populations are more susceptible to focal segmental glomerulosclerosis as opposed

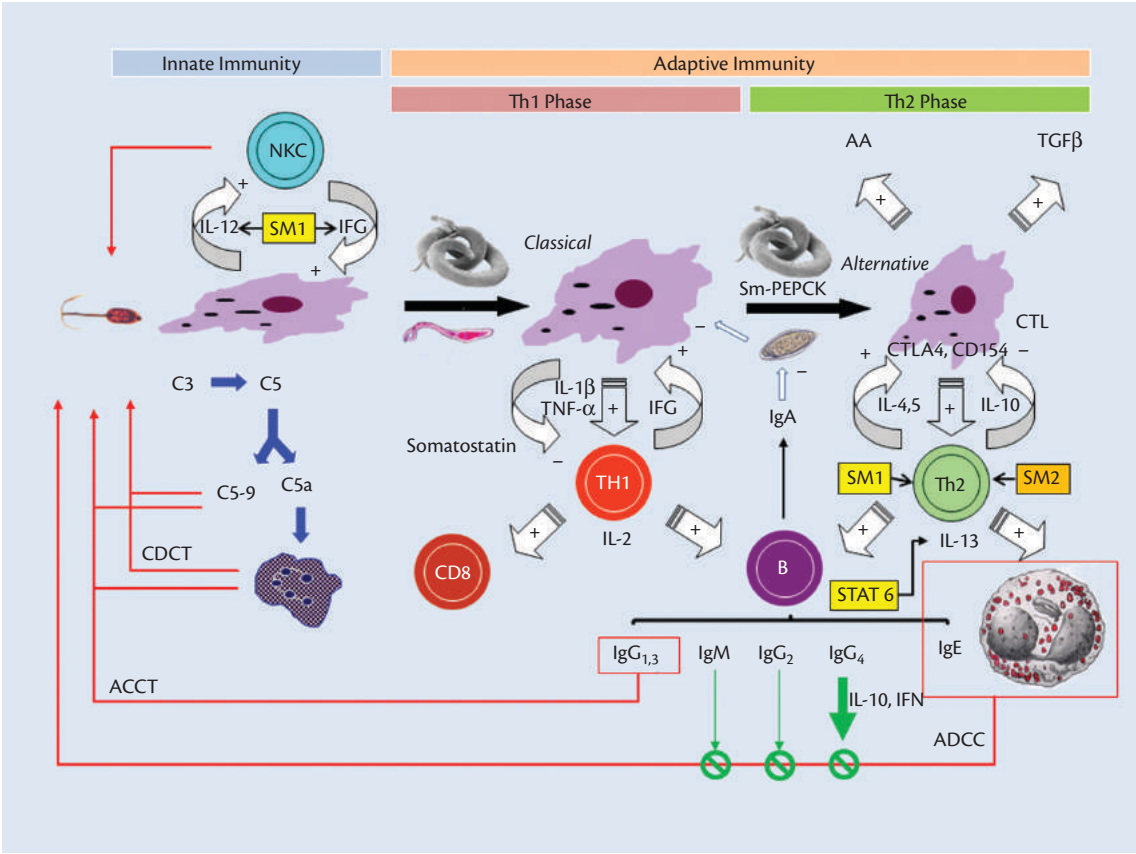

Fig. 181.2 Main components of the immune response to schistosomiasis. Lymphocytes are shown as circles. Critical genes are shown in yellow squares. ACCT = antibody and complement-dependent cytotoxicity; ADCC = antibody-dependent cell-mediated cytotoxicity; AA = amyloid-A protein; CDCT = complement-dependent cytotoxicity; Ig = immunoglobulin; NKC = natural killer cell; Th1 = T-helper 1; Th2 = T-helper 2.

to proliferative glomerulonephritis in Caucasians, irrespective of the degree of hepatic fibrosis (Lopes et al., 2002) (see Chapter 194).

Immunological response

Over several thousand years, schistosomes learnt to live and let live. It is not in their favour to overwhelm the host, nor to be vulnerable to his/her immunological artillery. Accordingly, successful infection requires a delicate balance between the parasite's antigenic challenge, its own immune system, and the host's immune response. This balance is often referred to as 'concomitant immunity'.

Circulating schistosomal antigens

While the majority of the circulating schistosomal antigens are gut derived, soluble egg, microsomal, and tegument-associated antigens (*vide supra*) also contribute. A variety of techniques have been used for the detection of circulating and urinary schistosomal antigens with varying degrees of sensitivity and specificity (Deelder et al., 1994). They include gel diffusion, precipitation, complement fixation, chromatography, immunoelectrophoresis, indirect haemagglutination, microfluorometry, radio-immunoassay, and various forms of enzyme-linked immunosorbent assay techniques.

Seropositivity varies in different reports, with increased frequency among the older population and with longer duration of infection. Patients with hepatosplenic schistosomiasis are usually seropositive; this is attributed to the intensity and longevity of infection. Circulating antigens are not detectable a few weeks after successful treatment.

The immune response

Innate immunity

The initial response to schistosomal infection is innate and non-specific, mainly targeting the schistosomulae. It includes phagocytosis by tissue macrophages and circulating monocytes, opsonization through direct complement activation, complement-dependent neutrophil-mediated cytotoxicity, and damage by IL-12-driven natural killer cells (Fig. 181.2). These mechanisms are able to destroy some 90% of the infection load.

Adaptive immunity

Schistosomulae which escape the innate mechanisms mature into adult worms which are even more resistant to innate mechanisms, and require the interception of the more powerful and specific acquired immunity. Indeed, the latter is triggered at the very moment of cercarial penetration, and is progressively amplified as the parasite's life cycle proceeds *in vivo*.

Three steps are required for achieving the ultimate termination of all phases of the parasite's life cycle in the host. These are (a) antigen recognition and proper presentation to lymphocytes, (b) integrated activation of the immunocompetent network to recruit and charge the killing machinery, and (c) 'pulling the trigger' for this artillery to damage the parasite (Fig. 181.2). Opposing this process are several parasite-dependent evasive mechanisms that modulate the immune response in order to establish a balanced concomitant immunity.

Antigen presentation

The cells principally involved in early schistosomal antigen recognition and presentation are Langerhans cells of the skin during the cercarial invasion stage, the circulating monocytes and B lymphocytes during schistosomular migration, and the hepatic macrophages during established infection.

Schistosomal antigens are presented on the surface of these cells in conjunction with class II MHC antigens to lymphocytes, mainly the CD4+, Th cells. These must be activated in order to respond to the antigen, a function that is mediated by cytokines which the APCs secrete. The downstream consequences depend on the APC cytokine profile, which gradually switches from pro-inflammatory to pro-fibrotic. During the initial phase, known as 'classical activation', the predominant cytokines are Il-1, IL-6, tumour necrosis factor alpha, and granulocyte- and granulocyte-monocyte colony-stimulating factors which lead to differentiation of the helper cells into a Th1 subset. (Stadecker, 1999), amplified by a positive feedback loop generated by interferon-gamma. The latter also upregulates a modulatory autocrine molecule, somatostatin, that checks 'overheating' of the system (Weinstock and Elliott, 2000). Somatostatin downregulates the APCs, many inflammatory cells, and fibroblasts in schistosomal granulomata through binding to a specific somatostatin receptor 2 (SSTR2) (Chatterjee and Van Marck, 2001).

The scenario is significantly changed as the worms reach maturity and start laying eggs. Adult worms release a new set of antigens, known as Sm-PEPCK, which trigger the transformation of APCs into phenotypically and functionally distinct 'plasmoid' cells (Pemberton et al., 1994). The eggs participate by clearing the scene for the latter cells through the release of soluble antigens that integrate with somatostatin in further suppressing the 'classical' response (Pearce and MacDonald, 2002).

Among the principal plasmoid cell proteins are CTLA4 and CD154 (Walsh et al., 2007), which switch lymphocyte differentiation into a predominantly Th2 response. This is maintained by a positive feedback loop involving IL-4 and IL-5, which is modulated by IL-10 (McManus and Loukas 2008).

Effector response

As explained above, adaptive immunity in schistosomiasis passes through two successive stages, namely the pro-inflammatory and the pro-fibrotic, being orchestrated by Th1 and Th2 cells respectively.

The major downstream product of the Th1 cell is IL-2, which recruits and activates cytotoxic lymphocytes (CD8+) and maturation of secretory (B) lymphocytes in favour of IgM and IgG1 and -2 production (McKenzie, 2000). Nude mice, which lack this response, die very rapidly after experimental infection, owing to massive tissue invasion with the parasite.

On the other hand, the main Th2 products are IL-4, -5, -10, -13 (Stadecker, 1999) and transforming growth factor beta (Omer et al., 2000). These act synergistically with parasite secretory products to recruit and regulate other leucocytes, mainly the eosinophils (Brombacher, 2000) and basophils (Henderson et al., 1992). They also switch the B lymphocytes to preferentially secrete IgE (under IL-13 control), IgG3 and -4 instead of IgG1 and -2, and IgA at the expense of IgM (under IL-10) (Barsoum et al., 1996).

Parasite elimination

Although neutrophils and CD8 cells are frequently seen in schistosomal granulomata, they seem to be of limited lethal capacity to the parasite. Similarly, while basophils may have some role

in the elimination of young schistosomulae (Henderson et al., 1992) they seem to mainly stimulate the subsequent inflammatory response through the secretion of eosinophil chemotactic factors (Owhashi et al., 1986). Antibodies have a similar role, being essential for several cell-mediated killing mechanisms in which eosinophils (de Brito et al., 1984) and neutrophils (Incani and McLaren, 1981) are involved. Certain antibodies, though, may have an immunomodulatory role by interrupting cell-mediated cytotoxicity, as shown experimentally with IgM (Khalife et al., 1986), IgA (de Brito et al., 1984), IgG2 (Grzych et al., 1984) and IgG4 (Hagan et al., 1991).

Eosinophils are by far the most lethal weapon in the host's artillery against schistosomiasis. They dominate the scene during the Th2 phase, being recruited by Th2 lymphocytes, basophils, as well as chemotactic factors of parasitic origin (Pemberton et al., 1994). Eosinophil cytotoxicity is essentially antibody dependent (de Brito et al., 1984). Activated eosinophils generate a powerful stream of reactive oxygen molecules which breach the parasite's surface. Through the resulting rents, the eosinophil pours its highly poisonous eosinophil catalytic protein (ECP) into the parasite's interior leading to massive proteolysis. A significant correlation was found between the urinary concentration of ECP and the inflammatory lesions in the urinary tract in humans (Jyding Vennervald et al., 2000).

Escape mechanisms

In established infection, adult worms seem to escape recognition by the host's APCs and specific antibodies. This tolerance is specific for a particular host, the parasite being rapidly killed if transferred into another host. The mechanism is uncertain. It may be related to the capacity of the parasite's tegument to mop up native host molecules, thereby being recognized as 'self'. Such molecules include the H blood group substance, immunoglobulins (mainly IgG), and the MHC antigens (McLaren and Terry, 1982).

Living adult worms also have the capacity of suppressing the host's immune response, an effect that increases with ageing of the parasite. The effects of parasitic antigen on the T-cell and macrophage suppressor cell population (Campi-Azevedo et al., 2007) are best known. IgG4, IgG2c, and circulating IgM immune complexes seem to block T-cell (Grzych et al., 1984; Khalife et al., 1986; Hagan et al., 1991) and eosinophil (Dunne et al., 1987) receptors. Other potential mechanisms include clonal exhaustion and/or deletion by persistent antigenic stimulation and 'diversion' of the immune system by polyclonal activation of the lymphocytes.

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CHAPTER 182

Schistosomiasis: clinical impact

Rashad S. Barsoum

Epidemiology

Schistosomiasis is a chronic debilitating disease that currently affects 207 million patients, of 700 million at risk, living in 76 countries that spread over five continents (Fig. 182.1). Much of the current information on the distribution and intensity of infection is based on modern tools using satellites, including satellite climatography and global information systems.

About 120 million infected subjects are symptomatic, while 20 million suffer from serious sequelae of the disease, particularly those living in China, the Philippines, Egypt, Brazil, northern Senegal, and Uganda, with an estimated directly related annual mortality of 20,000. This correlates with the intensity of infection which, in turn, depends on the regional prevailing parasitic strains, host susceptibility, and extent of exposure. A significant factor is the association of schistosomiasis with nutritional deficiency and other endemic diseases such as malaria, filariasis, leishmaniasis, salmonella, mycobacteria, staphylococci, hepatitis human papilloma, and human immunodeficiency viral infection among others.

Climatic factors influence the intensity of infection through their effect on snail and animal reservoir kinetics. Natural and man-made ecological changes, for example, the construction of dams and artificial lakes, have had a major impact on the prevalence and intensity of infection, in many parts of the world such as in Africa and China.

Of the human pathogenic species, the most widespread are (a) *Schistosoma haematobium*, which is endemic in most of Africa; (b) *S. mansoni*, also highly prevalent along the Egyptian Nile Valley and in the Near East, Yemen, South America, and the Caribbean; (c) *S. japonicum*, endemic in Japan, China, and the Philippines; (d) *S. intercalatum*, which is closely related to *S. mansoni*, localized in a small area in Central Africa including Zaire, the Gabon, and the Cameroons; and (e) *S. mekongi*, which is related to *S. japonicum*, mainly seen in Laos, Thailand, and Malaysia. Much less frequently encountered are *S. mattheei*, in South, Central, and Western Africa, and *S. bovis*, essentially an infection of cattle and higher primates, which very rarely affects humans.

Disease evolution

The clinicopathological evolution of schistosomiasis includes successive phases of invasion, migration, and established infection.

Invasion stage

The first response to infection is an immediate, local, immune-mediated, inflammatory skin lesion at the entry site of the parasite. Two patterns of such response are recognized: the swimmer's itch and cercarial dermatitis.

Swimmer's itch

This lesion occurs in infection-naïve individuals, usually expatriates. It is a hardly visible weal at the point of cercarial penetration, composed of oedema, dilated capillaries and a few cells, attributed to the local release of monokines. The duration and severity of this reaction depend on the length of schistosomular stay in the dermis. Therefore, the lesion is most pronounced in infections with non-human-pathogenic species of the parasite, whose schistosomulae cannot migrate. An Arthus skin reaction has been occasionally described in expatriates acquiring infection in endemic areas.

Cercarial dermatitis

This is a more visible macular lesion, 1–3 cm in diameter, also occurring around the site of cercarial penetration, in a pre-sensitized, previously infected individual. Its pathogenesis is similar to the swimmer's itch, yet with the additional contribution of adaptive immune mechanisms (see below).

Migration stage: systemic allergic reaction

This is an immune response to migrating schistosomulae, peaking 3–7 weeks after acquiring the infection. It varies from a relatively early, transient bronchial hyper-reactivity or pneumonitis that may pass unnoticed, to a later, acute serum-sickness-like illness coinciding with worm maturity. The latter, known as 'Katayama fever', is usually seen in expatriates in the Far East, perhaps owing to the high antigenicity of *S. japonicum*. It is characterized by fever, arthralgia, and vasculitic skin eruption. Eosinophilia and high serum immunoglobulin M (IgM) are typical, and cryoglobulinaemia has been occasionally described. The disease is self-limiting even without treatment.

Established infection

Established infection may lead to disease in three ways: immunogenic, amyloidogenic, or oncogenic. The pathogenesis of these conditions is essentially overlapping, so they must not be seen as totally separate entities.

Immune-mediated disease

Both cellular and humoral arms of the immune response (see Chapter 181) are involved in the pathology of schistosomiasis. The core expression of the cellular response is the granuloma, while that of the humoral response is immune-complex glomerulonephritis. Both start during the T-helper (Th)-1 phase, and either resolve or undergo further progression during the Th2 phase.

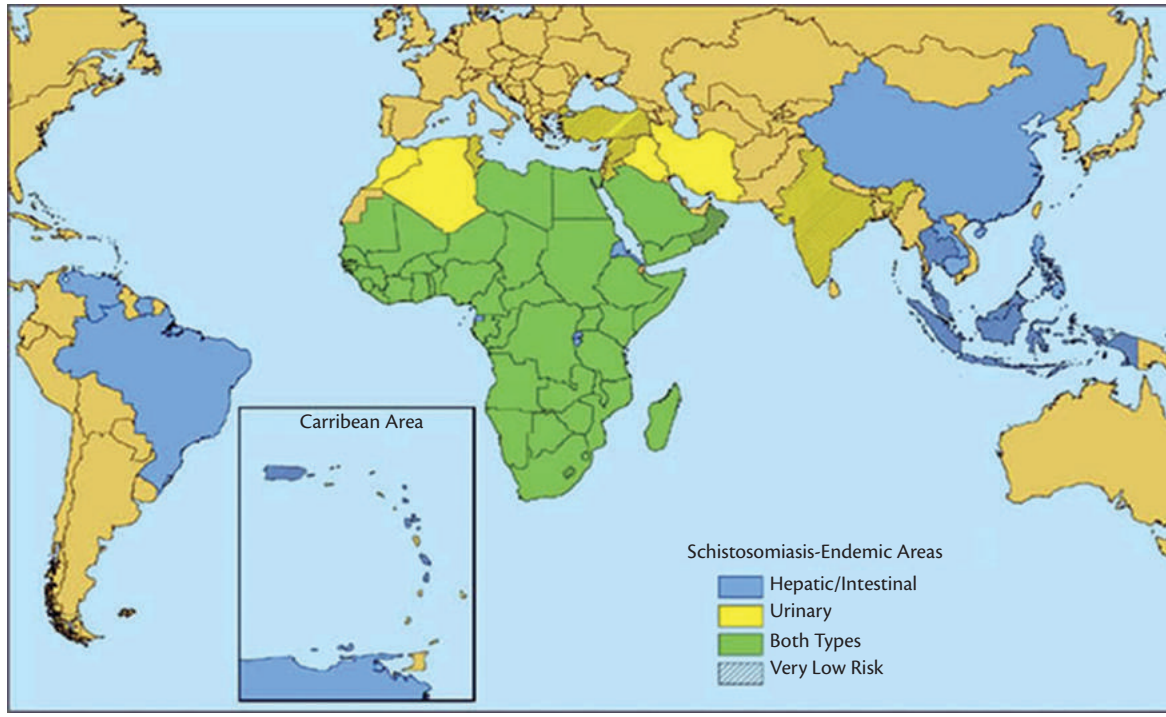

Fig. 182.1 Global distribution of schistosomiasis according to primary anatomical target.
<http://www.nathnac.org/pro/factsheets/schisto.htm>

The granuloma

This is a delayed cellular reaction that takes place around tissue-trapped single (*S. haematobium* and *S. mansoni*) or multiple (*S. japonicum*) ova, schistosomulae, or even adult worms (Fig. 182.2). Lymphocytes, plasma cells, eosinophils, basophils, and macrophages participate in the formation of the granuloma. Neutrophils are also seen during the initial phases, but suppuration does not occur. Macrophages frequently coalesce to form giant cells. Fibroblasts eventually shell off the periphery of the granuloma.

Ageing granulomata become progressively more fibrotic until they heal as firm nodules around shell remnants of dead ova. Calcification is common, particularly in the lower urinary tract with *S. haematobium* and the central nervous system with *S. japonicum* infections. The extent of fibrosis induced by these healing granulomata can be appreciated by considering the millions of ova produced by just one pair of worms during their lifespan of several years. Indeed, most of the features of schistosomiasis in its late stage are the sequelae of extensive fibrosis.

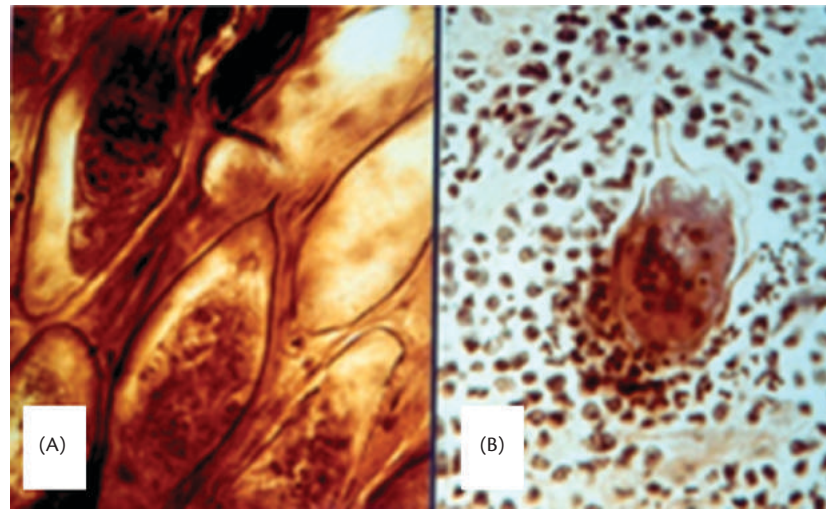

Fig. 182.2 Schistosomal haematobium. (A) Sheet of ova in bladder submucosa (silver stain). (B) Granuloma (haematoxylin-eosin stain). Note the damaged egg shell with a terminal spike surrounded by inflammatory cells and fibroblasts.

The evolution of cellular into fibrotic granulomata constitutes the essence of progression of schistosomiasis in different organs. With the possible exception of the spleen, all tissues may be affected. The most frequently involved are the lower urinary tract and the seminal vesicles, the colon, rectum, hepatic portal tracts, and the lungs. Lesions in the brain, spinal cord, skin, kidneys, pancreas, prostate, vagina, uterine cervix, and adnexae are less common.

Immune complexes

Immune complexes can be detected as early as 2 weeks following the initial infection, being mostly composed of schistosomal tegument antigens and IgM. They may take part in the pathogenesis of Takayama fever described earlier. Further immune complex formation takes place with an expanding spectrum of antigens and immunoglobulins leading to different forms of glomerulonephritis (see Chapter 181).

Amyloidosis

Secondary amyloidosis can be induced by experimental infection with *S. mansoni* and *S. japonicum* in mice and rabbits, and with *S. haematobium* in hamsters. It has also been reported in patients with long-standing infection with *S. mansoni, S. haematobium*, or both. The lesions were usually restricted to the kidneys, and were associated with the conventional *Schistosoma*-associated glomerular and interstitial lesions.

It is believed that *Schistosoma*-associated amyloidosis results from an imbalance between the formation and uptake of AA protein by the monocytes and hepatocytes. While synthesis is upregulated by interleukin (IL)-6, re-uptake is downregulated by IL-10. The abundance of these particular cytokines in late schistosomal lesions (see Chapter 181) may be responsible for the increased levels of circulating AA protein in late schistosomiasis. Selective deposition in the glomeruli is presumably related to the abundance of amyloidophilic proteoglycans as decorin and biglycan (Barsoum, 2004).

Malignancy

Schistosomiasis has been associated with the development of malignancy in the bladder, rectum, and spleen; the pathogenetic link being most firmly established with the former. In addition, the association of hepatosplenic mansoniasis with hepatitis B or C viral infections increases the risk of liver malignancy and non-Hodgkin lymphoma manyfold.

Bladder malignancy

Bladder neoplasia can be experimentally induced in baboons by *S. haematobium* infections. Its reported incidence in patients may be as high as 4.5% of those with urinary bilharziasis in Nigeria (Chugh et al., 1986). The histological type is squamous cell type in roughly 60%, transitional cell carcinoma in 20%, adenocarcinoma in 10%, and mixed in the rest. Schistosomal ova were detected in > 85% of bladder cancers in an Egyptian series of 1026 cases subjected to surgical cystectomy (Ghoneim et al., 1997). The tumour, particularly when of the squamous-cell type, remains localized for a long time before spreading to the surrounding pelvic tissues or distant site, thanks to the occlusion of lymphatics by the preceding fibrotic process.

Associated bacterial and viral infections, rather than parasitic products, are suggested to be the main pathogenetic factors. Associated infection with human papilloma virus has received considerable recent attention in this respect (el-Mawla et al., 2001), being encountered in about one-quarter of cases. Specific *p53* gene mutations have been shown in one-third of cases (Warren et al., 1995), being attributed to the effect of neutrophil-generated reactive oxygen molecules, cleavage of conjugated urinary carcinogens, or the production of nitrosamines by bacterial enzymes (Mostafa et al., 1999).

Other malignancies associated with schistosomiasis are less well documented. Colorectal cancer has been attributed to *S. japonicum* infection in China and Japan on the basis of finding a heavy egg load in the tumour tissue. However, a causative relationship has not been documented (Yosry, 2006).

A Burkitt's type of lymphocytic lymphoma associated with *S. mansoni* intestinal schistosomiasis was reported in a 14-year-old Zairian girl, with suggestive evidence of a cause-and-effect relationship (Chirimwami et al., 1991).

Clinical syndromes of established infection

About 3 months after initial infection, 10–20% of infected subjects develop one or both of the primary clinical syndromes, namely the urinary and/or the hepatointestinal. An unknown proportion of either may develop cardiopulmonary disease. An occasional patient may also suffer from the effects of metastatic granulomata, particularly in the central nervous system. Untreated, such 'early' syndromes gradually evolve into progressive disease that may result in organ failure.

Urinary schistosomiasis

This is discussed in Chapter 194.

Hepatointestinal schistosomiasis

This syndrome, which is usually seen with *S. mansoni* or *S. japonicum* infection, involves the colon, rectum, and liver. The usual clinical presentation is dysenteric. Chronic spastic colitis, the irritable colon syndrome, and colonic polyposis are also frequently encountered. Rarely, large pericolic rectal masses may be formed, which are often confused with malignancy.

The liver is involved in the majority of patients. Initially, it is mildly to moderately enlarged and tender with transient elevation of serum aspartate aminotransferase and alanine aminotransferase. A few weeks to months later, the spleen is also enlarged due to the lymphoid hyperplasia featuring the host's immune response.

At this stage, the diagnosis is made by finding *Schistosoma* ova in stools, rectal scrapings, or rectal snips. Proctocolonoscopic examination helps to establish the diagnosis and to categorize the histopathological patterns, which include ulcers, polyps, and sessile granulomas. Liver biopsy is rarely needed, but it provides a conclusive tissue diagnosis based on the finding of schistosomal granulomata around ova, egg remnants, or 'pigments'.

With the progressive fibrosis of schistosomal granulomata in the portal tracts ('pipe stem fibrosis'), the liver ultimately becomes firm and shrunken. Pre-sinusoidal portal hypertension develops and is clinically manifested by splenomegaly, portosystemic collaterals, and ascites.

Ultrasonography is extremely helpful in showing the specific pattern of hepatic fibrosis and in demonstrating portal vein dilatation, splenomegaly, and ascites (Pinto-Silva et al., 2010). Liver biopsy confirms the diagnosis and helps to exclude associated diseases.

Unless the disease is complicated by concomitant viral infection (usually hepatitis C or B virus), or associated non-alcoholic steatohepatitis, tests of hepatocellular function are not significantly affected until late in the disease.

Cardiopulmonary schistosomiasis

S. haematobium ova may be carried directly from the perivesical venous plexus, while *S. mansoni* or *S. japonicum* ova travel across portosystemic shunts to the inferior vena cava, and subsequently to the pulmonary capillaries where they usually stop short of the peri-alveolar shunts. They lead to granuloma formation at these sites, and also provoke immune-mediated endothelial proliferation in both pre-and post-alveolar capillaries (Hovnanian et al., 2010) leading to pulmonary hypertension ('bilharzial cor pulmonale') (Fig. 182.3). A restrictive pattern of right ventricular dysfunction was observed in some of these patients. Endomyocardial biopsy showed considerable subendocardial fibrosis, which is thought to represent a diffuse form of the cellular response to schistosomiasis. The specificity of this lesion has yet to be confirmed.

'Metastatic' lesions

Granulomas may develop around metastatic ova in different organs. They do not result in significant clinical manifestations except in the central nervous system. Brain granulomas (usually with *S. japonicum*) present with recurrent seizures, without notable neurological deficit. Spinal cord granulomas (usually with *S. haematobium*) lead to transverse myelitis. Both lesions usually respond to early treatment.

Metastatic involvement of the skin is rare. The most common sites are genital, where nodular lesions develop in the skin of the scrotum, penis, and vulva. They are usually asymptomatic, being non-tender, non-itchy, and non-ulcerative. Very rarely, similar lesions have been reported to occur around the umbilicus and overlying the scapulae and shoulders.

Nodular lesions have also been described in the palpebral conjunctiva in patients with extensive *S. haematobium* disease. However, no effects on the eyeball have been reported.

Management

Primary prevention of schistosomiasis is largely a matter of education and sanitation. Simple measures to interrupt the parasite's life cycle by avoiding human contact with contaminated water have been rewarded by remarkable success. Periodic mass treatment, which has become possible since the introduction of the effective and safe oral drug, praziquantel, has also been very effective in China and Egypt. However, there are certain drawbacks of mass treatment strategies including logistic and financial issues, possible development of drug resistance, lack of resistance to re-infection, and possible increase in the risk of hepatic disease with interrupted treatment. For these reasons, the search for an effective vaccine continues despite repeated disappointments with many attempts in the past.

Vaccines

Data from animal vaccination studies yielded important information that shaped human vaccine-development strategies. It is clear that an immune status is achieved by the integration of humoral and cellular mechanisms, dominated by upregulation of antigen-specific Th1and Th2 clones leading to a favourable IgE/IgG4 ratio (see Chapter 181).

It remains to identify the right target antigen. The most eligible candidates are the schistosomular tegument membrane antigens Sm23, SmTSP-2 and Sm29. Also eligible are egg antigens, targeting which would decrease parasite fecundity and egg viability. Proteomic and genomic studies (McManus and Loukas, 2008) are underway for integrating these antigens into a master mix, hoping to raise the effectiveness of vaccination over the current 70% success rate.

Treatment of active lesions

Active lesions readily respond to antischistosomal chemotherapy. The drug of choice today is praziquantel, a pyrazinoisoquinoline derivative. It is effective against all species of human pathogenic *Schistosoma* with a cure rate of 80%. However, it cannot be used for chemoprophylaxis, since it is active only against mature worms. The recommended therapeutic dose is 40 mg/kg body weight as a single morning dose for *S. haematobium* and *S. mansoni*. For *S. japonicum*, the dose should be increased to 60 mg/kg body weight given in two divided doses on the same day. The same dose is used for *S. mekongi*, preferably divided into three doses given in the same day. The drug is safe, but a few side effects have been reported including abdominal pains, headaches, dizziness, and skin rash.

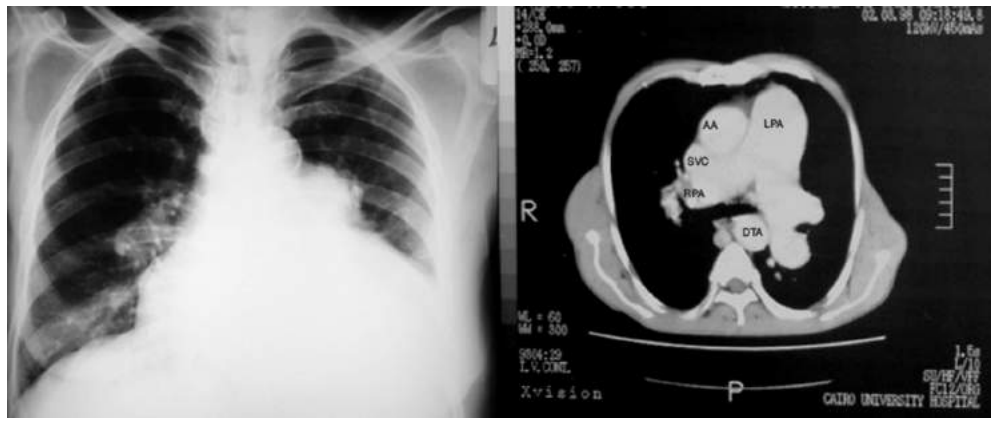

Fig. 182.3 Bilharzial cor pulmonale.

The organophosphorus preparation metrifonate is effective only against *S. haematobium* infections. The drug is safe and can be used in mass treatment. The recommended dose is 10 mg/kg body weight as a single dose, which may be repeated twice at fortnightly intervals in order to achieve a high cure rate.

Oxamniquine is a quinoline derivative (2-aminomethyl-tetrahydro-quinoline), which is effective against *S. mansoni* only infections. The recommended single-dose treatment is 20 mg/kg body weight.

Artemether, a derivative of the Chinese antimalarial qinghaosu alkaloids is a promising new agent that can effectively kill the invading cercariae, maturing schistosomulae, as well as the mature adult worms by interfering with the parasite's glycolytic pathways (Shuhua et al., 2000).

Adjuvant treatment with colchicine has been successful in reducing fibrosis in experimental murine schistosomiasis and the development of amyloidosis in Syrian hamsters. It has been widely used in patients with hepatosplenic schistosomiasis, yet without conclusive therapeutic benefit.

Results of treatment

Antischistosomal chemotherapy leads to parasitological cure in 40–80% of cases, depending on the drug used, the parasite species and strains, the host's nutritional state, and other factors. Even without such a cure, the intensity of infection is significantly reduced. The effectiveness of treatment can be tested by the progressive decline in the number of eggs excreted in urine and stools, to disappear within 3–4 months. Tissue biopsy from the bladder or rectal mucosa after effective treatment may still show trapped dead ova for many years. The titres of circulating gut and egg antigens rapidly decline with effective treatment. Persistence of the former after the disappearance of eggs from the excreta usually indicates the survival of sterile or single-sex worms. This outcome has the advantage of possibly conferring active immunity against re-infection, so much so that it is considered the aim of certain mass treatment programmes. Owing to the absence of ova, such a setting is certainly harmless from the point of view of granulomatous lesions. However, its effect on the development and propagation of immune-complex-mediated glomerular injury has not yet been elucidated.

The reversibility of established lesions after effective antischistosomal therapy depends on the species, the organ(s) affected, the duration of infection, and the degree of damage already sustained. Best results are achieved with early bladder lesions or back pressure in *S. hematobium* infections, early colonic or hepatic lesions in *S. mansoni* infections, or brain lesions in *S. japonicum* disease. Certain glomerular lesions confounded by concomitant infections may be reversible by dual therapy (see Chapter 194).

Treatment of fibrotic lesions

Many of the residual lesions need no surgical correction. Examples are colonic submucosal and pericolic fibrosis sparing motility, hepatosplenic schistosomiasis without portal hypertension, lower ureteric fibrosis without pelvicalyceal dilatation even when associated with mild to moderate reflux, and bladder fibrosis and calcification without significant urodynamic disturbances.

In certain instances, however, extreme degrees of portal hypertension may necessitate shunting operations and prominent oesophageal varices may require sclerotherapy. Lower urinary tract lesions are frequently treated by urological procedures that include percutaneous nephrostomies for the temporary relief of obstruction, endoscopic dilatation of stenosed ureters, subureteric silicone injection for the amelioration of reflux, ureterovesical implantation, ureteroplasty and cystoplasty, and the use of ileal loops for restoration of adequate urodynamic function.

Owing to the silence of cardiopulmonary lesions, the diagnosis is usually delayed beyond the point of any reversibility. Patients with schistosomal cor pulmonale tend to have progressive right ventricular failure which is barely affected by any form of treatment.

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