Urinary Tract Pathogens in Complicated Infection and in Elderly Individuals

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Complicated urinary tract infection (UTI) occurs in patients with a genitourinary tract that does not function normally, usually due to structural or functional abnormalities. There are a wide variety of diseases and interventions responsible for complicated UTI, including obstructive lesions, metabolic diseases, instrumentation, foreign bodies, or dysfunctional voiding primarily due to neurologic illnesses (figure 1). The wide variation in abnormalities means there is substantial variation in the clinical characteristics of UTI in these different populations.

For instance, in some patients with a nonfunctioning kidney, once infection is established, it usually cannot be eradicated, and relapsing infection with the same organism will persist. Another group of patients, those with neurogenic bladder and voiding managed by intermittent catheterization, have a high incidence of infection with new infecting organisms, which are constantly introduced into the urinary tract. In other instances, such as infection associated with obstruction when a stone is passed, correction of the abnormality (i.e., removal of the stone) will alleviate the complicating factor, and further infection is unlikely to occur. This great diversity in risk factors and natural history must be appreciated in any discussion of complicated UTI.

UTI among elderly populations is very common and is conceptually considered within the context of complicated UTI [1]; that is, the genitourinary tract is not functioning normally. In ambulant elderly women, prior genitourinary surgery and abnormalities, such as cystoceles, are associated with infection, and in men, prostatic hypertrophy is an important association with infection. These are common abnormalities recognized to be associated with an increased frequency of UTI at any age. In the institutionalized elderly population, the major contributing factors to infection are chronic comorbid neurologic illnesses with an associated neurogenic bladder. Thus, UTI in the institutionalized population is generally an accompaniment of incontinence and dementia.

Current Knowledge

Infecting organisms. A characteristic of complicated UTI is the wide variety of infecting organisms isolated (table 1).

Escherichia coli remains an important pathogen, and in many series is identified in 50%–60% of infections. Other Enterobacteriaceae also occur frequently, including Klebsiella, Enterobacter, and Serratia species, as do urease-producing organisms, such as Proteus mirabilis and Providencia stuartii. Pseudomonas aeruginosa and Candida albicans are common in some populations, and gram-positive organisms, particularly enterococci and coagulase-negative staphylococci, are also frequently isolated.

The distribution of species of organisms isolated varies with the population studied and is influenced by factors such as whether the infection is initial or recurrent, prior antimicrobial therapy, and whether genitourinary instrumentation with a potential for nosocomial acquisition of an organism has preceded infection. A first infection is frequently caused by E. coli and will not usually be with a highly resistant strain. Recurrent infection is more likely to be with organisms of increased resistance. Highly resistant organisms, such as P. aeruginosa and Candida species, are common among certain populations (e.g., intensive care unit patients receiving broad-spectrum antimicrobials and with indwelling catheters in place). While infections are usually caused by a single organism, patients with chronic indwelling catheters or other foreign bodies, such as ureteric stents, will usually have polymicrobial bacteriuria, with as many as 3–5 organisms isolated at any time.

The microbiologic observations are similar among elderly populations. There is a wide spectrum of infecting organisms and a tendency toward organisms of increased antimicrobial resistance relative to younger populations with uncomplicated UTI [1]. For women, E. coli is isolated in 50%–60% of infections, with P. mirabilis and Klebsiella pneumoniae also frequent. For men, P. mirabilis is the most frequently isolated organism in some populations, with E. coli, Enterococcus species, and coagulase-negative staphylococci also common. Very high frequencies of P. mirabilis, P. stuartii, P. aeruginosa, and Enterococcus species can be isolated from elderly subjects with chronic indwelling catheters.

Pathogenesis of UTI. Infection in complicated UTI is virtually always by the ascending route; organisms travel up the urethra to the bladder and, in some cases, ascend further to the kidneys. Unrestricted drainage of urine from the kidneys to the bladder with complete intermittent bladder emptying through voiding is the most important host defense in preventing UTI. In complicated UTI, there is failure of complete voiding, with persistence of infecting organisms within the genitourinary tract. Persistence may be due to obstruction within the genitourinary tract, with incomplete urine drainage. Or-
Figure 1. Underlying abnormalities associated with complicated urinary tract infection.

organisms sequestered within struvite stones will also persist, and where a foreign body is present, organisms may persist in a biofilm. The biofilm coats catheters and stents and is comprised of organisms, extracellular material, minerals, and Tamm-Horsfall protein. There may also be increased access of organisms to the genitourinary tract, as with catheterization. Thus, specific organism virulence factors are not necessary to promote infection; host abnormalities are sufficient.

With obstruction of the urinary tract or genitourinary trauma, infecting organisms may gain access to the bloodstream and cause invasive infection with systemic manifestations. Bacteremia in complicated UTI is usually due to gram-negative organisms, but even generally avirulent organisms, such as enterococci or coagulase-negative staphylococci, may be isolated.

Virulence of E. coli in complicated UTI. E. coli is the single most frequent uropathogen in complicated UTI, including UTI in the elderly, although it is isolated proportionally less frequently in uncomplicated than in uncomplicated UTI. Virulence factors of E. coli in uncomplicated UTI, particularly pyelonephritis, have been well described. Strains associated with acute nonobstructive pyelonephritis usually belong to a limited number of urovirulent O:K:H serotypes and have a high frequency of genes coding for phenotypic expression of P fimbriae, aerobactin, and hemolysin. These virulence genes frequently occur together in pathogenic islands. E. coli isolated from patients with complicated UTI have consistently shown a lower prevalence of virulence genes and phenotypic expression of virulence factors compared with E. coli strains isolated from uncomplicated infection.

Johnson et al. [3] reported that bacteremic E. coli from patients with an abnormal urinary tract or with urinary tract instrumentation or medical illness (e.g., diabetes, immunosuppression, cancer, and uremia) were significantly less likely to have P fimbriae expression than were bacteremic isolates from patients without these compromising features. Sandberg et al. [4] studied 175 urinary isolates of E. coli from women with community-acquired symptomatic UTI. Among women with uncomplicated pyelonephritis, 84% of urinary E. coli isolates were urovirulent serotypes, compared with only 10% from women with medical illness, 31% and 38% from women with major and minor urinary tract abnormalities, respectively, and 50% from pregnant women. The frequency of hemolysin production and presence of resistance was similar among the different clinical groups. However, 80% of uncomplicated pyelonephritis isolates expressed P fimbriae, compared with only 50%–67% of strains in the other patient groups. The proportion of urovirulent serotypes and strains with P fimbriae expression did not vary with age.

Benton et al. [5] also reported that among 70 E. coli strains isolated from the urine of patients with spinal cord injury, there was a low prevalence of urovirulent O serotypes and less phenotypic expression of virulence factors relative to that reported in uncomplicated acute pyelonephritis. Only 54% of the spinal cord patient strains belonged to urovirulent O serotypes, and only 17% expressed P fimbriae, 27% hemolysin, and 39% aerobactin.

Johnson et al. [6] further expanded their observations of bacteremic E. coli isolates from patients with and without complicating factors and reported a significantly lower frequency of genes for P fimbriae in strains isolated from patients with complicating factors. Using the same bacteremic E. coli isolates, he identified urovirulence-associated O groups, K types, and O:K:H serotypes [7]. These urovirulent serotypes were more likely to have chromosomal determinants for P fimbriae, he-

Table 1. Prevalence of gram-positive and -negative organisms isolated in complicated urinary infection [2].

<table>
<thead>
<tr>
<th>Organism</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>21%–54%</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>1.9%–17%</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>1.9%–9.6%</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>4.7%–6.1%</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>0.9%–9.6%</td>
</tr>
<tr>
<td>Providencia species</td>
<td>18%</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2%–19%</td>
</tr>
<tr>
<td>Others</td>
<td>6.1%–20%</td>
</tr>
<tr>
<td>Gram positive</td>
<td></td>
</tr>
<tr>
<td>Enterococci species</td>
<td>6.1%–23%</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>1.2%–3.5%</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>1.4%–3.7%</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0.9%–2.0%</td>
</tr>
<tr>
<td>Candida species</td>
<td>0%–5.0%</td>
</tr>
</tbody>
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molsyn, and aerobactin, and individuals with complicated UTI were less likely to have urovirulent strains isolated. O:K:H pyelonephritis strains were associated with a lower prevalence of host urinary tract abnormalities. Subsequently, with the same set of isolates, Johnson and colleagues [8] further reported that strains isolated from patients with complicated UTI were significantly less likely to possess the type II allele of P fimbriae, relative to uncomplicated pyelonephritis, and more likely to express the type III allele.

Thus, among different populations and in both urinary and bacteremic isolates, there is a consistent observation that *E. coli* isolated from patients with complicated UTI are less likely to possess urovirulence genes. This is, of course, consistent with the observation that specific organism virulence factors are not needed to establish or maintain infection in patients with a urinary tract abnormality.

Virulence factors do, however, likely have some impact in complicated UTI. While *E. coli* with more virulent phenotypes are identified less frequently in complicated than uncomplicated UTI, the virulence factors are found more frequently in *E. coli* isolates from complicated UTI cases than in *E. coli* colonizing feces. In one elderly group, mannose-resistant hemagglutination associated with P fimbriae expression was more frequent in strains isolated from elderly institutionalized women with bacteriuria than from transient colonizing organisms in urine from these patients: 8% of transient strains and 29% of infecting *E. coli* had mannose-resistant hemagglutination [9]. The 2 groups of *E.coli* isolates had a similar prevalence of phenotypic expression of mannose-sensitive hemagglutination or hemolysin. In addition, 1 woman developed acute pyelonephritis with an *E. coli* strain previously isolated with asymptomatic infection; the strain demonstrated new production of P fimbriae coincident with the symptomatic episode. The mechanism by which symptomatic infection occurred and the relative importance of host or organism factors was not, however, determined.

Urease-producing organisms. Urease producing organisms, including *P. mirabilis*, *P. stuartii*, and *Morganella morganii* are frequently isolated in complicated UTI. They are virtually never isolated in acute uncomplicated UTI, so comparison of potential virulence factors between strains isolated from complicated and uncomplicated infection is not possible. The effect of urease on ammonia in the urine may produce an alkaline urine with a high pH. The alkaline pH may be associated with a lower level of pyuria because of more rapid disintegration of leukocytes. Other effects of an alkaline urine, per se, have not been well studied. In a group of elderly women, a trend to increased urinary cytokines (interleukin-6 and -1α) in an alkaline urine was reported [10]. Struvite stone formation is a complication of infection with urease-producing organisms, particularly *P. mirabilis*. There are, however, many elderly subjects with prolonged infection with *P. mirabilis* who do not develop stones, and variables predicting stone formation need further study [1].

In patients with chronic indwelling urethral catheters, infection with *P. mirabilis* or *P. stuartii*, compared with infection with other organisms, is associated with recurrent obstruction, suggesting a greater likelihood of biofilm formation with these organisms. In elderly subjects with chronic indwelling catheters, *P. stuartii* was associated with a more prolonged infection than were other species [11]. Enterococci and coagulase-negative staphylococci persisted for the shortest duration. Further evaluation of these *P. stuartii* strains showed that strains with the longest duration of infection were significantly more likely to express mannose-resistant/Klebsiella-like hemagglutinins, and strains that persisted for a shorter duration were significantly more likely to produce mannose-sensitive hemagglutinins [11].

**Differential host response to infecting organisms.** A spectrum of host responses to UTI is anticipated in complicated UTI, given the wide variety of infecting organisms. UTI, of course, may be asymptomatic or symptomatic, and in the absence of major obstruction or trauma to the genitourinary tract, differential virulence of infecting organisms could be a determinant of whether infection will be symptomatic. In addition, variation in the degree of inflammatory or immunologic response within the urinary tract or systemically would be anticipated, at least in part, to be determined by variation in virulence among organisms. Thus, an increased level of pyuria, urine antibody, or urinary cytokines could be markers for infection with organisms with increased virulence. Identification of potential organism determinants influencing the host response has, however, not been studied other than for *E. coli*.

Several studies suggest a difference in distribution of organisms in symptomatic compared with asymptomatic infection. For instance, Benton et al. [5] reported that *E. coli* caused 40% of episodes of pyelonephritis in spinal cord–injured patients but only 14% of all infecting urinary isolates over an 18-month period. Harding et al. [12] reported that 39% of infections acquired by women during short-term catheterization were caused by *E. coli*, compared with 62% of symptomatic infections. Thus, *E. coli* has tended to be isolated more frequently in symptomatic than asymptomatic infection. In contrast, enterococcal species may be isolated more frequently from asymptomatic subjects.

Pyuria is a marker for the local urinary inflammatory response, and increased degrees of pyuria could suggest increased organism virulence. An association has consistently been reported between isolation of gram-negative organisms and a higher quantitative level of pyuria among different populations with asymptomatic infection. Less common but potentially more virulent gram-positive organisms, such as group B streptococci, also have higher levels of pyuria. This observation has been reported for spinal cord–injured populations, diabetic women, and catheterized patients.

In a group of diabetic women with asymptomatic infection [13], the mean level of pyuria was 345 ± 935 for *E. coli* and 43 ± 43 for coagulase-negative staphylococci. Tambyah and Maki [14] reported a mean urinary leukocyte level of 121 ± 335 for gram-negative bacilli and 39 ± 161 for gram-positive
coci in 82 episodes of nosocomial UTI in patients with short-term catheters. Within specific species groups, such as \textit{E. coli}, there is also a wide variation in the degree of pyuria, and it might be assumed that higher levels of pyuria reflect more virulent strains. However, there has been relatively little study of the variation of pyuria as stratified by organism factors, and other variables, such as urine pH and whether infection is localized to the bladder or kidney, will also influence the degree of pyuria.

\textbf{Commentary}

Complicated UTI is a heterogenous clinical entity with a wide variation in underlying abnormalities that promote infection and in infecting organisms. \textit{E. coli} strains isolated from complicated UTI cases are, as a group, less virulent that those isolated from uncomplicated infections. There is still, however, a spectrum of virulence characteristics among strains isolated from complicated UTI cases, and the clinical meaning of this variation is not well understood. Organisms such as coagulase-negative staphylococci and enterococci are generally recognized to be of low pathogenic potential but may cause UTI in subjects with an abnormal genitourinary tract. They may be less likely, however, to cause invasive UTI, and are consistently associated with a lower degree of inflammatory response in the urinary tract. Among gram-negative organisms, \textit{E. coli} may retain a unique pathogenicity in frequency and association with invasive infection, but further evaluation is necessary to support this observation.

Correcting the underlying genitourinary abnormality responsible for infection is paramount in the management of complicated UTI. If it can be achieved, this is the most useful intervention to prevent further infections. In many patients, however, the genitourinary abnormality promoting infection cannot be corrected, and persistent and recurrent infection will occur. While the impact of the organism is less important in establishing infection in complicated than uncomplicated UTI, organism variables are likely relevant in determining whether infection is symptomatic and whether infection will persist. A fuller understanding of organism variables may lead to creative strategies to assist in managing the difficult problem of complicated UTI.

\textbf{References}