Anatomical Pathophysiological and Pathogenesis of UTI

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ABSTRACT

UTI is initiated and caused by a number of factors, an understanding of the causation helps to Diagnose and treat it adequately. Organisms and host factors responsible for the occurrence and pathogenesis, are crucial in the diagnosis and treatment to prevent serious sequelae. Ecoli is a main organism causing UTI.

Keywords: UTI, Ecoli Treatment.

1. INTRODUCTION :

Urinary tract infection (UTI) is the most common disease in infants and the second most common infectious disease in toddlers.In children, UTI frequency, clinical symptoms and the causative pathogens vary according to sex and age. Moreover because of a wide variety of non-specific and systemic symptoms, it is difficult to perform tests for early diagnosis and the resultant inaccurate diagnosis may lead to antibiotic abuse. Thus in many cases, a severe renal injury occurs even before the UTI is diagnosed. For this reason, an early and accurate diagnosis through careful examination and tests can help in preventing severe renal injuries through adequate treatment and careful follow-up. UTI recurs easily if it is accompanied with anatomical anomalies of the urinary system. If it is not treated adequately or occurs recurrently, UTI may develop into chronic pyelonephritis resulting in hypertension and loss of renal function, a condition normally seen in 15–20% of the cases of chronic renal failure [1].

Pathophysiology and pathogenesis

UTI is thought to initiate when a bacterial clone from the intestinal flora colonizes the periurethra and then ascends into the bladder. E.coli typically colonizes the gastrointestinal tract of humans already within few hours after birth. Some well-established E. coli clones can acquire specific virulence attributes with increased ability to adapt to new niches [2]. Virulence properties are frequently encoded in specific genetic elements, so called 'pathogenicity islands'. Only the most successful combination of virulence factors has persisted to form a specific type uropathogenicE.coli. The subset of E.coli that causes uncomplicated cystitis and acute pyelonephritis is distinct from the commensal E.coli strains. These phenotypic characteristics include specific adhesins, toxins, siderophores, proteases and the capsule as well as hydrophobicity and serum resistance [3-4].

UropathogenicE.coli uses a multi-step scheme of pathogenesis which consists of adhesion and colonization, invasion, survival, multiplication and host damage. Accordingly, bacterial virulence factors could be divided into adhesion/colonization factors, survival/immune escape factors and toxins [5].

Virulence factors associated with E.Coli urinary tract infection isolates [5]:-

1) Expression of certain O: K: H Serotypes
2) K polysaccharide capsule
3) Adherence to uroepithelial cells
4) Resistance to serum bactericidal activity
5) Hemolysin production.
6) Aerobactin production
7) Possible factors include:

a) Bacterial generation time in urine
b) Bacterial ureteroplegic factor
c) Colicin V production
d) Salicin fermentation.

Adherence of bacteria to Uroepithelial cells is a prerequisite for colonization, persistence and infection. In a system of continuous urinary flow including the powerful effect of micturition, pathogens must bind to epithelial surface to cause disease [6]. According to

Zafriri D, Gron Y *et al* (1987) adherent bacteria not only persist within the urinary tract but may have growth advantages and enhanced toxicity as a result of proximity to products restricted in their diffusion that are secreted by eukaryotic cells. This could result in more effective delivery of toxins to the cells [7]. Varian S. *et al* (1980) observed relationship between in vitro adherence of E.Coli and severity of urinary tract infection in vivo [7]. Bacteria with P fimbriae are more likely to cause pyelonephritis. Between 76 and 94% of pyelonephritogenic strains of Escherichia coli have P. fimbriae, compared with 19-23% of Cystitis strains [8].

According to Thulesius O. *et al* (1987) lipopolysaccharide also acts to reduce ureteric peristalsis, hence facilitating ascent of Escherichia coli via the relatively dilated hypotonic ureters to the kidneys [8].Leying *et al* (1990) reported that capsular K1 expression is a prerequisite for serum resistance and loss of ability to synthesize K1 leads to loss of serum resistance [9].According to Hughes C. *et al* (1983) hemolysins are thought to contribute to spread of Escherichia coli within renal parenchyma [10].Stuart SJ *et al* (1980) identified two mechanisms of iron uptake in Escherichia coli, the hydroxymate type of siderophore, aerobactin and the catechol type of siderophore, enterochelin [11].

2. ADHESION AND COLONIZATION :

Pathogenic E. coli possess specific adherence factors that allow them to colonize different sites that E.coli do not normally inhabit. Adhesion to the cells could be a function of physiochemical surface properties of the bacterium as determined by a specific composition of lipopolysaccharides (LPS) and the capsule and often described as hydrophobicity [12,13]. The saccharide part of LPS is usually referred to as Oantigen. Interestingly, only a small number of O-serogroups has phenotypes that are epidemiologically associated with urinary tract infection [14,15].

In addition to LPS and the capsule, pathogenic E. coli express a number of distinct adhesins. Adhesins usually form definite morphological structures called fimbriae (also called pili) or fibrille. Fimbriae are rod-like structures of 5-10 nm in diameter. Fibrille on the other hand, are only 2-4 nm in diameter and are either long and wiry or curly and flexible .Uropathogenic E. coli are characterized by type 1 fimbriae, P. fimbriae, S. fimbriae, F1C fimbriae and adhesins [16,17]. In early stages of urinary tract infection, type 1 fimbriae seem to be important. Type 1 fimbriated E. coli attach to mannose moieties of the uroplakin receptors that coat transitional uroepithelial cells [18, 20]. In strains that cause cystitis, type 1 fimbriae are continually expressed and the infection is confined to the bladder [21]. In pyelonephritic strains, on the other hand, the type 1 fimbriae expression turns ‘off’ [22]. This may allow the organism to ascend through ureters to the kidneys, where the bacterium can attach by P fimbriae to digalactoside receptors that are expressed on the kidney epithelium [23, 25]. S. fimbriae and F1C fimbriae have also been shown to bind to epithelial and endothelial cells from the kidney and lower urinary tract [26,27]. Dr fimbriae on the other hand, bind to type IV collagen and decay-accelerating factor and enable E.coli to persist longer in the renal interstitium [28]. Thin aggregative fimbriae also called curli, are expressed on about 50% of urinary E. coli isolates. They have been suggested to promote the colonization of the perineal area and to initiate subsequent UTI. Some uropathogenic E. coli strains have been shown to also express flagella. Flagella are up to 15 μm long complex organelles, which contribute to bacterial mobility. In contrast to enterotoxigenic E. coli, the role of flagella in the colonization of urinary tract seems to be of a subordinate importance [29].

3. SURVIVAL AND IMMUNE ESCAPE :

Pathogenic E.coli has developed several strategies to survive in an environment, which is sometimes not very favourable and poor of nutrients. Similarly bacteria have learned to protect themselves from attacks of the immune system and exogenous antibiotics. Amongst these protective factors, siderophores, capsule and biofilm appear to be the most important. Aerobactin, an example of a siderophore, enhances iron uptake and thus promotes the survival and growth of bacteria within the urinary tract [30]. Recent findings indicate that bacteria in their natural environment grow in a rather complicated multicellular state,

biofilm[31].Curli fimbriae and cellulose are the major extracellular components of biofilm produced by the family Enterobacteriacae [32].Biofilm is a structurally complex and dynamic system that helps bacteria to survive in different environments and to be protected from both the immune system and the antibiotic treatment [33,34]. In addition to the biofilm formation, E. coli are able to produce a polysaccharide capsule, which substantially increases bacterial survival within the urinary tract and increases resistance to serum and to phagocytosis [35,36].

4. TOXINS :

E. coli produce a number of toxins, which are either associated with the membrane or secreted. Toxins participate in the pathogenesis of UTI by different mechanisms. LPS, bacterial endotoxin, a principal component of the bacterial cell membrane is recognized by the immune system and initiates local and systemic response. Its toxicity relates to the side effects of triggered immune reaction [37]. Secreted hemolysin can induce distinct oscillations of calcium concentration in renal epithelial cells or even cell necrosis [38].

The mechanisms of action of cytotoxic necrotizing factor-1 (CNF-1) involve the Rho-dependent rearrangement of the cytoskeleton in eukaryotic cells with a complex of consequences. CNF-1 can either hinder cells from apoptosis or even induce apoptosis depending on the cell type and the dose [39, 40]. Moreover, by influencing the phagocytosis and adherence of polymorphonuclear leukocytes, CNF-1 could facilitate the growth of bacteria in the urinary tract [41]. In addition, CNF-1 can enhance the secretion of proinflammatory cytokines in human uroepithelial cells [42]. Despite many in vitro effects, there have been conflicting results about the role of CNF-1 in vivo. Secretion of another toxin, Sat, damages glomeruli and causes vacuolization in the surrounding epithelium. Also Pic and Tsh proteases have been shown to be associated with uropathogenic and not fecal E. coli strains [43-45].

5. VIRULENCE FACTORS IN NON ESCHERICHIA COLI UROPATHOGENS

Staphylococcus sarprophyticus, an uncommon pathogen outside the urinary tract, is an important uropathogen in young adult women that predominantly causes cystitis. According to Hovelius B, Mardh PA *et al* (1984) Staphlococcussaprophyticus may have a predilection for causing urinary tract infection by virtue of its avid adherence to uroepthielial cells [46].

Other Enterobacteriaceae, including Klebsiella species and Proteus species as well as Providenciastuartii have been shown to express fimbriae that are important in both uroepithelial adherence and attachment to urinary catheters. Staphylococcus epidermidis uncommonly causes infection in non - catheterized patients and is a frequent cause of lower urinary tract infection in catheterized patients by virtue of its capacity to attach to and form a biofilm on foreign bodies, including catheters [47].

(1) ROUTES OF INFECTION

Microorganisms can reach the urinary tract by way of the ascending, hematogenous, or lymphatic routes.

(2) ASCENDING ROUTE OF INFECTION

Ascent of microorganisms within the urethra from external sources represents the most common pathway for urinary tract infection, especially for organisms of enteric origin, i.e. Escherichia coli and other Enterobacteriaceae. In females, the urethra is shorter and is more liable to contamination with colonic flora that resides on the perineal skin. In males, the greater length of urethra and the antibacterial properties of prostatic secretions are effective barriers to invasion by this route [48].

A single insertion of a catheter into the urinary bladder in ambulatory patients results in urinary infection 1% to 2% of the time according to Hinman F. Jr (1966). Indwelling catheters with open drainage systems result in urinary tract infection in almost 100% of cases within 3 to 4 days. Use of closed drainage systems, which greatly delays the onset of infection, is strong evidence for the ascending route in patients with catheters [49].

Bladder microorganisms may further ascend the ureters even against the downward flow of urine, especially if facilitated by vesicouretric reflux to reach the renal pelvis, where they may penetrate the kidney via backflow into the renal collecting system or via lymphatics [50].

(3) HAEMATOGENOUS ROUTE OF INFECTION

Haematogenous infection of the urinary tract is restricted to a few relatively uncommon uropathogens such as Staphylococcus aureus, Candida species, Salmonella and Mycobacterium tuberculosis, which cause primary infection elsewhere in the body [50].

(4) LYMPHATIC ROUTE OF INFECTION

Spread of infection to the primary tract via lymphatics remains speculative [50].

(5) HOST FACTORS

The urinary tract is one of the exclusive areas of the body which normally resists microbes' growth despite its close proximity to the outside environment and frequent bacterial entry. Various factors are involved in bacterial clearance, both constitutive and those inducible by the presence of a pathogen.Following spread of microorganisms to the urinary tract, the outcome depends on bacterial virulence factors and on host defences in the urine, bladder, ureters and kidneys [51].

(6) URINE

The urine may be inhibitory or even bactericidal against small inocula of uropathogens. The most important inhibitory factors in urine are high osmolality, urea concentration, organic acid concentration, low PH. Oligosaccharide and Uromucoid (Tamm - Horsfall protein) are found in normal urine which may competitively inhibit attachment of E.Coli to the mucosal surface of the urinary tract by aggregating bacteria in the urine. Finally antibody known to be released into urine in patients with renal disease has been shown to inhibit adherence to uroepithelial cells in vitro. Modification of the chemical composition of the urine in certain clinical conditions or with medication can alter ability of urine to support growth of microorganisms. For example, glucose in diabetic urine enhances the growth of uropathogens, such as Escherichia coli and Candida albicans. When the pH of the urine is about 5, the urine is inhibitory as a result of conversion of naturally occurring weak organic acids to the unionized form that has antibacterial activity [52].

Changes in the environment in the urine may have an opposite effect on host defences in other areas of the urinary tract. For example acidification stimulates renal production of ammonia which inactivates the fourth component of complement, an essential factor for phagocytosis in renal tissues. Thus acidification which may enhance urinary defences simultaneously diminishes renal defences. Water diuresis enhances urinary defences by a number of mechanisms. Water diuresis increases medullary blood flow, which enhances delivery of phagocytic cells and antibacterial substances to the renal tissues. It abolishes the normally high medullary osmolality which interferes with the action of complement and the migration of phagocytes into the renal parenchyma. Water diuresis bolsters bladder defences by increasing bladder emptying. Nevertheless, the delicate balance between host defences in various portions of the urinary tract and microbial multiplication can be altered by water diuresis in favour of renal infection by enhancing vesicoureteric reflux or by diluting the antibacterial substances in the urine [52].

The Tamm-Horsfall protein has been shown to block the adherence of type 1 piliatedE.coli to uroplakin receptors [53]. SecretoryIgA and low molecular weight sugars can block the adherence of uro-pathogens [54-56]. Lactoferrin inhibits the growth of bacteria by decreasing the accessibility of iron and the antimicrobial peptides cathelicidin and defensin directly kill bacteria by destroying their membrane [57-59].

(7) VAGINAL INTROITUS

The vaginal mucosa is normally colonized by lactobacillus, despite close proximity and probable frequent contamination with large number of enteric organisms. However, women at risk of urinary tract infection have been noted to have enteric organisms colonizing the mucosal surfaces of the vaginal introitus. This has been attributed to increased receptivity of vaginal and uroepithelial cells for attachment of E.Coli in these patients. The increased receptivity is perhaps controlled by genetic factors, as reflected by prevalence of certain HLA types or blood group substances among those with urinary tract infection. Blood group substances that appear on the surfaces of uroepithelial cells may either function as receptors for attachment of bacterial surface structures or block attachment to less prominent receptors [60].

(8) BLADDER

Mechanical removal of bladder microorganisms by dilution with fresh urine, followed by complete emptying of the bladder removes the bulk of contaminated urine. But micturition leaves behind a film of contaminated urine on the surface of the bladder mucosa that is sufficient to maintain colonization. However, the effectiveness of antibacterial properties of bladder mucosa in clearing surface contamination is established. Surface mucin coating of the bladder mucosa plays a role in preventing bacterial attachment and subsequent colonization. However, using mathematical simulation and in vivo models suggested that emptying of the bladder is only one of the defence mechanisms and additional antibacterial factors are essential [61-63]. The mucosa of the urinary bladder has been shown to possess bacteriostatic properties in vitro [64].

(9) URETER

Ureteral peristalsis facilities flow of urine from the kidney to the bladder. Diminished ureteral peristalsis contributes to the increased susceptibility to UTI during pregnancy. The efficacy of bladder emptying is maintained by competent vesicoureteral valve action which prevents contaminated bladder urine from going up the ureters during voiding and allows only fresh urine to flow into the bladder when voiding is complete. Althougheven under normal conditions, microorganisms can ascend against the flow of urine [65].

Vesicoureteral reflux is gross passage of bladder urine up the ureters on voiding. Reflux impairs the efficiency of bladder emptying by producing residual ureteral urine. Reflux occurs in children as a congenital developmental anomaly. In children if reflux is severe, it may exert sufficient hydrostatic pressure on the renal pelvis to impair renal growth even in the presence of sterile urine. In the presence of infected urine, reflux can rapidly destroy the kidney. As with reflux, extrarenal obstruction, due to stones, extrinsic compression of the ureters, congenital urinary tract anatomic anomalies or tumours can exert destructive hydrostatic pressure on the kidney and prevent efficient emptying of the urinary outflow tract. Although obstruction itself does not increase contamination of urine with uropathogens from external sources, the presence of obstruction increases the risk of renal infection.Studies have identified a heat sensitive calcium ionophore by some uropathogens that inhibits ureteral peristalsis [65,66].

(10) KIDNEY

The Renal cortex is much more resistant to infection than the medulla, for both gram-negative bacilli and gram positive cocci that reach the kidney by either the haematogenous or ascending routes. High concentration of ammonia, high osmolality, the relative anoxic state and relatively low blood flow in the renal medulla impede humoral and cellular defences [67].

6. IMMUNE RESPONSE :

The immune response appears to have limited role in both renal and bladder infection. Both systemic and local antibody production occur in renal infection, with type - specific antibody detectable in the urine even before antibody can be detected in the serum. Urinary antibody may function by decreasing adherence of bacteria to uroepithelial cells [68].

ANTI - ADHERENCE HOST DEFENSE MECHANISMS [69,70]

The anti-adherence mechanisms in the urinary tract may be specific or non-specific, interfering with colonization of all organisms.

1. The normal bacterial flora of the vaginal introitus, periurethral region, and urethra may cause stearic hindrance and make receptors less available.
2. The Uromucoid or urinary slime (Tamm - Horsfall protein) rich in mannose residues avidly bind E.Coli and may prevent attachment to uroepithelial cells.
3. ImmunoglobulinsIgG, IgA, and SIgA in the urine of patients with pyelonephritis have inhibited adherence of the responsible strain of E.Coli to the uroepithelial cells.
4. The transitional cells of bladder mucosa are coated by a thin layer of mucopolysaccharide which interferes with adhesion of microorganisms.
5. Normal urine contains numerous oligosaccharides including manno oligosaccharides that inhibit type 1 fimbriae attachment.
6. Finally the mechanical effect of flushing during bladder emptying is essential in preventing adherence [69, 70].

The presence of bacterium induces a robust immune response already after a brief short contact with uroepithelial cells. Bladder superficial epithelial cells express Toll-like receptor-4 (TLR-4) on their membranes which together with its co-receptors CD-14 and MD-2 recognize lipopolysaccharide from bacteria and activate innate immune response [71,72]. However, there are conflicting results regarding the expression of CD-14 on uroepithelial cells. Several studies showed the presence of CD-14 by protein and mRNA expression [73-75]. Other groups, in contrast, did not detect CD-14 on uroepithelial cells suggesting that the response of uroepithelial cells to LPS requires the presence of type 1 or P-fimbrie [76, 77].The latter mechanism could explain the strong immune response to virulent strains expressing fimbriae which is absent in the presence of non-virulent strains causing asymptomatic bacteriuria [78-79]. Alternatively urinary soluble CD-14 was proposed to co-mediate LPS-signalling, although it remains unclear if its urinary levels in health are high enough for such an effect [80].

During pyelonephritis, renal tubular epithelial cells are the main cells to react to the presence of bacteria [81]. However, the mechanism of sensing bacteria has also here been a matter of debate and conflicting results. Renal tubular cells neither expressedCD14 nor TLR-4 nor were hypo responsive to LPS stimulation. Others, in contrast were able to detect TLR-4 on renal tubular epithelial cells. Epithelial cells within the urinary tract appear to be not just a mechanical barrier but also an active part of the innate immune system sensing bacteria and triggering the cascade of immune response to them [82].

After contact with bacteria, epithelial cells react by different ways. First, bladder epithelium exfoliates superficial facet cells, which could clear the bacteria from the bladder. Epithelial cells may contribute to the defence by the production of substances toxic to bacteria, like cathelicidin and nitric oxideor by engagement of other cells by simultaneous production of chemokines and proinflammatory cytokines. Chemokines attract professional immune system cells and cytokines activate them. Out of a number of chemokines and proinflammatory cytokines, interleukin 8 (IL-8) seems to be of crucial importance because of its chemo attraction of neutrophils. Cytokine mediated up regulation of adhesion molecules and cytokine receptors facilitates the process of transmigration. Amongst them, CXCR1 receptor on renal epithelial cells has been shown to be of importance for transepithelial migration of granulocytes and bacterial clearance during urinary tract infection. Neutrophils kill bacteria by different mechanisms, either phagocytosis or the release of the toxic content of their granules. The influx of neutrophils is followed by an influx of other professional immune cells namely monocytes, macrophages and lymphocytes, which are predominantly important in later stages of infection [83].

7. CONCLUSION :

A host of factors predispose to UTI in children as described above, an understanding of the microbiological and the variety of non-specific and systemic symptoms, it is difficult to perform tests for early diagnosis and the resultant inaccurate diagnosis may lead to antibiotic abuse. Thus in many cases, a severe renal injury occurs even before the UTI is diagnosed. For this reason, an early and accurate diagnosis through careful examination and tests can help in preventing severe renal injuries through adequate treatment and careful follow-up. UTI recurs easily if it is accompanied with anatomical anomalies of the urinary system. If it is not treated adequately or occurs recurrently, UTI may develop into chronic pyelonephritis resulting in hypertension and loss of renal function, a condition normally seen in 15–20% of the cases of chronic renal failure [84].

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