CHAPTER 21

Host–Pathogen Interactions and Host Defense Mechanisms

Keira Melican • Ferdinand X. Choong • Agneta Richter-Dahlfors

Urinary tract infections (UTIs) represent the most common urologic disease in the United States based on the Centers for Disease Control's (CDC) statistics of visits to office-based physicians and hospital outpatient clinics. Women account for a majority of cases. The 2005/2006 Ambulatory Medical Care Utilization Estimates attributed an annual figure of approximately 8.1 million of all diagnosed patients with UTIs as the main ailment.[1a] Although no clear cost estimate is available currently, total expenditures in the year of 2000 alone was estimated to amount to US$3.5 billion.[2a]

The human urinary tract is a normally sterile environment that presents invading bacteria with numerous challenges of a dynamic nature. These challenges include the mechanical stress of urine flow, various physical barriers such as the mucosal epithelium, and the attack of invading immune cells that form part of the host's immune response. The dynamic nature of these challenges means that invading pathogens must rapidly adapt to their changing niche in order to enable colonization. Infections of the urinary tract occur when pathogens, often originating from fecal flora, enter the urethra. Although continuous cycles of urine production, storage, and voiding relentlessly expel invading organisms, pathogens are able to migrate to the bladder, where they may cause symptomatic cystitis or asymptomatic bacteriuria (ABU).[1] Pyelonephritis manifest when pathogens ascend further up to the kidney, colonizing the tubules of the nephrons.

Asymptomatic bacteriuria is defined as the presence of bacteria in the urinary tract, which do not cause any obvious clinical symptoms in the patient. ABU has been described as similar to a commensal state[2] where patients may carry up to 10^5 CFU per milliliter of urine without symptoms. ABU strains are genetically similar to those that cause symptomatic infections, but they notably tend to lack adhesion organelles.

Cystitis, or a lower UTI, occurs when the pathogens that have entered the urinary bladder attach themselves to cells of the bladder epithelial lining, where they start multiplying. A lower UTI often presents with clinical symptoms such as pain and urgency of urination. The urine of cystitis patients often appears cloudy due to the presence of bacteria, white blood cells (WBCs), and sloughed epithelial cells.[3] A urine examination and culture are essential for a diagnosis, and the infection is usually treated with antibiotics.

Further migration of bacteria up the ureters leads to an infection of the kidneys.[4] A bacterial infection of the kidney is medically termed pyelonephritis, indicating that the infection has reached the renal pelvis—the so-called pyelum—of the kidney (nephros). Upper UTI infections are more difficult to diagnose than cystitis. They show similar symptoms to a lower UTI but are often accompanied by a sudden increase in temperature and unilateral or bilateral flank pain.[5] Pyelonephritis is commonly defined as a tubulointerstitial disorder based on the pathologic picture observed in renal biopsies. This indicates that the tubules and interstitial tissue are most commonly involved.[6] In light of the greater level of inflammation, as compared to cystitis, pyelonephritis is considered a serious infection.[7] Gross pathology includes abscess formation in the renal parenchyma and edema, often leading to irreversible scar formation. Renal scar formation with fibrosis can contribute toward the development of renal insufficiency.[7]

The normal kidney is considered relatively resistant to infection but abnormalities in the structure and function of the urinary tract can increase susceptibility.[8] Risk factors in children include voiding dysfunction and vesicoureteral reflux, whereas in adults, genetic susceptibilities and behavioral risk factors are most relevant.[9]

An essential step in bacterial colonization and the initiation of a UTI is the bacterial binding to the urinary epithelium. However, the epithelia that line the urinary tract are far from uniform. The bladder is lined by a transitional stratified epithelium consisting of multiple layers, topped with facet or umbrella cells, and covered with apical plaques of hexagonal uroplakin.[10] The bladder epithelium, together with the transitional epithelium, covers the ureters and the renal pelvis and is also known as uroepithelium. The Bowman capsule (the epithelial structure that surrounds the glomerular capillary tufts) is lined with thin squamous epithelial cells. The tubular systems of the nephron all consist of a

single layer of epithelium, which expresses a unique structure and function depending on the tubule segment.[11,12,13,14] The proximal tubule consists of cuboidal/columnar epithelia covered with microvilli (~150 per square micrometer of cell surface), which function to increase the surface area for tubule reabsorption.[12] Distal tubule cells lack microvilli and constitute a tight epithelium, displaying low endocytic capacity and low permeability to water.[13,14] This suggests that bacteria do not only meet very different epithelial linings on their way up the urinary tract, but also that they do so while being exposed to a continuously altered composition of filtrate/urine.

Uropathogenic Escherichia coli (UPEC) are implicated as the causative agent in up to 80% of community-acquired UTIs, making it the leading urinary pathogen.[7] However, other gram-negative bacterial species are also associated with UTIs, including Klebsiella, Enterobacter, Pseudomonas, and Proteus mirabilis.[7] The latter accounts for more than 40% of UTIs in infant boys. Gram-positive bacteria implicated in UTIs include Staphylococcus strains, epidermidis, and aureus, as well as Enterococcus faecalis.[7] Using culture-based methods, a Canadian study of bacterial isolates in ambulatory patients with community-acquired UTIs revealed that 74.2% contained Escherichia coli, 6.2% contained Klebsiella pneumoniae, 5.3% contained Enterococcus, 2.8% contained Streptococcus agalactiae, 2% contained Proteus mirabilis, 1.4% contained Staphylococcus saprophyticus, 0.9% contained Viridans streptococci, 0.9% contained Klebsiella oxytoca, and 0.8% contained Pseudomonas aeruginosa.[15] Although the proportion of isolates vary depending on the region, the disease state, and the patient type, UPEC unanimously remains the major causative microbe for UTIs and, as such, has been used as the primary pathogen in a number of molecular studies of the UTI process. This chapter will accordingly focus on current knowledge gained from UPEC-induced UTIs.

VIRULENCE OF UROPATHOGENIC ESCHERICHIA COLI

Bacteria entering the urinary tract must rapidly adapt to their new environmental niche. To enable this adaptation, UPEC strains express specific genes that encode a class of proteins termed virulence factors. This name originates from the finding that these factors assist in the initiation and progression of the infection. UPEC strains have a larger genome and therefore contain more genes than their nonvirulent ABU or commensal E. coli counterparts. For example, the clinical isolate CFT073 has 590,209 more base pairs in its genome than the K-12 MG1655 strain.[16] Based on recent genetic approaches, it was proposed that UPEC, ABU, and commensal strains may have evolved from the same virulent ancestral parent, with the ABU and commensal strains having lost virulence factors.[17,18] Due to the relatively minor genetic variations between the UPEC, ABU, and a commensal gut E. coli, genetic mutations and differences in expression of certain genes may actually differentiate virulence potential rather than genomic content itself.[17]

The extra genes that confer virulence are commonly located in specific regions of the chromosome, termed pathogenicity-associated islands (PAIs).[19,20] This unique subset of genomic islands has been acquired by horizontal gene transfer.[21] PAIs were originally identified by Hacker and colleagues[22] when they analyzed segments of chromosomal regions that encode multiple, distinct virulence-associated phenotypes in UPEC strain 536.[23] Further characterization has demonstrated that PAIs are present in a wide range of bacterial pathogens, that PAI segments range from 10 to 200 kb in size, and that they are rich in virulence and antibiotic resistance gene insertion sequences or other mobile genetic elements. PAIs are easily identifiable by their unique G+C content,[24] and their location near or within tRNA genes. One bacterium may possess multiple PAIs,[25,26] as exemplified by UPEC strain 536, which contains six well-characterized PAIs.[27–29]

The chromosomes of E. coli appear highly diverse aside from a core genome that is highly homogeneous in G+C content.[24] A large proportion of this diversity arises from a variable pool of mobile genetic elements, conjugative plasmids, bacteriophages, transposons, insertion elements, as well as by the recombination of foreign DNA into host DNA.[24] This has been highlighted in comparative studies of the nonpathogenic E. coli K-12 lab strain MG1655,[28] the enterohemorrhagic O157:H7 strain EDL933,[30] and the UPEC strain CFT073.[16] They were shown to differ significantly in genome size, sharing only 39.2% of proteins in common.[16] The flexibility of bacterial genomes arising from mobile genetic elements may facilitate the timely emergence of new clones,[31,32] which provides new virulence and antibiotic resistance profiles.

However the genetics may look or may have evolved, it remains that pathogenic UPEC strains express proteins that are considered essential for virulence. These virulence factors characterize disease isolates.[33] Although the early definitions of virulence factors came from the basic epidemiology practice of comparing properties of fecal strains from healthy controls with urinary isolates from patients,[34] Falkow[35] introduced a new view in 1988, which he named the molecular Koch's postulates for pathogenesis. These postulates include[36]:

- The phenotype or property under investigation should be associated with the pathogenic members of a genus or pathogenic strains of a species.
- Specific inactivation of the gene(s) associated with the suspected virulence trait should lead to a measurable loss in pathogenicity or virulence, or the gene(s) associated with the supposed virulence trait should be isolated by molecular methods. Specific inactivation or deletion of the gene(s) should lead to loss of function in the clone.

- Reversion or allelic replacement of the mutated gene should lead to restoration of pathogenicity, or the replacement of the modified gene(s) for its allelic counterpart in the strain of origin should lead to a loss of function and a loss of pathogenicity or virulence. Restoration of pathogenicity should accompany the reintroduction of the wild-type gene(s).

Fifteen years later, Falkow[36] reviewed these postulates in light of the new advances in technology available to infection biologists. Here he described how the postulates should be considered as a "working hypothesis for the study of the genetic and molecular basis of pathogenicity" and not a ridged determination of virulence factors. Some virulence factors may play different roles in different model systems and, as technology advances, the definitions of what a virulence factor is may need to evolve. Some of these factors may also be considered as "fitness factors" (i.e., factors that enhance the growth and colonization of the bacteria but may not be absolutely essential for infection). Siderophores, which allow bacteria to sequester iron, have been annotated as fitness factors because their expression is advantageous but not essential to virulence.[37,38] Conversely, the acquisition of certain traits such as antibiotic resistance, which would appear advantageous for virulence, can have a negative effect on bacterial fitness.[39,40]

UROPATHOGENIC ESCHERICHIA COLI ADHESION

The traditionally annotated UPEC virulence factors include adhesion factors, exotoxins, lipopolysaccharides, capsules, proteases, and iron acquisition systems.[41,42] Research on these factors has been carried out in vitro and forms the foundation for their current definition. Thus, the expression of certain adhesion factors is still defined by their in vitro agglutination abilities.[34,42] In UPEC, the best described virulence factors are involved in bacterial adhesion to the uroepithelium, and these proteinaceous structures are referred to as fimbriae or pili.[20] These organelles allow UPEC to bind to the epithelium and help bacteria to withstand the stress of filtrate and urine flow. UPEC express numerous different fimbriae including P, type 1, F1C, S, and Afa/Dr adhesins.[42] The great redundancy in fimbriae expression is further illustrated by the fact that one bacterium contains the genes for many different fimbriae.[43] The current understanding of the roles of the various fimbriae in UTIs is described in detail in the following paragraphs.

Bacteria have many tools aiding their rapid adaptation to changing microenvironments. They contain genes for numerous different fimbriae and it has been shown there is a redundancy between these fimbriae.[43] Phase variation means the bacteria can vary their fimbriae expression, thereby altering their nature of adhesion depending on the microenvironment. This common feature not only allows for rapid adaptation but also, at the same time, allows for the development of a heterogeneous bacterial population.[44] A genetic switch, the so-called *fim* switch, controls the phase variation of type 1 fimbriae expression. This invertible element contains the main promoter for the fimbrial structural subunits.[44] Negative cross-talk between type 1 and P fimbriae has been demonstrated, with PapB being shown to repress the FimB-promoted off-to-on inversion of the *fim* switch.[45] This means that UPEC express either Type 1 or P fimbriae but it is unlikely that they express both simultaneously. A cross-talk between P fimbriae expression and motility has also been reported, showing that the expression of P fimbriae also regulates the synthesis of flagellum, a protein-based extrusion that mediates bacterial mobility. The PapX protein, encoded at the end of the pheV associated pap gene cluster in UPEC strain CFT073, represses motility by binding to the *flh*D promoter, thereby repressing transcription of $FlhD_2C_2$, the master regulator of flagella.[46] These regulatory mechanisms highlight one mechanism by which bacteria can fine-tune their expression to adapt to the challenging microenvironments they encounter upon infection.

Type 1 Fimbriae

Type 1 fimbriae are attachment organelles produced by the vast majority of E. coli strains, both commensal and pathogenic. Initially visualized in 1950,[47] type 1 fimbriae are mannose sensitive adhesion organelles, which means their ability to agglutinate erythrocytes is inhibited by mannose.[48,49] This feature, found in the mid 1950s, is still used today to define type 1 fimbrial expression.

The type 1 fimbriae are made up of 500 to 3,000 repeating subunits of the FimA protein, which is formed into a 7-nm thick right-handed helical rod. At the outermost end of the rod is located a 3-nm thick distal tip that contains several copies of the adapter proteins FimG and FimF as well as the tip adhesin FimH.[50–52] Assembly of the rod-like type 1 fimbriae occurs via the chaperone-usher pathway, which represents a common assembly pathway for fimbriae in gram-negative bacteria.[52] The chaperone and usher proteins required for the formation of type 1 fimbriae are all encoded in the *fim* operon.[51] FimC is the periplasmic chaperone, which delivers bound subunits to the outer membrane usher protein FimD. From here, the subunits are incorporated into the growing fimbriae.[51]

The ability of the tip adhesion FimH to bind mannose-containing glycoproteins means that type 1 fimbriated bacteria can adhere to a wide range of human target cells.[53,54] The crystal structure for FimH was recently resolved.[55,56] Whereas intestinal E. coli express certain variants of the FimH adhesion,[57,58] UPEC express a FimH that has an increased affinity for terminal monomannose (M1) residues[59] and displays a 20-fold higher ability to bind uroepithelium.[57,58,60] The traditional view of type 1–mediated binding is that the mannose moiety is present on cells or structures associated with the mucosal lining, or alternatively, that mannose is bound to abiotic surfaces. Whereas the first situation refers

to bacterial colonization on the mucosal lining, the latter is implicated in bacterial biofilm formation in vitro.[61] Recently, a novel alternative was presented, demonstrating the importance of type 1 fimbriae in mediating interbacterial contact and biofilm formation in vivo, thus providing a means for bacteria to withstand the shear stress from the renal filtrate (see the following text for further details).[62]

In UPEC strains, the role of type 1 fimbriae in cystitis has been extensively described. The uroplakins on the surface of bladder epithelium contain monomannose moieties to which FimH binds.[42,55] Therefore, uroplakins serve as anchoring sites allowing UPEC to gain a foothold in the bladder.[63] Although the kidney lacks mannose moieties, a new hypothesis was recently proposed in which the FimH tip adhesions of type 1 fimbriae facilitate interbacterial binding and, in synergy with P fimbriae, thus enable tubule colonization.[62] This broadens the role for type 1 fimbriae to infectious niches other than those with surface-bound mannose moieties.

The urinary tract represents a compartment continuously exposed to some degree of mechanical flow, primarily in the form of urine. Bacteria entering into this compartment will thus be exposed to shear stress generated by the flow of urine over the epithelial surface. Over recent years, it has become increasingly appreciated that the stress may affect bacterial adhesion. The UPEC FimH protein has been shown to display enhanced binding to mannosylated surfaces in vitro in the presence of shear stress.[64,65] This interaction is reported to operate via a force-enhanced allosteric catch-bond mechanism, functioning via a finger-traplike β sheet twisting mechanism.[64]

In the initial report of FimH shear-dependent binding, it was shown that at a shear of 0.02 dynes per cubic centimeter, the binding strength of FimH was weak, whereas as the shear increased to 0.8 dynes per centimeter, this binding became stronger.[65] The same laboratory also showed that UPEC positively select for a FimH variant that maintains an attachment following a drop in shear, as compared to fecal or vaginal E. coli isolates.[66] This variation in the signal peptide of FimH, which results in expression of less, though longer, fimbriae, may be very relevant under the fluctuating conditions facing UPEC in vivo. The fact that certain bacterial adhesion events are enhanced by tensile force, as opposed to bacteria being washed away, is particularly relevant in an environment such as the urinary tract where bacteria must bind in the face of fluctuating filtrate flow. Thus far, FimH is the best described bacterial adhesin in terms of shear-enhanced adhesion, whereas binding of PapG, the tip adhesion of P fimbriae, has been shown to be shear-independent, being able to mediate binding even under relatively low shear.[67]

Although the shear-mediated adhesion may assist type 1 adhesion to the bladder epithelium via mannose binding, it may also function during UPEC colonization of the renal tubule, albeit via a different mechanism. Within the nephron, FimH may mediate interbacterial binding and help prevent bacterial washout by renal filtrate.[62] Interestingly, FimH is present in all virotypes of E. coli,[60] and a role for FimH in interbacterial binding may explain a general function for these fimbriae in diverse perfused environmental niches.

Type 1 fimbriae have been found to fulfill molecular Koch's postulates. Microarray studies of an in vivo mouse model show high levels of type 1 expression.[68] A mutant unable to make FimH is severely deficient in colonization of the urinary tract in a mouse UTI model, and complementation of the mutant has been shown to restore virulence.[69]

P Fimbriae

P fimbriae were one of the first virulence factors associated with UPEC. In 1976, it was demonstrated that E. coli from patients with acute pyelonephritis adhered in greater numbers to uroepithelial cells in vitro than strains causing asymptomatic bacteriuria.[70] Their adherence was not inhibited by the prototypic type 1 inhibitor mannose, and further investigation led to the identification of P fimbriae. They were designated P because of their ability to agglutinate red blood cells (RBCs) of the P blood group when analyzed in vitro.[34,71] P fimbriae are encoded by the pap (pyelonephritis-associated pilus) operon, which consists of 11 genes located on chromosomal pathogenicity islands. Unlike the *fim* operon, the pap operon is selectively distributed in E. coli.[24,72] The morphology of this fimbriae is extremely similar to type 1 fimbriae.[73] P fimbriae are hetero-polymers consisting of a helical rod of PapA subunits with a tip consisting of the minor pilins PapE and PapF. The tip adhesion PapG mediates attachment to Galα1-4Galβ containing glycolipids, which are often found on the renal epithelium.[73,74] PapG is known to have at least three allele variants: class I, class II, and class III. Class II is primarily linked to human pyelonephritis and class III is linked to cystitis.[71,75,76] Some strains, such as the prototypical UPEC strain CFT073, carries two pap gene clusters, both of which encode for the PapGII allele.[16,71]

Although P fimbriae have long been considered an important virulence factor in UTIs, they do not fulfill the molecular Koch's postulates. P fimbriae are expressed by a majority, but not all, clinical isolates.[34,77] Approximately 80% of UPEC strains express P fimbriae,[78] and a strong relationship exists between the severity of infection and the prevalence of P fimbriae. Indeed, clinical isolates lacking PapG adhesin were observed to cause comparatively less kidney damage than the PapG positive counterpart. Interestingly, despite the known role of P fimbriae in the adhesion colonization capability of strains in both the kidneys and bladder, it was found to be independent of PapG mediated adhesion.[79–82]

Expression of P fimbriae is controlled by phase variation, and varies depending on environmental conditions. The reversible epigenetic switch that controls the initiation of pap operon transcription allows bacteria to fine-tune their P fimbriae expression to suit their changing environment in vivo.[44,83,84]

Recently, P fimbria were shown to facilitate the early stage of UPEC colonization of renal tubules.[62] Using high-resolution live animal imaging, it was shown that strains

expressing P fimbriae were able to bind and initiate colonization in the face of sheer stress from renal filtrate flow. It was also demonstrated that the P fimbriae act in synergy with type 1 fimbriae in a heterogeneous bacterial community to facilitate renal tubule colonization. P fimbriae were shown to mediate bacterial binding to the epithelium, whereas the type 1 fimbriae mediated interbacterial binding as the colony expanded into the tubule and away from the epithelium.[62] It is interesting to note that unlike type 1 fimbriae, only E. coli and not other gram-negative rods carry the genes for P fimbriae.[85]

Dr Adhesin

Aside from type 1 and P fimbriae, several other adhesins are implicated in mediating urinary tract infections, though their roles are not as established. The Dr adhesins family embraces fimbrial and afimbrial structures, which are found on the extracellular surface of E. coli, and have in common that they bind to Dr blood group antigens.[86] The Dr blood group antigen is a component of the decay-accelerating factor (DAF), a membrane protein that prevents host lysis by complement.[87,88] This binding leads to the internalization of Dr^+ E. coli into nonfusogenic intracellular vacuoles where bacteria are shielded from the host immune system.[89] Dr adhesin mediated binding of E. coli to the bladder epithelium has also been correlated with recurrent UTIs in young adults and with pyelonephritis in pregnant women.[90] Among the Dr adhesin family, only Dr fimbria possess the ability to bind both type IV collagen of basement membranes and DAF.[91] The latter is mediated via the subunit DraE.[92] When investigating the significance of DraE-type IV collagen binding, it was shown that disruption of this capability resulted in the inability of E. coli to cause a persistent kidney infection.[93]

F1C Fimbriae and the S Fimbria Family

Although the role of type F1C fimbriae for UTIs has not been fully determined, epidemiologic data suggest this fimbriae to be more prevalent in pyelonephritis and cystitis strains than among fecal strains of E. coli.[94] Data suggest these fimbriae are expressed in vivo and provide bacteria the capacity to adhere to human distal tubular and collecting tubular epithelium, as well as the vascular endothelium on kidney tissue sections.[95,96] The two minor glycosphingolipids, galactosylceramide and globotriaosylceramide, have been identified as target tissue receptors for F1C fimbriae in rats, canines, and humans. Galactosylceramide is found throughout the urinary tract, with the exception of the urethra, whereas globotriaosylceramide is unique to the kidney.[95] The binding of F1C-fimbriated bacteria to renal epithelial cells in vitro was shown to induce similar levels of interleukin (IL)-8 production as compared to those levels produced by the adhesion of type 1- and P-fimbriated bacteria, thus supporting a role for F1C in pyelonephritis.[95]

The S fimbriae bind terminal NeuAcα2, 3-galactose sequences present on glycoproteins. Although shown to bind several host cell types, the occurrence of S fimbriae expressing E. coli strains in UTIs is infrequent.[97,98] The role of S fimbriae in UPEC pathogenesis may thus be minor.

BACTERIAL TOXINS AND VIRULENCE FACTORS

α-Hemolysin

The 107 kDa lipoprotein α-hemolysin (Hly) is considered an important UPEC virulence factor, yet no more than 50% of pyelonephritogenic E. coli organisms express this toxin. The Hly operon is commonly located adjacent to genes encoding P fimbriae,[99,100] which may account for the two- to threefold higher probability of UPEC having hly genes over fecal strains.[101] Hly exerts concentration-dependent, biphasic activities on target cells. The traditional view focuses on Hlys cytotoxic effect. Hly is lytic for numerous cell types, including erythrocytes, polymorphonuclear leukocytes, monocytes, mast cells, basophils, and lymphocytes.[102,103] More recently, the sublytic concentration of Hly was shown to elicit Ca^{2+} signaling in primary proximal tubule cells.[104] Via frequency-modulated activation of the transcription factor nuclear factor-kappa B (NF-κB), Hly activated proinflammatory signaling in epithelial cells. When analyzing a role for Hly in vivo, intravital imaging of the infection process within a nephron of a rat was applied. This showed that the same end result was achieved whether or not UPEC expressed Hly. However, the kinetics of the tissue response was severely influenced.[105]

Cytotoxic Necrotizing Factor

CNF1 is a toxin contributing to UPECs invasion of the epithelium.[106,107] The toxin induces the formation of stress fibers via the deamination-dependent activation of small, actin-regulatory GTPase proteins of the Rho family.[108,109] The gene encoding CNF1 is positioned adjacent to hemolysin,[110,111] and coregulation of their expression is mediated by RfaH.[112,113] Although the role of CNF1 in vivo remains unclear, in vitro studies do suggest a role for the toxin in urinary tract disease.[114,115]

Secreted Autotransporter Toxin

Among the array of toxins studied in UTI models, the 107-kDa Sat protein is more frequently secreted from pyelonephritogenic E. coli strains than fecal isolates, suggesting a possible role of the toxin in pathogenesis.[116] Sat has serine protease activity and shows cytopathic effects (cytoplasmic vacuolization) on human bladder and kidney cell lines, and in the mouse kidney.[117] However, Sat is not required for kidney colonization.[117] Originally isolated from the prototypic UPEC strain CFT073, Sat was found to share homology with various virulence-related proteins from a range of E. coli pathotypes.[118] Among these, Sat possess a high similarity to Pet and EspC, two SPATE (serine protease autotransporters of Enterobacteriaceae) proteins.[118]

Siderophores

Mammals possess efficient systems such as the proteins transferrin and lactoferrin to efficiently scavenge free iron within the host. During an infection, the deprivation of free iron is used as a host defense mechanism as upregulation of iron acquisition and storage mechanisms are up-regulated. Low iron availability limits bacterial viability. To counteract this, bacteria produce low-molecular-weight chelators called siderophores (Greek sideros, iron; and phoros, bearing). Siderophores are secreted into the extracellular environment where they bind ferric iron (Fe^{3+}) and internalize it via receptor-mediated mechanisms. UPEC strains produce four distinct siderophore systems: enterobactin, salmochelin, yersiniabactin, and aerobactin. Among these, enterobactin is conserved in all isolates.[119,120] UPEC also expresses siderophore-associated receptors such as ireA[121] and iroN,[122] and other iron acquisition systems.[16,20] Strains with impaired iron acquisition capability were shown to have decreased fitness and virulence in mouse models.[123]

The precise contribution of each iron uptake mechanism to bacterial virulence is presently unclear. However, a study of coincident urinary and rectal strains from patients with recurrent UTIs suggested UPEC infections are facilitated by yersiniabactin and salmochelin.[119] Some UPEC strains express siderophore receptors but not siderophore. These strains are hypothesized to take advantage of neighboring siderophore-expressing bacteria in a polymicrobial setting by competitively scavenging excreted iron-bound siderophores.[20,124,125]

Lipopolysaccharide

The serotyping of E. coli strains is based on three determinants: the somatic antigen O, the capsular antigen K, and the flagella antigen H.[126] This system, developed by Kauffmann in 1940, has identified more than 50,000 different E. coli serotypes of various combinations of the 173 O, 80 K, and 56 H types, in addition to all nontypable strains. The association of O-antigen serogroups with UTIs is complex. Although studies have observed the presence of certain serogroups (O1, O2, O4, O6–8, O18, O25, and O75) to be more frequent in E. coli isolates in symptomatic UTIs,[127] the pattern of other potential virulence factors confound O-antigen-based epidemiology data.[128,129] Furthermore, the horizontal mobility of antigen determinant clusters obscures the phylogenetic relation of E. coli strains.[130] Employing isogenic mutants of O antigen synthesis, a possible link between UTI pathogenesis and the ability of a strain to synthesize an O antigen was observed.[131] However, there is yet to be clear experimental evidence closely correlating a particular O antigen type with a pathogenic tendency.

ORGANS OF THE URINARY TRACT

Host responses are initiated the very moment a bacterium starts interacting with the host tissue. In response to the accompanying microenvironmental changes, bacteria rapidly adapt their gene expression and alter their physiology to cope with the situation. The net effect of these opposing forces determines the duration of the infection and the end result: bacterial clearance, containment or commensalism, or the death of the host. Depending on the physiology and function of the organ, the nature of such challenges varies.

Urine

Urine is a highly variable and dynamic environment that both prevents and promotes infection. High osmolality, high urea concentrations, and low oxygen tension exhibit bacteriostatic and bactericidal effects.[129–134] On the other hand, thin films of urine retained at the bladder mucosa act as a reservoir of bacteria, allowing repopulation following each voiding event.[131,133–136]

The Bladder

The cascade of events that occur when urinary pathogens and, particularly, UPEC come into contact with the bladder epithelium has been well studied. Type 1 fimbriae bind to mannose residues on the surface of uroepithelia via the FimH adhesion. Once adhered, UPEC can withstand the forces of bladder emptying. However, FimH is believed to act not only as an adhesion, but also as an invasin that promotes bacterial entry into mast cells, macrophages, and the bladder epithelium.[137,138] Lipid raft domains on the host cells have been reported to facilitate type 1 fimbriated bacterial invasion with cholesterol, and caveolin-1 has been shown to cluster around the bacteria upon binding.[50,136,139] Localized rearrangement of host actin cytoskeleton is required for FimH-mediated epithelial invasion and is mediated via phosphoinositide-3-kinase signaling.[140] However, the internalization of bacteria into the bladder epithelium does not appear to be the end of the story; far from it. There are two alternative reported pathways for bacteria once they enter the bladder epithelium.[141] Upon internalization, bacteria multiply within intracellular bacterial communities (IBCs) present in membrane-bound vacuoles.[141,142] Within the IBC, bacteria change from a bacillary shape to a smaller, more coccoid shape[139] that forms pods within the facet cells. At this stage some bacteria on the periphery of the pod regain a bacillary shape and become motile, thus leading to bacterial spread.[143] There have been suggestions that the behavior of bacteria within these pods seems to be "biofilmlike."[139] Some bacteria within IBCs form long (<70 μm) filaments, which move extracellularly and induce reinfection via reseptation, thus leading to further rounds of IBC formation.[144]

Upon infection of the bladder epithelium, one host response includes an exfoliation of the infected cells.[143,145] Exfoliation results in a loss of surface epithelial cells from the underlying transitional layer. Although this functions well to clear many epithelial cells infected with IBCs, the bacteria have an alternative mechanism by which they can establish quiescent intracellular reservoirs (QIRs).[144] In QIRs, bacteria remain within the membrane-bound compartments with no extensive multiplication. When these transitional cells

develop into new facet cells, the QIRs remain intact and are proposed to be a possible source of recurrent UTIs.

The Kidney

Acute pyelonephritis is considered the most serious form of UTI and can lead to renal scarring, kidney damage, kidney failure, hypertension, and sepsis.[71] The study of infection in the kidney has slightly lagged behind the bladder when it comes to high-resolution molecular studies of host–pathogen interaction. Whereas Type 1 fimbriae play a major role in bladder infection, a limited role is implied in the kidney because renal epithelia lack uroplakin. Instead, P fimbriae have been considered a key player in the development of pyelonephritis due to its overrepresentation in pyelonephritogenic isolates.[146] However, experimental data have not yet proven P fimbriae to be essential for disease. Only subtle roles for P fimbriae–mediated adherence have been described in uroepithelial cell culture models,[146,147] and its role in ascending infection models has yielded inconsistent and conflicting results.[81,82,148] Early studies showed that lab strains of E. coli overexpressing P fimbriae persisted longer in mouse kidneys than strains lacking the pap operon.[149] However, bacterial numbers in the tissue never reached the same level as that of clinical strains, and it was accordingly suggested that P fimbriae are not the defining factor in virulence. Years later, when it was possible to genetically introduce a precise deletion of defined pap genes in UPEC isolates, it was demonstrated that a lack of P fimbriae did not significantly affect kidney colonization or pathophysiology 1 week after infection.[82]

Pyelonephritis does show a greater level of inflammation than cystitis, indicating the presence of a sensitive immune response system that detects colonizing bacteria.[150] Toll-like receptor family (TLR) and, particularly, TLR4 play a significant role in UTIs. An experimental ascending UTI model, using mice lacking TLR4 expression, failed to clear the invading pathogens and expressed less proinflammatory mediators.[151] The same group also reported that TLR4 expression on renal medullary collecting duct cells facilitated the translocation of bacteria across this epithelial barrier.[152]

Recently, live animal imaging applied to renal UPEC infection allowed for a high-resolution study of a live infection in real time.[62,153] In this rat model, GFP^+-expressing UPEC bacteria were slowly infused directly into the lumen of a superficial renal tubule to allow for spatial and temporal control of the infection. Fluorescence-based multiphoton microscopy showed that very few bacteria initially adhered to the tubule epithelium in the face of the flowing glomerular filtrate. These few bacteria rapidly adapted to the environment and began colonizing the tubule.[153] In this dynamic study of infection, new roles for the P and type 1 fimbriae in kidney infections were established, functions that had been undetectable in previously used infection models.[146,154] Bacterial P fimbriae expression demonstrated a fitness advantage in withstanding tubular filtrate flow and in mediating early phase adhesion to the epithelium, whereas type 1 was shown to mediate interbacterial binding and biofilm formation in the center of the tubule lumen, away from the epithelium. Synergy between the two fimbriae aids in the efficient colonization of the renal tubule. This work highlighted the narrow nature of the spatial resolution of an infectious niche with the center and periphery of a single tubule lumen exerting different pressures for adaptation.[154]

As an infection progresses, major alterations of the infected organ's physiology occur. One of the first significant findings relates to the rapidity of kidney responses to a local infection, with a majority of events occurring within the first 22 hours (Fig. 21.1A–D). Early tissue changes included vascular coagulation, epithelial breakdown, vascular leakage, immune cell recruitment, and general tissue destruction.[153,154] Coagulation in local peritubular capillaries (Fig. 21.2), and the subsequent vascular shut down, occurred within 5 to 6 hours of the infection, and accompanied a dramatic loss of local tissue oxygen.[155] Subsequent signs of ischemic injury were seen. This response was found to protect the host from urosepsis by keeping the infection site confined. Although extravasation of neutrophils inevitably causes tissue damage, the ischemic response efficiently hindered bacteria from gaining access to the bloodstream, thus giving time for neutrophils to clear the infection (Fig. 21.1E,F). Furthermore, bacterial colonization was shown to affect renal filtration, leading to obstruction.[3] Renal ischemia and obstruction are both well-studied physiologic injuries and both cause inflammation and tissue destruction in their own right.[156,157] Both are multifactorial and can vary in severity. Severe ischemia or obstruction can lead to end-stage renal failure, as can pyelonephritis. Thus, this study revealed that the pathophysiology of pyelonephritis is in fact a combination of infection and physiologic injuries such as ischemia and obstruction.

HOST RESPONSES TO INFECTION

The mammalian urinary tract is protected by numerous defense mechanisms, which together strive to maintain a sterile environment.[3,158] The physical defense of the epithelial barrier is complemented by mechanical defenses, including the sheer stress of urine flow, and chemical defenses, such as the expression of proinflammatory cytokines and antimicrobial peptides.[159,160] The colonization of the urinary tract can either lead to symptomatic disease, such as cystitis and pyelonephritis, or can develop into asymptomatic bacteriuria.[18,160] How the infectious process is developed is defined by the intimate interplay between features specific for the pathogen (i.e., virulence factors) and those defined by the host. One major host defense is the immune response, which usually is divided into the innate and the adaptive immune responses.[160,161] Innate responses are those mechanisms that recognize and respond immediately to the bacterial threat. Innate responses are nonspecific, whereas the adaptive immune response contains a memory that can build a specific immunity to a pathogen. The adaptive response can take days to weeks to develop to its full capacity.[162]

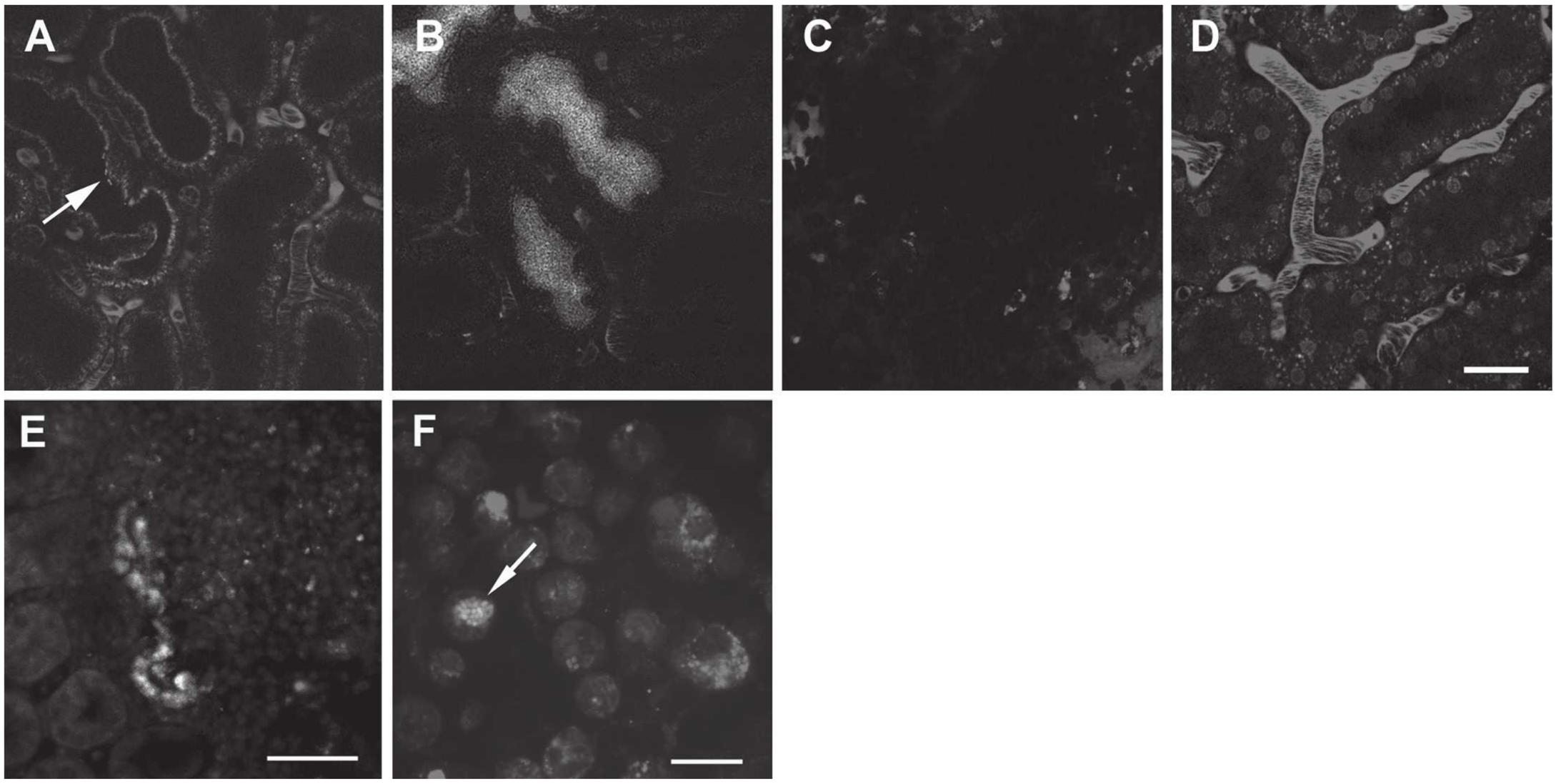

FIGURE 21.1 Real-time imaging using multiphoton microscopy of a uropathogenic *Escherichia coli* (LT004) infection. Labeled dextran outlines the injected tubule *(blue)* and blood flow *(red)*. Bacteria are visualized by their expression of GFP^+ *(green)*. **A:** One hour postinfection. **B:** Five hours postinfection. **C:** 22 hours postinfection. **D:** An adjacent, noninfected nephron of the same kidney 22 hours postinfection. Scale bar = 30 μm. **E:** An ex vivo analysis of image **C** by a confocal microscopy with the addition of nuclear stain Hoechst 33342 *(blue)* and leukocyte marker α-CD18-Cy3 *(red)*. Labeled dextran *(yellow)* outlines the injected tubule. Scale bar = 50 μm. **F:** A magnification of image **E** with an *arrow* indicating neutrophil phagocytosing bacteria. Note the lack of *green* present in images **C** and **E**, signifying bacterial clearance. Scale bar = 10 μm. (Reprinted from Månsson LE, et al. Real-time studies of the progression of bacterial infections and immediate tissue responses in live animals. *Cell Microbiol* 2007;9(2):413–424, with permission.) (See Color Plate.)

Shear Stress as a Natural Defense

One of the first defense mechanisms in the urinary tract is the shear stress caused by the flow of urine. In the bladder, this stress varies dramatically as the bladder fills and then empties upon voiding. In the kidney, this stress may be considered less extreme but it too fluctuates as the body regulates kidney function. Bacterial attachment to the epithelial lining of the urinary tract is considered extremely important to withstand this stress and the relationship between shear stress. Bacterial attachment was discussed in earlier sections of this chapter.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria (ABU), or infection with strains that do not cause clinical symptoms, has also been proposed as a mechanism to protect the urinary tract from more severe infections. Although ABU has been suggested to resemble commensalism due to the apparent lack of host immune response, it differs from the complex commensal flora of the intestine because it is normally a monoculture of only one bacterial strain.[162] The ABU strain E. coli 83972, isolated from a patient with long-term ABU, has been used extensively as a prophylaxis treatment to protect patients from symptomatic UTIs by outcompeting pathogens.

The Immune Response

Epithelia are equipped to rapidly recognize the presence of microbes. Toll-like receptors (TLRs) are closely related to the Drosophila toll protein,[161,162] which is known for its primary role in the innate immune system. Among a family of 10 characterized human TLRs and 12 mouse TLRs, TLR4, TLR5, and TLR11 have been linked to the urinary tract. When TLR recognizes specific bacterial molecules, so-called microbe-associated molecular patterns, activation of TLR signaling via coreceptor engagement leads to the onset of proinflammatory responses.[162] Uroepithelial cells expressing TLR4 are actually as sensitive to LPS, the endotoxin of gram-negative pathogens, as macrophages.[163–167] Though the ligand for TLR11 remains unknown, this receptor is important in a mouse model of UTIs,[168] and so is TLR5, which recognizes bacterial flagellin.[169]

The renal expression of TLR4 has been a matter of some debate, with reports showing that renal cells do[167] or do not[165] express TLR4. This discrepancy may be explained by experimental design, which includes infected as well as noninfected conditions. In uninfected animals, TLR4 is predominantly located at the apical surface of the distal tubule.[170] However, under septicemia, all kidney segments show TLR4 expression,

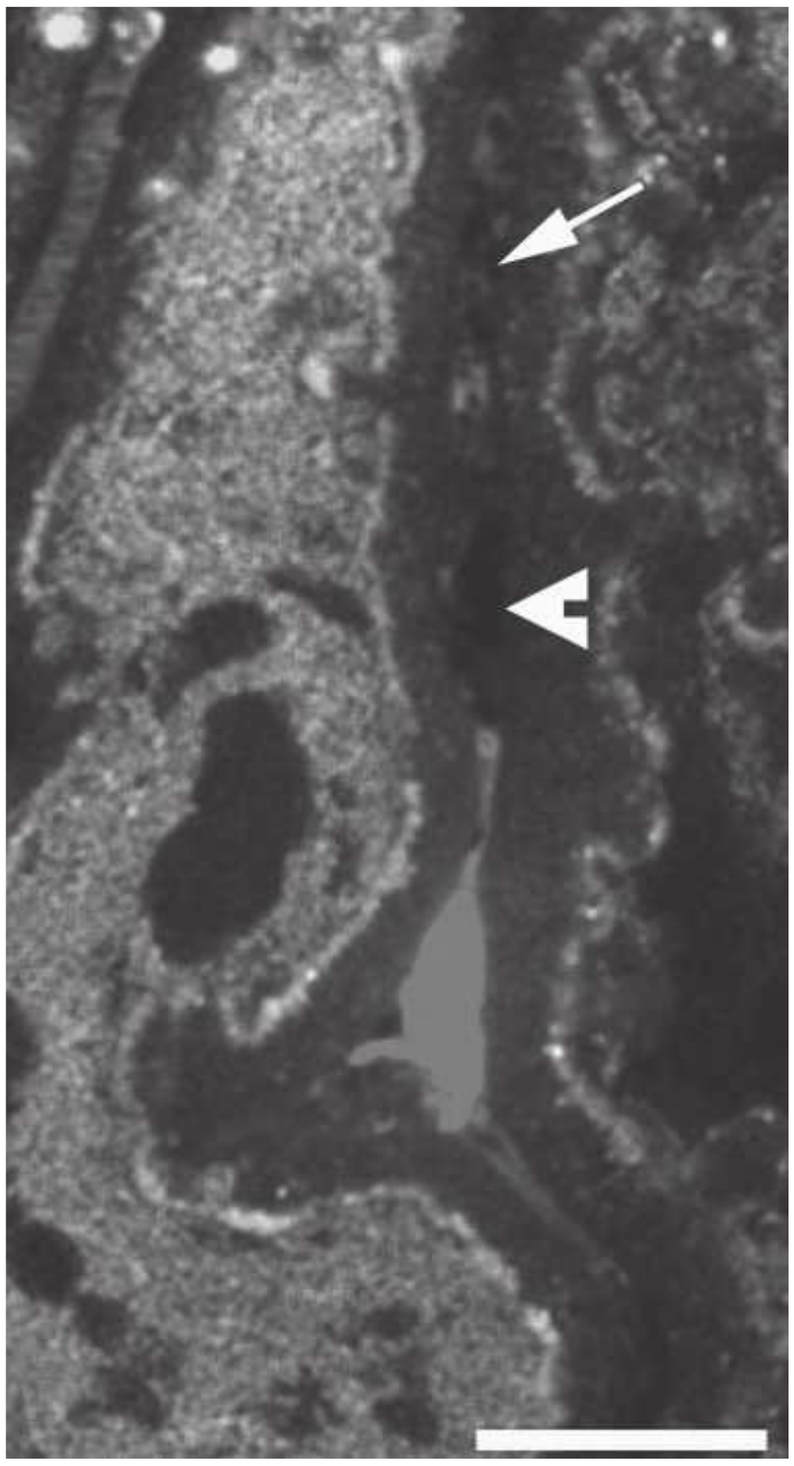

FIGURE 21.2 Blood clotting in mucosal infections. The live multiphoton image shows black silhouettes *(arrow)*, indicative of platelets, within the blood vessels *(red)* surrounding an LT004-infected *(green)* proximal tubule *(blue)* 2.5 hours postinfection. Black masses adhering to the wall of the vessel *(arrowhead)* suggest platelet aggregates. The intense *red* seen in the area represents stagnant flow, indicating a lack of red blood cell movement. Scale bar = 30 μm. (Reprinted from Melican K, et al. Bacterial infection-mediated mucosal signalling induces local renal ischaemia as a defence against sepsis. *Cell Microbiol* 2008;10(10):1987–1998, with permission.) (See Color Plate.)

suggesting TLR4 is upregulated during inflammation. The TLR4 expression pattern is thought to affect an individual's susceptibility to UTIs.[171] Children prone to ABU have reduced TLR4 expression on neutrophils[171,172] and those carrying the TLR4 A(896)G allele are prone to develop recurrent UTIs.[173]

In response to TLR4 signaling, cytokines are produced that orchestrate the immune response. Polymorphonuclear neutrophils (PMNs) and other inflammatory cells extravasate into the tissue as they follow this chemotactic gradient to the infection site. IL-8 is the main human chemokine (MIP-2 in mice) involved in the promotion of transepithelial PMN migration, which involves the IL-8 receptor CXCR1.[174] Studies have identified disease-associated polymorphisms and mutations in the CXCR1 gene of patients prone to pyelonephritis,[175] thus highlighting the importance of this receptor for a proper immune response. Neutrophils are commonly regarded as the primary cell type involved in the eradication of bacteria. Recent studies based on real-time intravital imaging of pyelonephritis in rat kidneys revealed that PMNs started to appear at the infection site as early as 3 to 4 hours postinfection, and by 8 hours, they constituted approximately 20% to 40% of nucleated cells present in the vasculature.[105] Not until hours later were neutrophils the predominant cell type at the infection foci. Although there is little doubt that PMNs are actively engaged in the clearance of bacteria in pyelonephritis, it appears that other cell types of hitherto unknown origin may also be involved in the early inflammatory process. PMNs are expected to kill bacteria via phagocytosis, and their ingestion of pathogens can occur with or without prior opsonization. The latter event is mediated by the main opsonins IgA and IgG, and by antimicrobial peptides.

Neutrophil recruitment is associated with severe tissue damage. The liberation of neutrophil granules containing antimicrobial peptides, proteins, and proteolytic enzymes can lead to the dissolution of extracellular matrix, can harm cell structures or cell function, and can induce acute and potentially irreparable damage.[174] PMN isolates from experimental acute pyelonephritis were observed to kill syngeneic renal epithelial cells in a culture within 24 to 48 hours.[176] In contrast, the suppression of acute suppuration in in vivo models reduced tubular epithelial cell damage and renal scarring despite the greater bacterial burden.[177,178] Furthermore, in IL-8 receptor knockout mice, impaired PMN translocation and unproductive accumulation in the subepithelial space resulted in kidney scarring and abscesses.[179] A picture has started to emerge that tissue damage results from the coherent action of bacteria, the inflammatory response, and physiologic injuries such as ischemia and obstruction.[62]

The antibody response in UTIs occurs both locally and systemically. Elevated levels of IgA, IgG, and occasionally, IgM have been observed in both the urine and the blood of UTI patients.[180,181] Systemic antibody titers vary distinctly between kidney and bladder infections,[182,183] with cystitis patients often showing titers as low as control groups.[180,184] Similarly, bacteria coated with antibodies are less frequently observed in patients with cystitis rather than with pyelonephritis.[182,183] Antibodies in urine play an important role in host protection. They may act as opsonins in opsonophagocytosis for PMNs recruited to the site, or they may target bacterial adhesins and, therefore, are likely to interfere with bacterial attachment to uroepithelial cells.[185] Another possibility is that antibodies trigger the agglutination of bacteria, thereby promoting bacterial clearance by voiding. They may also act to neutralize the detrimental effects of virulence factors.[186–188]

In cystitis and pyelonephritis, cell-mediated immunity is activated a day or more following the acute phase, as observed by an increased number of T cells in the infected organ

of the human. Earlier studies showing a close association between CD4 and plasma cells seemed to demonstrate the involvement of CD4 cells in host responses during repeated infections.[189,190] Experimental evidence now suggests that cell-mediated (T and B cells) immune responses appear to have a larger role in the kidney's response to chronic and repeat infections, rather than against acute infections. This is in contrast to bladder infections where the cell-mediated immune response is implicated in the acute phase. To illustrate this, T-cell depletion or deficiency does not have a significant effect on the outcome of kidneys under experimental bacterial infection.[191,192] γδ T lymphocytes are abundant in the mucosa, where they are known to modulate inflammation in response to various insults.[193] The central importance of γδ T lymphocytes in the clearance of bacteria from the bladder was recently demonstrated because these cells acted as the major source of IL-17A, which is a key mediator for the innate immune response to UTIs.[194]

Antimicrobial Proteins and Peptides

Host defenses against bacteria have been hypothesized to be dependent on epithelial-derived antimicrobial proteins that hinder survival of uropathogenic bacteria. The Tamm-Horsfall protein (THP) is the most abundant protein in human urine. THP is an evolutionarily conserved glycoprotein produced exclusively by epithelial cells of the ascending Henle loop.[195,196] Rich in mannose and sialic acid sequences, THP was shown to bind directly to type 1 fimbriated E. coli, and was therefore initially postulated to alleviate bacterial burden by sequestering bacteria within the urine for voiding.[197,198] This hypothesis was later discarded when the role of THP as a potent activator of innate and adaptive immune responses was revealed.[199,200] Examples include (1) the cell-specific stimulation of granulocyte toward IL-8 production,[199,201] (2) the upregulation of costimulatory molecules and MHC expression on dendritic cells (DCs), (3) cytokine production, and (4) DC maturation via TLR-4 signaling. So potent is the effect of THP that overstimulation of the immune system can lead to interstitial nephritis.[199,200]

Other important antimicrobial peptides in UTIs are the β-defensins and α-defensins, which are secreted from the local renal epithelium and the infiltrating neutrophils, respectively[200,201] Defensins possess a two-pronged effect, showing direct antimicrobial activity on invading bacteria and indirectly via the enhancement of the innate and acquired immune response. In the latter, defensin-induced secondary signaling arising from target cells and tissues have been implicated in acute inflammation regulation, immune cell recruitment, angiogenesis, and wound healing.[200] Examples include mast cell degranulation, the promotion of neutrophil chemotaxis, and naive T-cell and immature dendritic recruitment.[200]

Cathelicidins, such as LL-37, are antimicrobial peptides with direct bactericidal action. LL-37 is produced by neutrophils, myeloid bone marrow cells, epithelial cells of the skin, the gastrointestinal tract, the epididymis, and the lungs.[157,202] In the urinary tract, the peptide is produced from uroepithelial and tubular renal cells with a subsequent release into the lumen.[203] Given the presence of high cathelicidin-related antimicrobial peptides in the early stages of an infection well before leukocyte infiltration, a two-stage process was proposed in which the main source of the peptide shifts from the epithelium to leukocytes as the infection progresses.[203,204] Interestingly, cathelicidins exhibit a greater effect on pathogenic bacteria that cause UTIs as compared to urogenital commensal bacteria.[205] UPEC strains associated with severe UTIs also tend to have higher resistance to the peptide.[206]

Lactoferrin and lipocalin restrict the bacterial availability of essential iron. Lactoferrin is present in the luminal surface of distal collecting tubules where it exhibits its bactericidal activity indirectly by the chelation of iron, and directly by disrupting membrane integrity.[203] Lipocalin, on the other hand, limits iron availability by targeting bacterially expressed siderophores.[207,208]

Genetic Variability in Hosts

Genetic profiles have been observed that influence UTI susceptibility in patients. The genetic variation falls broadly into two groups: (1) factors involving bacterial colonization and (2) components of the host response. Variation in glycolipid receptor expression, which varies with the P blood group, has been shown to be associated with susceptibility to UTIs. Patients prone to UTIs tend to be of the blood group P1 and possess a high density of cell surface receptors for P fimbriae.[209] At present, there is insufficient statistical evidence to substantiate the inverse hypothesis (i.e., that individuals lacking receptors would be resistant to P-fimbriated E. coli).[210] However, treatment with N-butyl-deoxynojirimycin to mimic the previous receptor deficient state showed a protective effect on mice against colonization and inflammation.[211]

Two host factors, TLR4 and CXCR1 (the CXC chemokine receptor for IL-8), have been in focus when linking genetic variation to UTI susceptibility. A deficiency in mouse TLR4 signaling results in an asymptomatic carrier state that can persist for large proportions of the subject's lifespan before the onset of mortality.[33,212] This sequence of events closely resembles untreated ABU patients. CXCR1 is the receptor for the cytokine IL-8, which induces migration and the activation of neutrophils. CXCR1 has been suggested to function in protecting the host against severe infection.[137,213] Subjects with a deficient CXCR1 expression present with symptoms typical of acute pyelonephritis and renal scarring, as both the host's innate defenses and neutrophil migration are disrupted.[143] Children with lower CXCR1 expression and protein levels arising from a single nucleotide polymorphism are prone to pyelonephritis.[140,213] Furthermore, mice unable to express this IL-8 receptor have a higher titer of bacteria, a more rapid progression to bacteriuria, and renal scarring during an infection.

Intracellular Bacterial Reservoirs for Persistent Colonization

Recurrent infections are generally associated with repeated infections by the same bacterial strain. To persistently colonize the host UPEC have been proposed to enter into cells, thus generating a refuge by protecting bacteria from host defense systems. However, the significance of such intracellular reservoirs (IR) in UPEC persistence is not ubiquitous across the urinary tract.

Within the bladder, IRs appear to confer great advantage to UPEC survival. IRs are established when UPEC interacts with integral membrane proteins via FimH-mediated binding to uroplakin, which in turn triggers host cell signaling cascades that results in bacterial internalization.[131,190] The luminal surface of the mammalian bladder is lined by thick cell layers of pseudostratified transitional epithelia. Several studies have observed an intracellular transition of bacteria 12 hours postinfection,[139,141,154,214] after which IRs are established as bacteria rapidly multiply. Once an IR has become established in one cell, neighboring cells are invaded as UPEC progenies exit the host cell and invade other surrounding cells.[215,216] Although an exfoliation of superficial facet cells occurs, it does not appear to significantly deter UPEC persistence. While substantial IRs are removed with sloughed cells, the inadvertent exposure of the underlying cell layer allows UPEC to establish new IRs.

In the kidney the situation is different. Here, sloughing of the proximal tubule epithelium arising from ensued ischemia appears to negate the survival advantage of bacterial internalization.[217] During early periods of infection, ischemia-induced actin rearrangement and the associated relocalization of membrane-bound intergrins breaks the epithelial barrier function,[154,214] and detachment of epithelial cells from the tubular basement membrane occurs.[218] Loss of the epithelial barrier, however, did not compromise the host. The naked tubular basement membrane hinders the immediate bacterial dissemination into the interstitium.[139,154] while giving time for host responses to occur, such as the cessation of blood flow and PMN recruitment. Moreover, loss of the tubular integrity does not appear to solely benefit the invading pathogen because paracellular movement of UPEC enhances the neutrophil's accessibility to the tubular lumen.

The formation of IRs within the bladder is a highly effective strategy for UPEC persistence in which IRs or bacteria have been observed months after the initial infection, albeit with antibiotic treatment.[215–217] Yet, because of distinct histologic differences of the kidney from the bladder, IR establishment does not provide UPEC the same survival advantage within the kidney.[102,107,154,219]

Acute Kidney Damage

Infection and subsequent injury to the kidney causes extensive damage, which may affect kidney function and which may lead to kidney failure. Over the years, a number of proposed mechanisms for this injury have been suggested. A direct damaging effect of infecting bacteria is possible for those UPEC strains that express tissue-damaging toxins.[176,178,220,221] The strong inflammatory response to pyelonephritis has also implicated a role for collateral damage. Suppression of the immune response in experimental models has shown reduced kidney scarring despite a high bacterial load.[222,223] It has also been shown that neutrophils isolated from acute pyelonephritis can kill syngeneic kidney cells in vitro,[154] and neutrophil-mediated oxidative injury of kidney cells has been confirmed in vivo.[154]

Though physiologic alterations that accompany ischemia–reperfusion injury previously have been implicated in renal scarring,[224] recent data show renal infections do in fact cause ischemia.[154] Ischemia is a restriction in blood supply to a tissue or an organ that is closely associated with tissue oxygen delivery and tension (pO_2). Each kidney nephron has an intertwined peritubular vasculature. During the first hours (4 to 5 hours) of a UPEC infection in the proximal convoluted tubule, epithelia-endothelia signaling initiates the clotting cascade in peritubular capillaries (Fig. 21.2). This clotting leads to localized ischemia that manifests prior to the major infiltration of immune cells. Tissue pO_2 drops significantly, reaching 0 mm Hg within 3 to 4 hours.[154] This infection-mediated ischemia was demonstrated to act as an innate defense mechanism, preventing the systemic dissemination of the pathogen because anticoagulant therapy to prevent this response led to fatal sepsis within a few hours.[154] Although a massive engagement of neutrophils cleared the bacteria (Fig. 21.1E,F), no indications of reperfusion or repair were seen within the first 24 hours. Renal scarring thus appeared to be the end result of infection.

Another physiologic injury that is known to cause tissue damage in its own right is kidney obstruction. Real-time monitoring of renal filtrate flow in a live animal model of pyelonephritis showed how bacterial colonization of the renal tubules affects the flow of filtrate, with complete stoppage occurring within 8 hours. Kidney ischemia and obstruction are both well-studied physiologic injuries and both can cause inflammation and tissue destruction in their own right.[154,155,216,225–232] Both are multifactorial and can vary in severity. Severe ischemia or obstruction can lead to end-stage kidney failure, as can pyelonephritis. Thus, the emerging view is that the pathophysiology of pyelonephritis is in fact a combination of infection and physiologic injuries.[154]

Treatment

A UTI is most commonly treated by antibiotics. Wagenlehner et al.[233] present a comprehensive statistic of clinically prescribed antibiotics and their respective efficacies. The group describes UTIs as broadly divided into uncomplicated and complicated cases, against which treatment is tailored.[233,234]

The following paragraph is adapted from Wagenlehner et al.[233]

> Uncomplicated UTI denotes UTI without relevant structural and functional abnormalities arising from the urinary tract (uropathies), without relevant kidney diseases (nephropathies) and without relevant comorbidities. Conversely, complicated UTI is a complex condition of the following conditions: (1) Anatomical, structural or functional alterations of the urinary tract. (2) Impaired renal function by parenchymal and renal nephropathies. (3) Accompanying diseases or conditions that impair the patients' immune status.

In the treatment of uncomplicated UTIs, the choice of prescription is made based on five considerations[233]: (1) the individual risk to antibiotic treatment; (2) the bactericidal spectrum of the antibiotic and the known susceptibility of the bacterium to the antibiotic; (3) the clinical data of the effectiveness of the antibiotic; (4) the effect of the antibiotic on commensal microbial flora; and (5) side effects.

Complex UTIs require a two-pronged treatment strategy directed at the treatment of complicating factors and the invading pathogen.[234] In complex UTIs, pathogens can be a heterogeneous population of gram-positive and gram-negative strains with a wide range of antibiotic susceptibility and resistance.[233] Very often, the devised treatment must account for the possibility of the resistance development and cross-resistance among antibiotics of the same family.[233]

In general, the treatments of uncomplicated and complicated UTIs share two fundamental aims, namely, to use rapid acting therapy with high efficacy for recurrent infections within a patient, and to prevent the generation of pathogens resistant to the treatment.[233] When treatment is delayed or ineffective, uncomplicated UTIs can progress to sepsis and severe sepsis, requiring specific sepsis therapy. At this point, treatment of urosepsis becomes a combination of (1) eradicating the pathogen, (2) resolving the cause of the infection and the complications (e.g., obstruction), (3) providing life-supportive care, and (4) providing appropriate antimicrobial therapy.[233]

Aside from clinical treatments, folk remedies are commonly used in the treatment of UTIs. Although there are a variety in existence, cranberry juice is by far one of the most common. Cranberry juice and tablets have been used extensively as a remedy for infections of the urinary tract. Originally thought to be due to the bactericidal acidification of the urine by hippuric acid, recent studies have dispelled this mechanism of action. Cranberries contain proanthocyanidins, which inhibit P fimbriae–mediated bacterial adherence,[235,236] and fructose, which inhibits type 1–mediated adherence.[237] Despite the apparent positive effect of cranberries, no definitive findings have been determined in clinical trials.

CONCLUSION

Data presented in this chapter reveal that our current knowledge of UPEC and host–pathogen interactions in UTIs primarily originate from molecularly well-defined in vitro systems. The simplicity of such systems zooms in on specific reactions, controlling for and filtering out the myriad of relevant but confounding interactions that occur simultaneously in the host during an infection. Applying this wealth of information as a foundation and coupled with advanced imaging platforms for real-time studies in the live animal, researchers can now advance from "cellular microbiology" to "tissue microbiology," in their attempt to generate an integrated view on host–pathogen interactions. Such coherent models will help to not only identify both the cross-talk between host and pathogen, but also the dynamic changes occurring in the immediate environment in response to an infection. Murine intravital models of pyelonephritis have shown these changes include tissue oxygen tension and the cessation of blood flow to the infected site. These are but a few of the many factors that need to be tracked during an infection. Across the globe, interdisciplinary research coupling all fields of science is blooming and working to create new technologies. And as our understanding of host–pathogen interactions advances, so will clinical diagnostics, treatment, and patient care.

REFERENCES

1. Hill GS. Renal infection. In GS Hill, Ed. Uropathology. New York: Churchill Livingstone, 1989. p. 333–429.

1a. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2006. Med Care. 2008;8:1–29.

2. Watts RE, Hancock V, Ong CLY, et al. Escherichia coli isolates causing asymptomatic bacteriuria in catheterized and noncatheterized individuals possess similar virulence properties. J Clin Microbiol. 2010;48(7):2449–2458.

2a. Litwin M, Saigal C, Washington D. Introduction. In S Mark, CS Saigal, eds. Urologic diseases in America. HHS PHS NIH NIDDK GPO NIH publication 37 2007:7–5512.

3. Mims AD, Norman DC, Yamamura RH, et al. Medical Microbiology. Philadelphia: Mosby Inc; 2004:660.

4. Schaeffer AJ. Infections of the urinary tract. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. Campbells Urology. 8th ed. Vol. 1. Philadelphia: Saunders; 2002:515–602.

5. Walsh P, Campbell MF, Walsh PC, et al. Campbells urology. WB Saunders Co., 2002.

6. Vercellone A, Stratta. Historical review of concepts of pyelonephritis. In A Amerio, P Coratelli, SG Massry, eds. Tubulo-Interstitial Nephropathies. Proceedings of the 4th Bari Seminar in Nephrology. Boston: Kluwer Academic Publishers; 1990:197–205.

7. Ronald A, Tract R, Nicolle LE. Infections of the upper urinary tract. In RW Schrier, ed. Diseases of the Kidney and Urinary. Philadelphia: Lippincott, Williams & Wilkins; :941–969.

8. Jackson GG, Grieble HG. Pathogenesis of renal infection. AMA Arch Intern Med. 1957;100(5):692–700.
http://www.ncbi.nlm.nih.gov/pubmed/13468813

9. Finer G, Landau D. Pathogenesis of urinary tract infections with normal female anatomy. Lancet Infect Dis. 2004;4(10):631–635.

10. Mulvey MA, Schilling JD, Martinez JJ, et al. Bad bugs and beleaguered bladders: interplay between uropathogenic Escherichia coli and innate host defenses. Proc Natl Acad Sci USA. 2000;97(16):8829–8835.

11. Vander A, Eaton DC, Paoler J, et al. Vander's renal physiology. McGraw-Hill, 2009.

12. Lote CJ. Principles of Renal Physiology. New York: Springer; 2000.

13. Koeppen BM, Stanton BA. Structure and function of the kidneys. In: Koeppen BM, Stanton BA, eds. Renal Physiology. Mosby Inc; 2007: 228.

14. Koeppen K, Reuter P, Kohl S, et al. Functional analysis of human CNGA3 mutations associated with colour blindness suggests impaired surface expression of channel mutants A3(R427C) and A3(R563C). Eur]Neurosci. 2008;27(9): 2391–2401.
http://www.ncbi.nlm.nih.gov/pubmed/18445228

15. Foxman B. The epidemiology of urinary tract infection. Nature reviews. Urology. 2010;7(12):653–660.

16. Welch RA, Burland V, Plunkett G, et al. Extensive mosaic structure revealed by the complete genome sequence of uropathogenic Escherichia coli. Proc NatlAcad Sci USA. 2002;99(26):17020–17024.

17. Vejborg RM, Friis C, Hancock V, et al. A virulent parent with probiotic progeny: comparative genomics of Escherichia coli strains CFT073, Nissle 1917 and ABU 83972. Mol Genet Genomics. 2010;283(5):469–484.
http://www.ncbi.nlm.nih.gov/pubmed/20354866

18. Zdziarski J, Svanborg C, Wullt B, et al. Molecular basis of commensalism in the urinary tract: low virulence or virulence attenuation? Infect Immun. 2008;76(2):695–703.
http://www.ncbi.nlm.nih.gov/pubmed/18039831

19. Hacker J. Genetic determinants coding for fimbriae and adhesins of extraintestinal Escherichia coli. Curr Top Microbiol Immunol. 1990;151:1–27.
http://www.ncbi.nlm.nih.gov/pubmed/1973366

20. Wiles TJ, Kulesus RR, Mulvey MA. Origins and virulence mechanisms of uropathogenic Escherichia coli. Exp Mol Pathol. 2008;85(1):11–19.
http://www.ncbi.nlm.nih.gov/pubmed/18482721

21. Oelschlaeger TA, Dobrindt U, Hacker J. Pathogenicity islands of uropathogenic E. coli and the evolution of virulence. Int J Antimicrob Agents. 2002;19(6):517–521.
http://www.ncbi.nlm.nih.gov/pubmed/12135843

22. Hacker J, Knapp S, Goebel W. Spontaneous deletions and flanking regions of the chromosomally inherited hemolysin determinant of an Escherichia coli O6 strain. J Bacteriol. 1983;154(3):1145–1152.

23. Falkow S. Molecular Koch's postulates applied to microbial pathogenicity. Rev Infect Dis. 1988;10(Suppl 2):S274–S276.

24. Schmidt H, Hensel M. Pathogenicity islands in bacterial pathogenesis. Clin Microbiol Rev. 2004;17(1):14–56.
http://www.ncbi.nlm.nih.gov/pubmed/14726454

25. Knapp S, Hacker J, Jarchau T, et al. Large, unstable inserts in the chromosome affect virulence properties of uropathogenic Escherichia coli O6 strain 536. J Bacteriol. 1986;168(1):22–30.
http://www.ncbi.nlm.nih.gov/pubmed/2875989

26. Swenson DL, Bukanov NO, Berg DE, et al. Two pathogenicity islands in uropathogenic Escherichia coli J cosmid cloning and sample sequencing. Infect Immun. 1996;64(9):3736–3743.
http://www.ncbi.nlm.nih.gov/pubmed/8751923

27. Dobrindt U, Chowdary MG, Krumbholz G, et al. Genome dynamics and its impact on evolution of Escherichia coli. Med Microbiol Immunol. 2010;199(3):145–154.
http://www.ncbi.nlm.nih.gov/pubmed/20445988

28. Blattner FR, Plunkett G, Bloch CA, et al. The complete genome sequence of Escherichia coli K–12. Science. 1997;277(5331):1453–1462.

29. Kuehn MJ, Normark S, Hultgren SJ. Immunoglobulin-like PapD chaperone caps and uncaps interactive surfaces of nascently translocated pilus subunits. Proc Natl Acad Sci USA. 1991;88(23):10586–10590.

30. Perna NT, Plunkett G, Burland V, et al. Genome sequence of enterohaemorrhagic Escherichia coli O157:H7. Nature. 2001;409(6819):529–533.
http://www.ncbi.nlm.nih.gov/pubmed/11206551

31. Manges AR, Johnson JR, Foxman B, et al. Widespread distribution of urinary tract infections caused by a multidrug-resistant Escherichia coli clonal group. N Engl J Med. 2001;345(14):1007–1013.
http://www.ncbi.nlm.nih.gov/pubmed/11586952

32. Manges AR, Dietrich PS, Riley LW. Multidrug-resistant Escherichia coli clonal groups causing community-acquired pyelonephritis. Clin Infect Dis. 2004;38(3):329–334.

33. Svanborg C, Bergsten G, Fischer H, et al. Uropathogenic Escherichia coli as a model of host-parasite interaction. Curr Opin Microbiol. 2006;9(1):33–39.

34. Johnson JR. Virulence factors in Escherichia coli urinary tract infection. Clin Microbiol Rev. 1991;4(1):80–128.
http://www.ncbi.nlm.nih.gov/pubmed/1672263

35. Falkow S. Molecular Koch's postulates applied to microbial pathogenicity. Rev Infect Dis. 1998;10(Suppl2):S274–S276.

36. Falkow S. Molecular Koch's postulates applied to bacterial pathogenicity—a personal recollection 15 years later. Nat Rev Microbiol. 2004;2(1):67–72.
http://www.ncbi.nlm.nih.gov/pubmed/15035010

37. Kummerli R. Viscous medium promotes cooperation in the pathogenic bacterium Pseudomonas aeruginosa. Proc Biol Sci. 2009;276(1672):3531–3538.
http://www.ncbi.nlm.nih.gov/pubmed/19605393

38. Ratledge C, Dover LG. Iron metabolism in pathogenic bacteria. Annu Rev Microbiol. 2000;54:881–941.
http://www.ncbi.nlm.nih.gov/pubmed/11018148

39. Andersson DI, Levin BR. The biological cost of antibiotic resistance. Curr Opin Microbiol. 1999;2(5):489–493.
http://www.ncbi.nlm.nih.gov/pubmed/10508723

40. Andersson DI, Hughes D. Antibiotic resistance and its cost: is it possible to reverse resistance? Nat Rev Microbiol. 2010;8(4):260–271.

41. Johnson JR. Microbial virulence determinants and the pathogenesis of urinary tract infection. Infect Dis Clin North Am. 2003;17(2):261–278,viii.

42. Wright KJ, Hultgren SJ. Sticky fibers and uropathogenesis: bacterial adhesins in the urinary tract. Future Microbiol. 2006;1:75–87.
http://www.ncbi.nlm.nih.gov/pubmed/17661687

43. Snyder JA, Haugen BJ, Lockatell CV et al. Coordinate expression of fimbriae in uropathogenic Escherichia coli. Infect Immun. 2005;73(11):7588–7596.
http://www.ncbi.nlm.nih.gov/pubmed/16239562

44. Holden NJ, Gally DL. Switches, cross-talk and memory in Escherichia coli adherence. J Med Microbiol. 2004;53(Pt 7):585–593.
http://www.ncbi.nlm.nih.gov/pubmed/12808081

45. Holden NJ, Uhlin BE, Gally DL. PapB paralogues and their effect on the phase variation of type 1 fimbriae in Escherichia coli. Mol Microbiol. 2001;42(2):319–330.

46. Simms AN, Mobley HLT. PapX, a P fimbrial operon-encoded inhibitor of motility in uropathogenic Escherichia coli. Infect Immun. 2008;76(11):4833–4841.
http://www.ncbi.nlm.nih.gov/pubmed/18710869

47. Houwink A, van Iterson W. Electron microscopical observations on bacterial cytology: a study on flagellation. Biochim Biophys Acta. 1950;5(1):10–44.
http://www.ncbi.nlm.nih.gov/pubmed/15433975

48. Brinton C, Buzzell A, Lauffer M Jr. Electrophoresis and phage susceptibility studies on a filament-producing variant of the E. coli B bacterium. Biochim Biophys Acta. 1954;15(4):533–542.
http://www.ncbi.nlm.nih.gov/pubmed/13230101

49. Duguid JP, Smith IW, Dempster G, et al. Non-flagellar filamentous appendages (fimbriae) and haemagglutinating activity in Bacterium coli. Bacteriol. 1955;70(2):335–348.
http://www.ncbi.nlm.nih.gov/pubmed/13295908

50. Bower JM, Eto DS, Mulvey MA. Covert operations of uropathogenic Escherichia coli within the urinary tract. Traffic. 2005;6(1):18–31.

51. Capitani G, Eidam O, Glockshuber R, et al. Structural and functional insights into the assembly of type 1 pili from Escherichia coli. Microbes Infect. 2006;8(8):2284–2290.

52. Schilling JD, Mulvey MA, Hultgren SJ. Structure and function of Escherichia coli type 1 pili: new insight into the pathogenesis of urinary tract infections. J Infect Dis. 2001;183(Suppl 1):S36–S40.

53. Ofek I, Mirelman D, Sharon N. Adherence of Escherichia coli to human mucosal cells mediated by mannose receptors. Nature. 1977;265(5595):623–625.
http://www.ncbi.nlm.nih.gov/pubmed/323718

54. Yamamoto T, Fujita K, Yokota T. Adherence characteristics to human small intestinal mucosa of Escherichia coli isolated from patients with diarrhea or urinary tract infections. J Infect Dis. 1990;162(4):896–908.
http://www.ncbi.nlm.nih.gov/pubmed/1976131

55. Choudhury D, Thompson A, Stojanoff V, et al. X-ray structure of the FimC-FimH chaperone-adhesin complex from uropathogenic Escherichia coli. Science. 1999;285(5430):1061–1066.
http://www.ncbi.nlm.nih.gov/pubmed/10446051

56. Hung CS, Bouckaert J, Hung D, et al. Structural basis of tropism of Escherichia coli to the bladder during urinary tract infection. Mol Microbiol. 2002;44(4):903–915.
http://www.ncbi.nlm.nih.gov/pubmed/12010488

57. Sokurenko EV, Chesnokova V, Doyle RJ, et al. Diversity of the Escherichia coli type 1 fimbrial lectin. Differential binding to mannosides and uroepithelial cells. J Biol Chem. 1997;272(28):17880–17886.

58. Sokurenko EV, Courtney HS, Maslow J, et al. Quantitative differences in adhesiveness of type 1 fimbriated Escherichia coli due to structural differences in fimH genes. J Bacteriol. 1995;177(13):3680–3686.

59. Sokurenko EV, Chesnokova V, Dykhuizen DE, et al. Pathogenic adaptation of Escherichia coli by natural variation of the FimH adhesin. Proc Natl Acad Sci USA. 1998;95(15):8922–8926.
http://www.ncbi.nlm.nih.gov/pubmed/9671780

60. Le Bouguénec C. Adhesins and invasins of pathogenic Escherichia coli. Int J Med Microbiol. 2005;295(6–7):471–478.
http://www.ncbi.nlm.nih.gov/pubmed/16238021

61. Schembri MA, Klemm P. Biofilm formation in a hydrodynamic environment by novel fimh variants and ramifications for virulence. Infect Immun. 2001;69(3):1322–1328.
http://www.ncbi.nlm.nih.gov/pubmed/11179294

62. Melican K, Sandoval R, Kader A, et al. Uropathogenic Escherichia coli P and type 1 fimbriae act in synergy in a living host to facilitate renal colonization leading to nephron obstruction. PLoS Pathog. 2011;7(2):333–429.
http://www.ncbi.nlm.nih.gov/pubmed/21383970

63. Wu XR, Sun TT, Medina JJ. In vitro binding of type 1-fimbriated Escherichia coli to uroplakins Ia and Ib: relation to urinary tract infections. Proc Natl Acad Sci USA. 1996;93(18):9630–9635.

64. Le Trong I, Aprikian P, Kidd BA, et al. Structural basis for mechanical force regulation of the adhesin FimH via finger trap-like beta sheet twisting. Cell. 2010;141(4):645–655.

65. Thomas WE, Trintchina E, Forero M, et al. Bacterial adhesion to target cells enhanced by shear force. Cell. 2002;109(7):913–923.
http://www.ncbi.nlm.nih.gov/pubmed/12110187

66. Ronald LS, Yakovenko O, Yazvenko N, et al. Adaptive mutations in the signal peptide of the type 1 fimbrial adhesin of uropathogenic Escherichia coli. Proc Natl Acad Sci USA. 2008;105(31):10937–10942.
http://www.ncbi.nlm.nih.gov/pubmed/18664574

67. Nilsson LM, Thomas WE, Trintchina E, et al. Catch bond-mediated adhesion without a shear threshold: trimannose versus monomannose interactions with the FimH adhesin of Escherichia coli. J Biol Chem. 2006;281(24): 16656–16663.

68. Snyder JA, Haugen BJ, Buckles EL, et al. Transcriptome of uropathogenic Escherichia coli during urinary tract infection. Infect Immun. 2004;72(11): 6373–6381.
http://www.ncbi.nlm.nih.gov/pubmed/15501767

69. Connell I, Agace W Klemm P, et al. Type 1 fimbrial expression enhances Escherichia coli virulence for the urinary tract. Proc Natl Acad Sci USA. 1996;93(18):9827–9832.
http://www.ncbi.nlm.nih.gov/pubmed/8790416

70. Edén CS, Hanson LA, Jodal U, et al. Variable adherence to normal human urinary-tract epithelial cells of Escherichia coli strains associated with various forms of urinary-tract infection. Lancet. 1976;1(7984):490–492.

71. Lane MC, Mobley HLT. Role of P-fimbrial-mediated adherence in pyelonephritis and persistence of uropathogenic Escherichia coli (UPEC) in the mammalian kidney. Kidney Int. 2007;72(1):19–25.
http://www.ncbi.nlm.nih.gov/pubmed/17396114

72. Boyd EF, Hartl DL. Chromosomal regions specific to pathogenic isolates of Escherichia coli have a phylogenetically clustered distribution. J Bacteriol. 1998;180(5):1159–1165.
http://www.ncbi.nlm.nih.gov/pubmed/9495754

73. Antao EM, Wieler LH, Ewers C. Adhesive threads of extraintestinal pathogenic Escherichia coli. Gut Pathog. 2009;1(1):22.
http://www.ncbi.nlm.nih.gov/pubmed/20003270

74. Wullt B, Bergsten G, Samuelsson M, et al. The role of P fimbriae for Escherichia coli establishment and mucosal inf ammation in the human urinary tract. Int J Antimicrob Agents. 2002;19(6):522–538.
http://www.ncbi.nlm.nih.gov/pubmed/12135844

75. Johnson JR, Russo TA, Brown JJ, et al. papG alleles of Escherichia coli strains causing first-episode or recurrent acute cystitis in adult women. J Infect Dis. 1998;177(1):97–101.

76. Strömberg N, Marklund Bl, Lund B, et al. Host-specificity of uropathogenic Escherichia coli depends on differences in binding specificity to Gal alpha l-containing isoreceptors. EMBO J. 1990; 9(6):2001–2010.

77. Plos K, Carter T, Hull S, et al. Frequency and organization of pap homologous DNA in relation to clinical origin of uropathogenic Escherichia coli. J Infect Dis. 1990;161(3):518–524.
http://www.ncbi.nlm.nih.gov/pubmed/1968935

78. Donnenberg M, Welch R, Mobley H, et al. Virulence determinants of uropathogenic Escherichia coli. In: Mobley HLT, Warren JW, eds. Urinary Tract Infections: Molecular Pathogenesis and Clinical Management. Washington, DC: American Society for Microbiology; 1996:135.

79. Westerlund B, Siitonen A, Elo J, et al. Properties of Escherichia coli isolates from urinary tract infections in boys. J Infect Dis. 1988;158(5):996–1002.

80. Johnson JR, Roberts PL, Stamm WE. P fimbriae and other virulence factors in Escherichia coli urosepsis: association with patients' characteristics. J Infect Dis. 1987;156(1):225–229.

81. Roberts JA, Marklund BI, Ilver D, et al. The Gal(alpha 1-4)Gal-specific tip adhesin of Escherichia coli P-f mbriae is needed for pyelonephritis to occur in the normal urinary tract. Proc Natl Acad Sci USA. 1994;91(25):11889–11893.

82. Mobley HL, Jarvis KG, Elwood JP, et al. Isogenic P-fimbrial deletion mutants of pyelonephritogenic Escherichia coli: the role of alpha Gal(1-4) beta Gal binding in virulence of a wild-type strain. Mol Microbiol. 1993;10(1): 143–155.

83. Blyn LB, Braaten BA, Low DA. Regulation of pap pilin phase variation by a mechanism involving differential dam methylation states. EMBO J. 1990;9(12):4045–4054.
http://www.ncbi.nlm.nih.gov/pubmed/2147413

84. Holden N, Totsika M, Dixon L, et al. Regulation of P-fimbrial phase variation frequencies in Escherichia coli CFT073. Infect Immun. 2007;75(7): 3325–3334.
http://www.ncbi.nlm.nih.gov/pubmed/17452474

85. Hull RA, Hull SI, Falkow S. Frequency of gene sequences necessary for pyelonephritis-associated pili expression among isolates of Enterobacteriaceae from human extraintestinal infections. Infect Immun. 1984;43(3):1064–1067.

86. Nowicki B, Labigne A, Moseley S, et al. The Dr hemagglutinin, afimbrial adhesins AFA-I and AFA-III, and F1845 fimbriae of uropathogenic and diarrhea-associated Escherichia coli belong to a family of hemagglutinins with Dr receptor recognition. Infect Immun. 1990;58(1):279–281.

87. Nowicki B, Hart A, Coyne KE, et al. Short consensus repeat-3 domain of recombinant decay-accelerating factor is recognized by Escherichia coli recombinant Dr adhesin in a model of a cell-cell interaction. J Exp Med. 1993;178(6): 2115–2121.
http://www.ncbi.nlm.nih.gov/pubmed/7504058

88. Nowicki B, Truong L, Moulds J, et al. Presence of the Dr receptor in normal human tissues and its possible role in the pathogenesis of ascending urinary tract infection. Am J Pathol. 1988;133(1):1–4.
http://www.ncbi.nlm.nih.gov/pubmed/3052090

89. Selvarangan R, Goluszko P, Popov V, et al. Role of decay-accelerating factor domains and anchorage in internalization of Dr-fimbriated Escherichia coli. Infect Immun. 2000;68(3):1391–1399.
http://www.ncbi.nlm.nih.gov/pubmed/10678952

90. Nowicki B, Selvarangan R, Nowicki S. Family of Escherichia coli Dr adhesins: decay-accelerating factor receptor recognition and invasiveness. J Infect Dis. 2001;183Suppl 1:S24–S27.

91. Westerlund B, Kuusela P, Risteli J, et al. The O75X adhesin of uropathogenic Escherichia coli is a type IV collagen-binding protein. Mol Microbiol. 1989;3(3):329–337.

92. Van Loy CP, Sokurenko EV, Samudrala R, et al. Identification of amino acids in the Dr adhesin required for binding to decay-accelerating factor. Mol Microbiol. 2002;45(2):439–452.

93. Selvarangan R, Goluszko P, Singhal J, et al. Interaction of Dr adhesin with collagen type IV is a critical step in Escherichia coli renal persistence. Infect Immun. 2004;72(8):4827–4835.

94. Donnenberg MS. Entry of enteropathogenic Escherichia coli into host cells. Curr Top Microbiol Immunol. 1996;209:79–98.
http://www.ncbi.nlm.nih.gov/pubmed/8742247

95. Bäckhed F, Alsén B, Roche N, et al. Identification of target tissue glycosphingolipid receptors for uropathogenic, F1C-fimbriated Escherichia coli and its role in mucosal inf ammation. J Biol Chem. 2002;277(20):18198–18205.
http://www.ncbi.nlm.nih.gov/pubmed/11877427

96. Korhonen TK, Virkola R, Westerlund B, et al. Tissue tropism of Escherichia coli adhesins in human extraintestinal infections. Curr Top Microbiol Immunol. 1990;151:115–127.
http://www.ncbi.nlm.nih.gov/pubmed/1973367

97. Parkkinen J, Rogers GN, Korhonen T, et al. Identification of the O-linked sialyloligosaccharides of glycophorin A as the erythrocyte receptors for S-fimbriated Escherichia coli. Infect Immun. 1986;54(1):37–42.

98. Korhonen TK, Parkkinen J, Hacker J, et al. Binding of Escherichia coli S fimbriae to human kidney epithelium. Infect Immun. 1986;54(2):322–327.
http://www.ncbi.nlm.nih.gov/pubmed/2876958

99. High N, Hales B, Jann K, et al. A block of urovirulence genes encoding multiple fimbriae and hemolysin in Escherichia coli OK12:H. Infect Immun. 1988;56(2):513–517.
http://www.ncbi.nlm.nih.gov/pubmed/2892797

100. Guyer DM, Kao JS, Mobley HL. Genomic analysis of a pathogenicity island in uropathogenic Escherichia coli CFT073: distribution of homologous sequences among isolates from patients with pyelonephritis, cystitis, and catheter-associated bacteriuria and from fecal samples. Infect Immun. 1998;66(9): 4411–4417.

101. Mobley HL, Island MD, Massad G. Virulence determinants of uropathogenic Escherichia coli and Proteus mirabilis. Kidney Int Suppl. 1994;47:S129–S136.

102. Trifillis AL, Donnenberg MS, Cui X, et al. Binding to and killing of human renal epithelial cells by hemolytic P-fimbriated E. coli. Kidney Int. 1994;46(4):1083–1091.
http://www.ncbi.nlm.nih.gov/pubmed/7861702

103. Cavalieri SJ, Snyder IS. Effect of Escherichia coli alpha-hemolysin on human peripheral leukocyte viability in vitro. Infect Immun. 1982;36(2):455–461.
http://www.ncbi.nlm.nih.gov/pubmed/7044971

104. Uhlén P, Laestadius A, Jahnukainen T, et al. Alpha-haemolysin of uropathogenic E. coli induces Ca2+ oscillations in renal epithelial cells. Nature. 2000;405(6787):694–697.
http://www.ncbi.nlm.nih.gov/pubmed/10864327

105. Månsson LE, Melican K, Boekel J, et al. Real-time studies of the progression of bacterial infections and immediate tissue responses in live animals. Cell Microbiol. 2007;9(2):413–424.
106. Doye A, Mettouchi A, Bossis G, et al. CNF1 exploits the ubiquitin-proteasome machinery to restrict Rho GTPase activation for bacterial host cell invasion. Cell. 2002;111(4):553–564.
http://www.ncbi.nlm.nih.gov/pubmed/12031343
107. Island MD, Cui X, Foxman B, et al. Cytotoxicity of hemolytic, cytotoxic necrotizing factor 1-positive and -negative Escherichia coli to human T24 bladder cells. Infect Immun. 1998;66(7):3384–3389.
108. Flatau G, Lemichez E, Gauthier M, et al. Toxin-induced activation of the G protein p21 Rho by deamidation of glutamine. Nature. 1997;387(6634):729–733.
http://www.ncbi.nlm.nih.gov/pubmed/9192901
109. Schmidt G, Sehr P, Wilm M, et al. Gln 63 of Rho is deamidated by Escherichia coli cytotoxic necrotizing factor-1. Nature. 1997;387(6634):725–729.
http://www.ncbi.nlm.nih.gov/pubmed/9192900
110. Blanco J, Alonso MP, González EA, et al. Virulence factors of bacteraemic Escherichia coli with particular reference to production of cytotoxic necrotising factor (CNF) by P-fimbriate strains. J Med Microbiol. 1990;31(3):175–183.
http://www.ncbi.nlm.nih.gov/pubmed/1968978
111. Blum G, Falbo V, Caprioli A, et al. Gene clusters encoding the cytotoxic necrotizing factor type 1, Prs-fimbriae and alpha-hemolysin form the pathogenicity island II of the uropathogenic Escherichia coli strain J96. FEMS Microbiol Lett. 1995;126(2):189–195.
http://www.ncbi.nlm.nih.gov/pubmed/7705611
112. Landraud L, Gibert M, Popoff MR, et al. Expression of cnf1 by Escherichia coli J96 involves a large upstream DNA region including the hlyCABD operon, and is regulated by the RfaH protein. Mol Microbiol. 2003;47(6):1653–1667.
http://www.ncbi.nlm.nih.gov/pubmed/12622819
113. Nagy G, Dobrindt U, Schneider G, et al. Loss of regulatory protein RfaH attenuates virulence of uropathogenic Escherichia coli. Infect Immun. 2002;70(8):4406–4413.
http://www.ncbi.nlm.nih.gov/pubmed/12117951
114. Johnson DE, Drachenberg C, Lockatell CV, et al. The role of cytotoxic necrotizing factor-1 in colonization and tissue injury in a murine model of urinary tract infection. FEMS Immunol Med Microbiol. 2000;28(1):37–41.
http://www.ncbi.nlm.nih.gov/pubmed/10767605
115. Rippere-Lampe KE, O'Brien AD, Conran R, et al. Mutation of the gene encoding cytotoxic necrotizing factor type 1 (cnf(1)) attenuates the virulence of uropathogenic Escherichia coli. Infect Immun. 2001;69(6):3954–3964.
116. Guyer DM, Henderson IR, Nataro JP, et al. Identification of sat, an autotransporter toxin produced by uropathogenic Escherichia coli. Mol Microbiol. 2000;38(1):53–66.
http://www.ncbi.nlm.nih.gov/pubmed/11029690
117. Guyer DM, Radulovic S, Jones FE, et al. Sat, the secreted autotransporter toxin of uropathogenic Escherichia coli, is a vacuolating cytotoxin for bladder and kidney epithelial cells. Infect Immun. 2002;70(8):4539–4546.
http://www.ncbi.nlm.nih.gov/pubmed/12117966
118. Henderson IR, Navarro-Garcia F, Nataro JP. The great escape: structure and function of the autotransporter proteins. Trends Microbiol. 1998;6(9):370–378.
http://www.ncbi.nlm.nih.gov/pubmed/9778731
119. Henderson JP, Crowley JR, Pinkner JS, et al. Quantitative metabolomics reveals an epigenetic blueprint for iron acquisition in uropathogenic Escherichia coli. PLoS Pathog. 2009;5(2):e1000305.
120. Clermont O, Bonacorsi S, Bingen E. The Yersinia high-pathogenicity island is highly predominant in virulence-associated phylogenetic groups of Escherichia coli. FEMS Microbiol Lett. 2001;196(2):153–157.
http://www.ncbi.nlm.nih.gov/pubmed/11267772
121. Russo TA, Carlino UB, Johnson JR. Identification of a new iron-regulated virulence gene, ireA, in an extraintestinal pathogenic isolate of Escherichia coli. Infect Immun. 2001;69(10):6209–6216.
122. Russo TA, McFadden CD, Carlino-MacDonald UB, et al. IroN functions as a siderophore receptor and is a urovirulence factor in an extraintestinal pathogenic isolate of Escherichia coli. Infect Immun. 2002;70(12):7156–7160.
123. Torres AG, Redford P, Welch RA, et al. TonB-dependent systems of uropathogenic Escherichia coli: aerobactin and heme transport and TonB are required for virulence in the mouse. Infect Immun. 2001;69(10):6179–6185.
124. Johnson JR, Kaster N, Kuskowski MA, et al. Identification of urovirulence traits in Escherichia coli by comparison of urinary and rectal E. coli isolates from dogs with urinary tract infection. J Clin Microbiol. 2003;41(1):337–345.
125. Johnson JR, Stell AL. Extended virulence genotypes of Escherichia coli strains from patients with urosepsis in relation to phylogeny and host compromise. J Infect Dis. 2000;181(1):261–272.
http://www.ncbi.nlm.nih.gov/pubmed/10608775
126. O'Hanley P, Low D, Romero I, et al. Gal-Gal binding and hemolysin phenotypes and genotypes associated with uropathogenic Escherichia coli. N Engl J Med. 1985;313(7):414–420.
http://www.ncbi.nlm.nih.gov/pubmed/2862582
127. Achtman M, Mercer A, Kusecek B, et al. Six widespread bacterial clones among Escherichia coli K1 isolates. Infect Immun. 1983;39(1):315–335.
http://www.ncbi.nlm.nih.gov/pubmed/6218094
128. Russo T, Brown JJ, Jodush ST, et al. The O4 specific antigen moiety of lipo-polysaccharide but not the K54 group 2 capsule is important for urovirulence of an extraintestinal isolate of Escherichia coli. Infect Immun. 1996;64(6):2343–2348.
129. Anderson JD, Eftekhar F, Aird MY, et al. Role of bacterial growth rates in the epidemiology and pathogenesis of urinary infections in women. J Clin Microbiol. 1979;10(6):766–771.
http://www.ncbi.nlm.nih.gov/pubmed/230198
130. Kaye D. Antibacterial activity of human urine. J Clin Invest. 1968;47(10):2374–2390.
http://www.ncbi.nlm.nih.gov/pubmed/4877682
131. Norden CW, Green GM, Kass EH. Antibacterial mechanisms of the urinary bladder. J Clin Invest..1968;47(12):2689–2700.
132. Schlegel JU, Cuellar J, O'Dell RM. Bactericidal effect of urea. J Urol. 1961;86:819–822.
http://www.ncbi.nlm.nih.gov/pubmed/14498520
133. O'Grady F, Cattell WR. Kinetics of urinary tract infection. II. The bladder. Br J Urol. 1966;38(2):156–162.
http://www.ncbi.nlm.nih.gov/pubmed/5934769
134. Baorto DM, Gao Z, Malaviya R, et al. Survival of FimH-expressing enterobac-teria in macrophages relies on glycolipid traffic. Nature. 1997;389(6651):636–639.
http://www.ncbi.nlm.nih.gov/pubmed/9335508
135. Cox CE, Hinman F Jr. Experiments with induced bacteriuria, vesical emptying and bacterial growth on the mechanism of bladder defense to infection. J Urol. 1961;86:739–748.
http://www.ncbi.nlm.nih.gov/pubmed/13881887
136. Martinez JJ, Mulvey MA, Schilling JD, et al. Type 1 pilus-mediated bacterial invasion of bladder epithelial cells. EMBO J. 2000;19(12):2803–2812.
http://www.ncbi.nlm.nih.gov/pubmed/10856226
137. Duncan MJ, Li G, Shin JS, et al. Bacterial penetration of bladder epithelium through lipid rafts. J Biol Chem. 2004;279(18):18944–18951.
http://www.ncbi.nlm.nih.gov/pubmed/14976212
138. Abraham S, Shin J, Malaviya R. Type 1 fimbriated Escherichia coli mast cell interactions in cystitis. J Infect Dis. 2001;183(Suppl 1):S51–S55.
139. Justice SS, Hung C, Theriot JA, et al. Differentiation and developmental pathways of uropathogenic Escherichia coli in urinary tract pathogenesis. Proc Natl Acad Sci USA. 2004;101(5):1333–1338.
http://www.ncbi.nlm.nih.gov/pubmed/14739341
140. Mulvey MA, Schilling JD, Hultgren SJ. Establishment of a persistent Escherichia coli reservoir during the acute phase of a bladder infection. Infect Immun. 2001;69(7):4572–4579.
141. Anderson GG, Palermo JJ, Schilling JD, et al. Intracellular bacterial biofilm-like pods in urinary tract infections. Science. 2003;301(5629):105–107.
http://www.ncbi.nlm.nih.gov/pubmed/12843396
142. Hunstad DA, Justice SS. Intracellular lifestyles and immune evasion strategies of uropathogenic Escherichia coli. Annu Rev Microbiol. 2010;64:203–221.
http://www.ncbi.nlm.nih.gov/pubmed/20825346
143. Mulvey MA, Lopez-Boado YS, Wilson CL, et al. Induction and evasion of host defenses by type 1-piliated uropathogenic Escherichia coli. Science. 1998;282(5393):1494–1497.
http://www.ncbi.nlm.nih.gov/pubmed/9822381
144. Lane MC, Alteri CJ, Smith SN, et al. Expression of flagella is coincident with uropathogenic Escherichia coli ascension to the upper urinary tract. Proc Natl Acad Sci USA. 2007;104(42):16669–16674.
145. Källenius G, Möllby R, Svenson, SB, et al. Occurrence of P-fimbriated Escherichia coli in urinary tract infections. Lancet. 1981;2(8260–8261):1369–1372.
http://www.ncbi.nlm.nih.gov/pubmed/6171697
146. Mansson L. Real-time studies of the progression of bacterial infections and immediate tissue responses in live animals. Cell Microbiol. 2007;9(2):413–424.
http://www.ncbi.nlm.nih.gov/pubmed/16953802
147. Melican K, Richter-Dahlfors A. Real-time live imaging to study bacterial infections in vivo. Curr Opin Microbiol. 2009;12(1):31–36.
http://www.ncbi.nlm.nih.gov/pubmed/19135408
148. Tseng CC, Huang JJ, Wang MC, et al. PapG II adhesin in the establishment and persistence of Escherichia coli infection in mouse kidneys. Kidney Int. 2007;71(8):764–770.
http://www.ncbi.nlm.nih.gov/pubmed/17290293

149. Hagberg L, Engberg I, Freter R, et al. Ascending, unobstructed urinary tract infection in mice caused by pyelonephritogenic Escherichia coli of human origin. Infect Immun. 1983;40(1):273–283.
http://www.ncbi.nlm.nih.gov/pubmed/6339403
150. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. Am J Med. 2002;113(Suppl 1A):14S–19S.
151. Chassin C, Goujon JM, Darche S, et al. Renal collecting duct epithelial cells react to pyelonephritis-associated Escherichia coli by activating distinct TLR4-dependent and -independent inf ammatory pathways. J Immunol. 2006;177(7):4773–4784.
152. Chassin C, Vimont S, Cluzeaud F, et al. TLR4 facilitates translocation of bac-teria across renal collecting duct cells. J Am Soc Nephrol. 2008;19(12): 2364–2374.
http://www.ncbi.nlm.nih.gov/pubmed/18753256
153. Melican K, Boekel J, Ryden-Aulin M, et al. Novel innate immune functions revealed by dynamic, real-time live imaging of bacterial infections. Crit Rev Immunol. 2010;30(2):107–117.
http://www.ncbi.nlm.nih.gov/pubmed/20370624
154. Melican K, Boekel J, Mansson LE, et al. Bacterial infection-mediated mucosal signalling induces local renal ischaemia as a defence against sepsis. Cell Microbiol. 2008;10(10):1987–1998.
155. Tanner GA, Knopp LC. Glomerular blood f ow after single nephron obstruction in the rat kidney. Am J Physiol. 1986;250(1 Pt 2):F77–F85.
156. Chassin C, Hornef MW, Bens M, et al. Hormonal control of the renal immune response and antibacterial host defense by arginine vasopressin. J Exp Med. 2007;204(12):2837–2852.
157. Chromek M, Slamová Z, Bergman P, et al. The antimicrobial peptide cathelicidin protects the urinary tract against invasive bacterial infection. Nat Med. 2006;12(6):636–641.
158. Nicolle LE. Asymptomatic bacteriuria: review and discussion of the IDSA guidelines. Int J Antimicrob Agents. 2006;28(Suppl 1):S42–S48.
159. Roos V, Nielsen EM, Klemm P. Asymptomatic bacteriuria Escherichia coli strains: adhesins, growth and competition. FEMS Microbiol Lett. 2006;262(1): 22–30.
http://www.ncbi.nlm.nih.gov/pubmed/16907735
160. Janeway C, Stanley J, Janeway C, et al. Immunobiology. Garland Pub. 2005:823.
161. Lemaitre B, Nicolas E, Michaut L, et al. The dorsoventral regulatory gene cassette spätzle/Toll/cactus controls the potent antifungal response in Drosophila adults. Cell. 1996;86(6):973–983.
http://www.ncbi.nlm.nih.gov/pubmed/22611248
162. Uematsu S, Akira S. Toll-like receptors and innate immunity. J Mol Med. 2006;84(9):712–725.
http://www.ncbi.nlm.nih.gov/pubmed/16924467
163. Backhed F, Soderhall M, Ekman P, et al. Induction of innate immune responses by Escherichia coli and purified lipopolysaccharide correlate with organ- and cell-specific expression of Toll-like receptors within the human urinary tract. Cell Microbiol. 2001;3(3):153–158.
http://www.ncbi.nlm.nih.gov/pubmed/11260138
164. Backhed F. Structural requirements for TLR4-mediated LPS signalling: a biological role for LPS modifications. Microbes Infect. 2003;5(12):1057–1063.
165. Backhed F. Induction of innate immune responses by Escherichia coli and purified lipopolysaccharide correlate with organ-and cell-specific expression of Toll-like receptors within the human urinary tract. Cell Microbiol. 2001;3(3): 153–158.
166. Poltorak A, He X, Smirnova I, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science. 1998;282(5396): 2085–2088.
http://www.ncbi.nlm.nih.gov/pubmed/9851930
167. Samuelsson P, Hang L, Wullt B, et al. Toll-like receptor 4 expression and cytokine responses in the human urinary tract mucosa. Infect Immun. 2004;72(6):3179–3186.
http://www.ncbi.nlm.nih.gov/pubmed/15155619
168. Zhang D, Zhang G, Hayden MS, et al. A toll-like receptor that prevents infection by uropathogenic bacteria. Science. 2004;303(5663):1522–1526.
169. Andersen-Nissen E, Hawn TR, Smith KD, et al. Cutting edge: Tlr5-/- mice are more susceptible to Escherichia coli urinary tract infection. J Immunol. 2007;178(8):4717–4720.
170. El-Achkar TM, Huang X, Plotkin Z, et al. Sepsis induces changes in the expression and distribution of Toll-like receptor 4 in the rat kidney. Am J Physiol Renal Physiol. 2006;290(5):F1034–F1043.
171. Ragnarsdóttir B, Fischer H, Godaly G, et al. TLR-and CXCR1-dependent innate immunity: insights into the genetics of urinary tract infections. Eur J Clin Invest. 2008;38(Suppl 2):12–20.
172. Ragnarsdóttir B, Samuelsson M, Gustafsson MC, et al. Reduced toll-like receptor 4 expression in children with asymptomatic bacteriuria. J Infect Dis.2007;196(3):475–484.
http://www.ncbi.nlm.nih.gov/pubmed/17597463
173. Karoly E, Fekete A, Banki NF, et al. Heat shock protein 72 (HSPA1B) gene polymorphism and Toll-like receptor (TLR) 4 mutation are associated with increased risk of urinary tract infection in children. Pediatr Res. 2007;61(3): 371–374.
http://www.ncbi.nlm.nih.gov/pubmed/17314700
174. Heinzelmann M, Mercer-Jones MA, Passmore JC. Neutrophils and renal failure. Am J Kidney Dis. 1999;34(2):384–399.
http://www.ncbi.nlm.nih.gov/pubmed/10430993
175. Lundstedt AC, McCarthy S, Gustafsson MCU, et al. A genetic basis of susceptibility to acute pyelonephritis. PloS One. 2007;2(9):e825.
176. Williams TW, Lyons JM, Braude AI. In vitro lysis of target cells by rat polymorphonuclear leukocytes isolated from acute pyelonephritic exudates. J Immunol. 1977;119(2):671–674.
177. Glauser MP, Lyons JM, Braude AI. Prevention of chronic experimental pyelonephritis by suppression of acute suppuration. J Clin Invest. 1978;61(2): 403–407.
http://www.ncbi.nlm.nih.gov/pubmed/621280
178. Sullivan M, Harvey R, Shimamura T. The effects of cobra venom factor, an inhibitor of the complement system, on the sequence of morphological events in the rat kidney in experimental pyelonephritis. Blood. 1977;50(3):267.
http://www.ncbi.nlm.nih.gov/pubmed/329591
179. Svensson M, Irjala H, Alm P, et al. Natural history of renal scarring in susceptible mIL-8Rh-/- mice. Kidney Int. 2005;67(1):103–110.
180. Winberg J, Andersen H, Hanson L, et al. Studies of urinary tract infections in infancy and childhood. I. Antibody response in different types of urinary tract infections caused by coliform bacteria. Br Med J. 1963;2(5356): 524–527.
http://www.ncbi.nlm.nih.gov/pubmed/14042765
181. Kantele A, Papunen R, Virtanen E, et al. Antibody-secreting cells in acute urinary tract infection as indicators of local immune response. J Infect Dis. 1994;169(5):1023–1028.
182. Thomas V, Shelokov A, Forland M. Antibody-coated bacteria in the urine and the site of urinary-tract infection. N Engl J Med. 1974;290(11):588–590.
http://www.ncbi.nlm.nih.gov/pubmed/4591064
183. Jones SR, Smith JW, Sanford JP. Localization of urinary-tract infections by detection of antibody-coated bacteria in urine sediment. N Engl J Med. 1974;290(11):591–593.
http://www.ncbi.nlm.nih.gov/pubmed/4591065
184. Vosti KL, Monto AS, Rantz LA. Host-parasite interaction in patients with infections due to Escherichia coli. II. Serologic response of the host. J Lab Clin Med. 1965;66(4):613–626.
http://www.ncbi.nlm.nih.gov/pubmed/4954172
185. Svanborg-Edén C, Svennerholm AM. Secretory immunoglobulin A and G antibodies prevent adhesion of Escherichia coli to human urinary tract epithelial cells. Infect Immun. 1978;22(3):790–797.
http://www.ncbi.nlm.nih.gov/pubmed/83303
186. Emödy L, Batai I Jr, Kerényi M, et al. Anti-Escherichia coli alpha-hemolysin in control and patient sera. Lancet. 1982;2(8305):986.
http://www.ncbi.nlm.nih.gov/pubmed/6127482
187. Seetharama S, Cavalieri SJ, Snyder IS. Immune response to Escherichia coli alpha-hemolysin in patients. J Clin Microbiol. 1988;26(5):850–856.
http://www.ncbi.nlm.nih.gov/pubmed/2454938
188. O'Hanley P, Lalonde G, Ji G. Alpha-hemolysin contributes to the pathogenicity of piliated digalactoside-binding Escherichia coli in the kidney: efficacy of an alpha-hemolysin vaccine in preventing renal injury in the BALB/c mouse model of pyelonephritis. Infect Immun 1991;59(3):1153–1161.
189. Kurnick JT, McCluskey RT, Bhan AK, et al. Escherichia coli-specific T lymphocytes in experimental pyelonephritis. J Immunol. 1988;141(9):3220–3226.
http://www.ncbi.nlm.nih.gov/pubmed/2459249
190. Sivan Y, Griffel B, Medalia O, et al. Comparative histology of the mouse bladder following initial infection and re-infection with Escherichia coli. J Pathol. 1982;138(4):353–364.
http://www.ncbi.nlm.nih.gov/pubmed/6757396
191. Miller T, Burnham S, Simpson G. Selective deficiency of thymus-derived lymphocytes in experimental pyelonephritis. Kidney Int. 1975;8(2):88–97.
192. Hedges S, Linder H, de Man P, et al. Cyclosporin-dependent, nu-independent, mucosal interleukin 6 response to gram-negative bacteria. Scand J Immunol. 1990;31(3):335–343.
http://www.ncbi.nlm.nih.gov/pubmed/2320952
193. Komori HK, Meehan TF, Havran WL. Epithelial and mucosal gamma delta T cells. Curr Opin Immunol. 2006;18(5):534–538.
http://www.ncbi.nlm.nih.gov/pubmed/16837181

194. Sivick KE, Schaller MA, Smith SN, et al. The innate immune response to uropathogenic Escherichia coli involves IL-17A in a murine model of urinary tract infection. J Immunol. 2010;184(4):2065–2075.
http://www.ncbi.nlm.nih.gov/pubmed/20083670
195. Orskov I, Ferencz A, Orskov F. Tamm-Horsfall protein or uromucoid is the normal urinary slime that traps type 1 fimbriated Escherichia coli. Lancet 1980;1(8173):887.
http://www.ncbi.nlm.nih.gov/pubmed/6103253
196. Dulawa J, Jann K, Thomsen M, et al. Tamm Horsfall glycoprotein interferes with bacterial adherence to human kidney cells. Eur J Clin Invest. 1988;18(1):87–91.
http://www.ncbi.nlm.nih.gov/pubmed/3130265
197. Lynn KL, Shenkin A, Marshall RD. Factors affecting excretion of human urinary Tamm-Horsfall glycoprotein. Clin Sci (Lond). 1982;62(1):21–26.
http://www.ncbi.nlm.nih.gov/pubmed/7198948
198. Säemann MD, Weichhart T, Hörl WH, et al. Tamm-Horsfall protein: a multilayered defence molecule against urinary tract infection. Eur J Clin Invest. 2005;35(4):227–235.
http://www.ncbi.nlm.nih.gov/pubmed/15816991
199. Zasloff M. Antimicrobial peptides, innate immunity, and the normally sterile urinary tract. J Am Soc Nephrol. 2007;18(11):2810–2816.
200. Selsted ME, Ouellette AJ. Mammalian defensins in the antimicrobial immune response. Nat Immunol. 2005;6(6):551–557.
201. Lehrer RI. Multispecific myeloid defensins. Curr Opin Hematol 2007;14(1):16–21.
http://www.ncbi.nlm.nih.gov/pubmed/17133095
202. Turner J, Cho Y, Dinh NN, et al. Activities of LL-37, a cathelin-associated antimicrobial peptide of human neutrophils. Antimicrob Agents Chemother. 1998;42(9):2206–2214.
http://www.ncbi.nlm.nih.gov/pubmed/9736536
203. Weichhart T, Haidinger M, Hörl WH, et al. Current concepts of molecular defence mechanisms operative during urinary tract infection. Eur J Clin Invest. 2008;38(Suppl 2):29–38.
http://www.ncbi.nlm.nih.gov/pubmed/18826479
204. Abrink M, Larsson E, Gobl A, et al. Expression of lactoferrin in the kidney: implications for innate immunity and iron metabolism. Kidney Int. 2000;57(5):2004–2010.
205. Gudmundsson GH, Agerberth B, Odeberg J, et al. The human gene FALL39 and processing of the cathelin precursor to the antibacterial peptide LL-37 in granulocytes. Eur J Biochem. 1996;238(2):325–332.
http://www.ncbi.nlm.nih.gov/pubmed/8681941
206. Oren Z, Lerman JC, Gudmundsson GH, et al. Structure and organization of the human antimicrobial peptide LL-37 in phospholipid membranes: relevance to the molecular basis for its non-cell-selective activity. Biochem J. 1999;341(Pt 3):501–513.
207. Lomberg H, Jodal U, Eden CS, et al. P1 blood group and urinary tract infection. Lancet. 1981;1(8219):551–552.
http://www.ncbi.nlm.nih.gov/pubmed/6111646
208. Nielubowicz GR, Mobley HLT. Host-pathogen interactions in urinary tract infection. Nature reviews. Urology. 2010;7(8):430–441.
http://www.ncbi.nlm.nih.gov/pubmed/20647992
209. Hagberg L, Hull R, Hull S, et al. Difference in susceptibility to gram-negative urinary tract infection between C3H/HeJ and C3H/HeN mice. Infect Immun. 1984;46(3):839–844.
http://www.ncbi.nlm.nih.gov/pubmed/6389367
210. Fischer H, Yamamoto M, Akira S, et al. Mechanism of pathogen-specific TLR4 activation in the mucosa: fimbriae, recognition receptors and adaptor protein selection. Eur J Immunol. 2006;36(2):267–277.
http://www.ncbi.nlm.nih.gov/pubmed/16385628
211. Godaly G, Bergsten G, Frendéus B, et al. Innate defences and resistance to gram negative mucosal infection. Adv Exp Med Biol. 2000;485:9–24.
http://www.ncbi.nlm.nih.gov/pubmed/11109082
212. Hang L, Frendéus B, Godaly G, et al. Interleukin-8 receptor knockout mice have subepithelial neutrophil entrapment and renal scarring following acute pyelonephritis. J Infect Dis. 2000;182(6):1738–1748.
213. Frendéus B, Godaly G, Hang L, et al. Interleukin 8 receptor deficiency confers susceptibility to acute experimental pyelonephritis and may have a human counterpart. J Exp Med. 2000;192(6):881–890.
214. Schilling JD, Lorenz RG, Hultgren SJ. Effect of trimethoprim-sulfamethoxazole on recurrent bacteriuria and bacterial persistence in mice infected with uropathogenic Escherichia coli. Infect Immun. 2002;70(12): 7042–7049.
215. Goldfarb DA, Nally, JV Jr, Schreiber, MJ Jr. Etiology, pathogenesis and man-agement of renal failure. In: Wein, AJ, Kavoussi, LR, Novick, AC, Partin, AW, Peters CA, eds. Campbell-Walsh urology. 9th ed. Philadelphia: Elsevier, 2007.
216. Molitoris BA, Marrs J. The role of cell adhesion molecules in ischemic acute renal failure. Am J Med. 1999;106(5):583–592.
http://www.ncbi.nlm.nih.gov/pubmed/10335732
217. Goligorsky MS, Lieberthal W, Racusen L, et al. Integrin receptors in renal tubular epithelium: new insights into pathophysiology of acute renal failure. Am J Physiol. 1993;264(1 Pt 2):F1–F8.
218. Kerrn MB, Struve C, Blom J, et al. Intracellular persistence of Escherichia coli in urinary bladders from mecillinam-treated mice. J Antimicrob Chemother. 2005;55(3):383–386.
http://www.ncbi.nlm.nih.gov/pubmed/15681580
219. Keane WF, Welch R, Gekker G, et al. Mechanism of Escherichia coli alpha-hemolysin-induced injury to isolated renal tubular cells. Am J Pathol. 1987;126(2):350–357.
http://www.ncbi.nlm.nih.gov/pubmed/3030115
220. Mobley HL, Green DM, Trifillis AL, et al. Pyelonephritogenic Escherichia coli and killing of cultured human renal proximal tubular epithelial cells: role of hemolysin in some strains. Infect Immun. 1990;58(5):1281–1289.
221. Roberts JA. Pathogenesis of pyelonephritis. J Urol. 1983;129(6):1102–1106.
http://www.ncbi.nlm.nih.gov/pubmed/6343637
222. Roberts JA, Roth JK, Domingue G, et al. Immunology of pyelonephritis in the primate model. V. Effect of superoxide dismutase. J Urol. 1982;128(6): 1394–1400.
http://www.ncbi.nlm.nih.gov/pubmed/6759691
223. Meylan PR, Markert M, Bille J, et al. Relationship between neutrophil-mediated oxidative injury during acute experimental pyelonephritis and chronic renal scarring. Infect Immun. 1989;57(7):2196–2202.
224. Kaack MB, Dowling KJ, Patterson GM, et al. Immunology of pyelonephritis. VIII. E. coli causes granulocytic aggregation and renal ischemia. J Urol. 1986;136(5):1117–1122.
http://www.ncbi.nlm.nih.gov/pubmed/3534307
225. Ashworth SL, Sandoval RM, Hosford M, et al. Ischemic injury induces ADF relocalization to the apical domain of rat proximal tubule cells. Am J Physiol Renal Physiol. 2001;280(5):F886–F894.
226. Bonventre JV, Zuk A. Ischemic acute renal failure: an inflammatory disease? Kidney Int. 2004;66(2):480–485.
http://www.ncbi.nlm.nih.gov/pubmed/15253693
227. Evan AP, Tanner GA. Proximal tubule morphology after single nephron obstruction in the rat kidney. Kidney Int. 1986;30(6):818–827.
http://www.ncbi.nlm.nih.gov/pubmed/3820934
228. Misseri R, Rink RC, Meldrum DR, et al. Inflammatory mediators and growth factors in obstructive renal injury. J Surg Res. 2004;119(2):149–159.
http://www.ncbi.nlm.nih.gov/pubmed/15145697
229. Molitoris BA. Ischemia-induced loss of epithelial polarity: potential role of the actin cytoskeleton. Am J Physiol. 1991;260(6 Pt 2):F769–F778.
230. Schwartz N, Hosford M, Sandoval RM, et al. Ischemia activates actin depolymerizing factor: role in proximal tubule microvillar actin alterations. Am J Physiol. 1999;276(4 Pt 2):F544–F551.
231. Sutton TA, Mang HE, Campos SB, et al. Injury of the renal microvascular endothelium alters barrier function after ischemia. Am J Physiol Renal Physiol. 2003;285(2):F191–F198.
232. Tanner GA. Effects of kidney tubule obstruction on glomerular function in rats. Am J Physiol. 1979;237(5):F379–F385.
233. Wagenlehner FME, Weidner W, Perletti G, et al. Emerging drugs for bacterial urinary tract infections. Expert Opin Emerg Drugs. 2010;15(3):375–397.
234. Wagenlehner FME, Naber KG. Treatment of bacterial urinary tract infections: presence and future. Eur Urol. 2006;49(2):235–244.
http://www.ncbi.nlm.nih.gov/pubmed/16413668
235. Foo LY, Lu Y, Howell AB, et al. A-Type proanthocyanidin trimers from cranberry that inhibit adherence of uropathogenic P-fimbriated Escherichia coli. J Nat Prod. 2000;63(9):1225–1228.
http://www.ncbi.nlm.nih.gov/pubmed/11000024
236. Foo LY, Lu Y, Howell AB, et al. The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-fimbriated Escherichia coli in vitro. Phytochemistry. 2000;54(2):173–181.
237. Zafriri D, Ofek I, Adar R, et al. Inhibitory activity of cranberry juice on adherence of type 1 and type P fimbriated Escherichia coli to eucaryotic cells. Antimicrob Agents Chemother. 1989;33(1):92–98.