Urinary tract infections

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ABSTRACT

Urinary tract infections (UTI) are one of the most prevalent bacterial infections found in humans. 20. Uropathogenic Escherichia coli (UPEC) account for over 90% of uncomplicated UTI subsequently making it the most common etiological agent answerable for uncomplicated UTI. WW Pathogenic E. coli such as UPEC typically express virulence factors – molecules directly concerned with pathogenesis but accessory/ancillary to normal metabolic function. Accordingly this confers an advantage on the pathogens by enabling them to exploit their hosts in ways inaccessible to commensal strains. 10. The UPEC genome accommodates an array of virulence and fitness factors specifically enabling it to colonise, survive and infect the mammalian urinary tract. WW +8. They utilise a number of fimbriae such as Type-1, P-, S- and F1C-fimbriae as adhesins to the mucosal epithelium as well as toxins, iron acquisition systems and factors involved in evading the host immune system such as capsular polysaccharide.

INTRODUCTION

Urinary tract infections can be broadly split into two types – complicated and uncomplicated. The former referring to a UTI of an anatomically unobstructed urinary tract, where the individual maintains a normal immune status whereas the latter involves the possession of an abnormal urinary tract and immuno-compromisation. 22. An assortment of mechanical factors predispose an individual to contracting a complicated UTI, i. e. anything that causes disruption to i) normal urine flow, ii) complete emptying of bladder or iii) facilitates organisms access to the bladder. Hooton. Particularly prone are people who have lost neurologic control of their bladder and sufferers of

vesico-urethral reflux (a condition where urine moves back up the ureters from the bladder). 11 In general women are fourteen times more likely than their male counterparts to suffer from a UTI.. the female urethra is not only very short at only 5cm long hence easier to traverse but also is positioned at a hazardous proximity to the anus, in comparison the male urethra is surrounded by a drier environment and is much longer.

In females the causative organism can be propelled into periurethral tissues during sexual intercourse consequently assisting the progression of bacteria up the urethra.

Pregnancy is another contributing factor due to the resulting lethargic action of the bladder muscle wall.

The pathogenesis of UTI begins when the uropathogens position themselves at a location outside the urinary tract and thus form a reservoir for infection 20. These organisms colonize form the perineal region or the feces and ascend to the bladder via the urinary tract WW+8. The ‘ ascending route’ is how UPEC is considered to enter, whereby the bacteria ascend up the urethra into the bladder causing cystitis. However if left untreated the UPEC sometimes travel up even further to the kidneys via the urethers thus causing pyelonephritis. 12 + ww. The ‘ hematogenous route’ involves seeding of the kidney during bacteremia and is a lot less common; gram positive bacteria such as Staphylococcus aureus are the main causative agents. 12 Cystitis and pyelonephritis are the two fundamental types of infection involved in UTI. Cystitis is a lower urinary tract infection whereby the bladder becomes inflamed through infection with UPEC. Symptoms

include frequency, urgency, dysuria (painful voiding), cloudy or foul smelling urine (due to pyuria) and suprapubic pain. Mims

Pyelonephritis (from the Greek pyelum – pelvis, nephros- of the kidney) is a more serious infection however as it is an upper urinary tract infection affecting the kidneys. This presents symptoms such as dysuria, fever, rigors, malaise, loin pain and tenderness. Wikipedia.

Uropathogenic E. coli are the predominant cause of UTI with over 40% of women and 12% of men likely to experience at least one UTI in their lifetime. This coupled with the fact that in the U. S. A alone the estimated cost to society is over three billion dollars means it is essential we learn as much about the pathogenesis of UPEC as possible. WW.

The word pathogenesis comes from the Latin “ pathos” meaning disease and “ genesis” meaning creation. It can be described as the mechanism by which an etiological factor causes a disease. UPEC yields numerous virulence factors that aid in the colonisation of the urinary tract and also induce fitness on the pathogen. Adherence can be described as the first step in the pathogenesis of UPEC in UTI as adhesion is necessary to allow colonisation, then to penetrate. After colonisation it allows penetration but also confers other advantages such as a) secreted exotoxin is in close contact with target cells b) increased protection from host defences and most importantly in the initial stages c) resistance to the hydrodynamic force of urine flow. 12

UPEC utilize a number of surface expressed appendages called adhesions or fimbriae to achieve adhesion to uroepithelial cells 8. Type-1 fimbriae are one of the most imperative virulence factors involved in the pathogenesis of

UPEC as it is through their adherence to the uroepithelial cells that achieves the establishment of UTI. 3

These fimbriae are highly conserved in UPEC, being found in over 90% of isolates. 1, 20. The fim gene cluster encodes for Type-1 fimbriae with five of the genes responsible for structural proteins: – FimA, FimI, FimF, FimG and FimH. Jones et 96- 20. In vivo microarray studies present's data that show the fim genes are expressed 12-72 times more than all of the 11 other fimbrial gene clusters. 5 In regards to the actual structural appearance of Type-1 fimbriated UPEC approximately 200-500 peritrichously arranged fimbriae are seen on the surface. Schembri et al '02 – 20. The initial binding of UPEC to uroepithelial cells is conferred by the FimH adhesin to terminally positioned D-mannose moieties of glycoproteins exposed on the apical surface. 7. The stratified bladder epithelium is characterized by a superficial layer of " umbrella cell"

It is a specific integral membrane protein, UP1a, which has been identified as the urothelial receptor for the FimH adhesin of Type-1 fimbriae. 7.

UP1a is part of a unique membrane structure called the asymmetric unit membrane (AUM) that is comprised of 3 other integral membrane proteins, the uroplakins (UP's) UPIa, Ib, III and IIIa. 15. The AUM looks like rigid plaques and structurally form a 16nm receptor complex assembled into hexagonally packed two-dimensional crystals that are essential in maintaining the permeability barrier function. 15

In addition to creating the foothold for infection in the pathogenesis of UPEC in UTI through adherence, Type-1 fimbriae also play a role in the invasion of

host cells. FimH binding triggers host cell signaling cascades enabling UPEC to be internalized via a ‘ zipper-type’ invasion mechanism. 7 Overall Type-1 fimbriae play a crucial role in establishment of lower UTI through key roles in adhesion and invasion within the bladder.

It is P-fimbriae that are noted to play an essential part in pathogenesis of upper UTI, i. e. pyelonephritis. 12 The pap (pyelonephritis-associated pilli) gene cluster, found on the UPEC chromosome itself, encodes for P-fimbriae. 20.

This pap gene cluster is made up of eleven genes with six encoding for structural proteins that form the P-fimbria structural unit: – PapA, PapK, PapF, PapG, PapE and PapH. 20. P-fimbrial lectins, (specifically the PapG adhesin) recognise a digalactoside component of the P blood group antigen and also Gal (a 1-4) Gal b galbiose disaccharide receptors extensively positioned on the surface of uroepithelial cells in 99% of the population. 12+13 The expression of P-fimbriae undergoes phase variation (ON/OFF) with this being controlled by a combination of Dam methylation, leucine-responsive regulatory protein (Lrp) and the PapB and PapI regulators. 3, 20 Despite the strong epidemiological association of P-fimbriae with UPEC strains causing acute pyelonephritis, it’s precise function during the pathogenesis of a UTI remains elusive. 1. However the plethora of P-fimbrial receptors in human renal tissue coupled with their association with acute disease severity (found in 90% acute pyelonephritis) suggests that P-fimbriae are indeed necessary for colonisation and perhaps invasion of the upper urinary tract. 20+Johnson.

In addition to Type-1 and P-fimbriae, there are a number of other fimbriae found to be albeit not as imperative, but nonetheless associated with the pathogenesis of UPEC in UTI. F1-C (Foc) fimbriae bear a resemblance to Type-1 fimbriae in their organelle structure and genetic organisation. The F1-C fimbriae mediate binding to globotriaosylceramide targets found solely in the kidneys as well as galactosyleramide on epithelial cells in the bladder and kidneys.