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Evolution of Urinary Tract Infection Understanding: From Ancient Insights to Contemporary Perspectives

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ABTRACT

This research delves into the historical understanding and evolutionary trajectory of urinary tract infections (UTIs) from ancient descriptions to modern comprehension. The study explores the historical perspectives from ancient Egyptian insights to Hippocratic beliefs and traces the evolution of management approaches until the discovery of microorganisms as causative agents. Advancements in antimicrobial therapy and the changing landscape of UTI treatment strategies are also outlined, considering the emergence of antibiotic resistance. Defining UTI, the research emphasizes the differentiation between asymptomatic bacteriuria and UTI, highlighting crucial aspects and clinical implications. The prevalence of UTIs across different demographics and regions, especially in children, is examined. Variations in prevalence rates and contributing factors are explored in detail, considering regional disparities, age groups, and gender differences. Moreover, the research identifies several risk factors contributing to UTI occurrence, including gender, age, uncircumcision in males, improper toilet training, vesicoureteral reflux, and other anatomical and behavioral aspects. It also delves into the pathophysiology of UTIs, elucidating the multifaceted factors involved, such as aetiologic agents, anatomical variations, immunological factors, and genetic influences affecting the location, course, and prognosis of UTIs. The clinical forms of UTIs, namely acute pyelonephritis and cystitis, are outlined, delineating the symptoms, diagnostic approaches, and clinical implications associated with each form. The research emphasizes the importance of accurate differentiation between these clinical forms for appropriate treatment and long-term consequences, particularly renal scarring and other complications associated with pyelonephritis. In summary, this comprehensive review consolidates historical insights, epidemiological trends, risk factors, pathophysiological mechanisms, and clinical manifestations to offer a holistic understanding of UTIs, providing valuable insights for effective management and future research directions.

Keywords: Urinary tract infection, historical perspective, prevalence, risk factors, pathophysiology, clinical forms, antimicrobial therapy.

Historical Perspective of Urinary Tract Infection

Urinary tract infections have been recognized since ancient times with the first documented description in the Ebers Papyrus dated to 1550 B.C [1]. It was described by the Egyptians as "sending forth heat from the bladder" [2]. Hippocrates believed that the disease was caused by disharmony of the four humours and accordingly diagnosed urinary disorders [3]. The early 19th century provided detailed descriptions of UTIs without the knowledge that

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they were caused by microorganisms [4]. Management included hospitalization, bed rest, attention to diet, plasters, narcotics, herbal enemas, douches and judicial bleeding (direct bleeding, cupping, and leeches) [5,6].

In the later part of the 19th century, microorganisms were discovered as the causative agents of infectious diseases in general and inflammation associated with urinary diseases in particular provided a basis for physicians to critically examine management approaches and develop evidence based strategies for urinary tract infection treatment [1]

The most profound advancement in UTI management occurred during the 20th century with the discovery of antimicrobial agents [3]. Nitrofurantoin was the first confirmed effective and safe antimicrobial therapy for UTI but its spectrum of activity was limited [3]. The first quinolone (nalidixic acid) was introduced in 1962 and was only used for treatment of UTIs [3]. Amoxicillin and other beta-lactam antimicrobials were introduced in the 1970s. However, the wide spread use of these antibiotics led to the emergence of resistance [3]. Following this development there was a gradual change to trimethoprim-sulfamethoxazole (TMP/SMX) as first line therapy for UTI. Similarly, the extensive use of TMP/SMX also led to progressive development of resistance, limiting the clinical usefulness of the drug in the modern management of UTI [3]. The first fluoroquinolone (ciprofloxacin) was introduced in the 1980s and was found to be more potent and had a wider spectrum of activity than nalidixic acid [3].

Definition of Urinary Tract Infection

Urinary tract infection (UTI) is a pure growth of an acknowledged uropathogen in the urinary tract [6-9]. Broadly, UTI can also refer to any infection that affects any part of the urinary tract including urethra, bladder, ureters and kidneys [10-12]. Infection of the lower urinary tract is known as cystitis whereas the infection of the upper urinary tract consisting of the kidney and its pelvis is known as pyelonephritis [13-15]. Asymptomatic bacteriuria should not be misinterpreted as urinary tract infection hence it is important to highlight the differences between it and UTI to avoid unnecessary antibiotic administration. Asymptomatic bacteriuria refers to a condition in which there is a positive urine culture without any clinical manifestation of infection [16-20]. It can also be referred to as the presence of bacteria in the urine in the absence of any symptoms of lower or upper urinary tract infection [5]. The condition is benign and does not cause renal injury [8]. However in persons with certain conditions such as diabetics, pregnant women , those who have undergone renal transplantation and the elderly , asymptomatic bacteriuria predisposes to a UTI including acute pyelonephritis if untreated [8]. In the general population of children screening and treatment of asymptomatic bacteriuria have not been proven to be beneficial [23-24].

Prevalence of Urinary Tract Infection

UTI is a common infection in children, with its prevalence varying with age and clinical characteristics in different regions of the world. [3,4,5] in a multicentre study of over a thousand children younger than two months in USA documented a prevalence of 9%. Similarly, [26] in a cohort study of 3066 infants also in USA reported a prevalence of 9%. In the same vein [5] in a prospective study of 5000 febrile infants aged one to thirty six months in Taiwan documented a prevalence of 11%. However, in the United Kingdom [4, 26], reported lower prevalence of 5.9% and 2.2% respectively among febrile under-five children. The higher prevalence observed by Zorc [25,26] may have been due to the age of the study participants which were young infants less than three months of age who are more prone to UTI. Similarly [5] attributed the higher prevalence in their study to the high rate of uncircumcision among Taiwanese boys. Review of available literature suggests that UTI may be more common in children in developing countries compared to those in developed countries. In Kumasi Ghana, Adjei and Opoku [6] reported a prevalence of 30% among febrile infants while [28] in Uganda observed a prevalence of 17.8% among febrile under-five children. [29-30],in Tanzania documented prevalence of 39.7% and 16.8% among febrile under-five children while in India [31] reported a prevalence of 10.9% also among febrile under-five children. The varying prevalence reported may be due to the differences in the characteristics of the study participants, as well as, the methodologies employed. The prevalence documented by [6] in Ghana may have been due to the study participants being only infants, which is usually associated with a high rate of congenital anomalies of the kidneys and urinary tract (CAKUT) [32]. On the contrary, while [30] included study participants already receiving antibiotics, [28] excluded children without urinary symptoms and [31] cultured only urine with significant pyuria; these reasons may have accounted for the lower prevalence reported by the researchers. In Nigeria, the prevalence of UTI among febrile under-five children varies across the different regions of the country. [9] in Enugu documented a prevalence of 11%, [10] and [33] observed prevalence of 9% and 6.3% in Benin City and Ibadan respectively. A much lower prevalence of 4.4% and 4.6% were documented by [34] in Calabar and [35] in Jos respectively. The lower prevalence observed in Calabar and Jos could be attributed to the high temperature set point for fever used by [34] (>38°C) compared to [9] who used a lower temperature set point of ≥37.6°C and also the fact that [35] cultured only urine of subjects positive for nitrite, leucocyte esterase or both. Thus these authors may have missed some cases of UTI. On the contrary, Rabasa and Gofama[11] in Maiduguri observed a higher prevalence of 13.7% in febrile under-five children. The higher

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prevalence observed by Rabasa and Gofama[11] may have been due to the significant proportion of the study participants being malnourished and thus increasing the risk of infections, including UTI [11].

Risk Factors for Urinary Tract Infection

Identified risk factors for UTI include female gender, age, uncircumcised male, vesicoureteral reflux, toilet training, voiding dysfunction, obstructive uropathy, urethral instrumentation, wiping from back to front in girls, tight clothing (underwear) [8]. Other risk factors include pinworm infestation, constipation, anatomic abnormality (labial adhesion), neuropathic bladder, sexual activity and pregnancy [8].

Female Gender

Females have been found to be at more risk of UTI compared to males [8]. This has been attributed to the shortness of the urethra and its close proximity to the anus which makes for easy translocation of faeces into the urethra and then into the bladder especially during cleaning after defecation [8]. This has been corroborated by studies in both developed and developing countries [7,9,11,26,36,37,38]. In Philadelphia USA [36] in a study of over 2000 febrile infants, recorded a higher rate (18.8%) of UTI among females compared to the 4.3% among the male participants. Similarly, [26] in a study of over 3000 infants younger than 3months of age, also in the USA, observed that UTI was commoner in females (13%) than males (7%). Similarly, [7] in a study of 500 febrile preschool children in Tamil Nadu, India, observed a prevalence of UTI in females to be 5.5% higher than the 2.9% in boys. In the same way, [37] in a study of 1000 children under 15 years of age in Hazara, Pakistan, documented a very high prevalence of (90.4%) among the females in comparison to the 9.6% prevalence observed in males; though, their study had a high female to male ratio (9.4:1). In Tanzania, both [38, 39] also observed higher prevalence of UTI among females. [38] in a study of 231 febrile children in Mwanza city documented prevalence of 27.0% in females and 12.4% in males while [29] recorded a prevalence of 24% among females and 15.6% among males.

In Nigeria, [9] in Enugu observed a prevalence of 15.9% among females and 7.1% among male participants. Also, in Maiduguri, Rabasa and Gofama [11] documented a higher prevalence of UTI among females (60%) compared to males (40%) and [39] in a case -control study of febrile sickle cell anaemia patients also reported higher prevalence among females in both case and control groups. In contrast, [40] in a study of 169 febrile under-five children in Port Harcourt and [34] in a study of 180 febrile under-five children in Calabar documented a higher prevalence of UTI in males. . Both studies by [34-40] had a larger proportion of males among the study participants and thus may have contributed to their observation.

Age

The predisposition to UTI has been found to vary with age, with the highest risk of UTI seen during infancy [8]. This increased risk in infancy has been attributed to the immaturity of the immune system and the higher prevalence of congenital anomalies of the kidneys and urinary tract (CAKUT), as well as, the dysfunctional voiding especially at the time of toilet training [32]. [4], in a study of 357 children under five years of age in the UK, noted the highest prevalence of 12.5% in subjects younger than three months of age while those three years and older had the least prevalence of 3.2%. Similarly, [9] in a study of 200 febrile under -five in Enugu documented a higher prevalence of 21.1% among infants in contrast to 8.6% among non- infants just as [40] in a similar study in Port Harcourt also observed a higher prevalence of 40.3% among infants. The high prevalence reported by [40] could be due to infants constituting the highest number among the study participants.

On the contrary, some authors have documented higher prevalence of UTI after infancy. [31] in Tamil Nadu, India documented a higher prevalence of 11.9% among participants aged two to five years while in Hazara Pakistan, [37] observed a higher prevalence of 38.1% among 1000 children between three and ten years. This may have been due to the fact that older children constituted a greater proportion of the participants.

Penile Uncircumcision

Studies have shown that uncircumcised males are more prone to UTI than those who have been circumcised [8]. Uncircumcised males are at a higher risk of UTI as a result of colonization of the periurethral area by bacterial pathogens which usually arise from the flora beneath the prepuce [8] [25] in a multicentre study in the USA involving 1025 children 60 days and younger noted a higher prevalence of UTI (21.3%) among uncircumcised males as opposed to 2.3% seen in the circumcised. Similarly, [36] in a cross-sectional study of 2411 children less than two years of age in Philadelphia, USA, documented a higher UTI (8.0%) in uncircumcised males compared to their circumcised counterparts (1.2%). Also the authors found that uncircumcised males were eight times more likely to have UTI than the circumcised. Likewise, [40-43] in a study of 162 febrile infants eight weeks and younger in Taiwan, documented a very high prevalence of UTI (81.8%) among male participants and that all of them were uncircumcised. On the contrary, [43] in Israel, documented a higher rate of UTI among circumcised febrile male infants after the eight day of life, a prevalence of 24.7% was documented against 8.4% in females. [43], attributed this unusual high rate among circumcised infants to the procedure being carried out by the ritual circumcisers

(Mohels), who in a bid to achieve haemostasis cause urinary stasis which subsequently predispose to UTI. However, it was observed that when the circumcision was carried out by physicians the rates of UTI was reduced [44].

Improper Toilet Training

Urinary tract infections have been found to occur more around the onset of toilet training due to the voiding dysfunction that occurs at that age [8]. This includes high pressure turbulent urine flow, incomplete and uncoordinated bladder emptying causing urinary stasis which increases the likelihood of bacteria proliferation and possible ascending infection. [8, 44], in a study of risk factors associated with febrile UTI in 79 children aged one month to fourteen years observed that improper toilet practices was the commonest risk factor associated with febrile UTI occurring in 73.4% of the participants. Similarly, [45] in a cross-sectional study in India and [46] in a case-control study in Bangladesh documented improper toilet training as significantly associated with UTI.

Vesicoureteral Reflux (VUR)

Reflux predisposes to UTI by facilitating the transport of bacteria from the bladder to the upper urinary tract and preventing complete emptying of the bladder [8]. [47], in a prospective cohort study of 500 children with and without VUR aged less than six years observed that over a two-year period those with VUR had a significantly increased rate (25.4%) of recurrent febrile or symptomatic UTI in contrast to 17.3% recurrence rate seen in subjects without VUR. Similarly, [48-50] in a study of 290 children under five years of age with first UTI at the Royal Alexandra Hospital for children Sydney observed a high rate (34%) of VUR among the subjects with both recurrent and non-recurrent UTI. In the same vein, [49] in Iran and [50] in Turkey documented higher rates of VUR 39% and 41% respectively among subjects with UTI. There is paucity of data with regards to the relationship of VUR to UTI in Nigerian children. [33] in a study of 300 febrile under-five children in Ibadan reported the prevalence of UTI to be 6.3%. The author in assessing for VUR among the 19 participants diagnosed with UTI, could not make a conclusion on the effect of VUR on UTI since only three participants had micturating cystourethrogram (MCUG) done. Most of the parents defaulted with follow-up and the remaining participants declined to continue with the study.

Obstructive Uropathy

Obstructive uropathy refers to any structural or functional hindrance of normal flow of urine [51]. In children it may be due to anatomic abnormalities such as posterior urethral valves (PUV) or strictures and stenosis at the ureterovesical or ureteropelvic junction [8, 51]. Obstruction in the urinary tract leads to stasis and stagnant urine is a good culture medium for bacterial infections as it enhances the proliferation of uropathogens [8]. [52], in a case -control study in Bangladesh and [22] *in* a study of 1974 children in India found PUV as a common risk factor for development of UTI in the study participants. Some Nigerian authors have also reported obstructive uropathy as a risk factor for UTI in children. [52-54] in a study in of 20 males aged four weeks to 13 years with obstructive uropathy in Port Harcourt Nigeria observed that 50% of the study participants had UTI. Similarly [55] in a cohort study of 40 male children with PUV in Ibadan Nigeria also reported that 40% of the study participants developed UTI. Frequent association of UTI with obstructive uropathies underlies the recommendation in most guidelines to screen for CAKUT in children with UTI. Also, the high prevalence of unrecognized CAKUT is one of the reasons for increased prevalence of UTI in neonates and infants [56].

Constipation

Constipation is reported to be one of the predisposing factors to UTI in children. Constipation causes the stool deposit to exert pressure against the urethra and bladder leading to voiding dysfunction with associated incomplete emptying of the bladder and stasis which promotes proliferation of the uropathogens [57]. Furthermore, the association of faecal incontinence with constipation increases the risk of peri-urethral colonization with uropathogenic organisms. [58], in a case -control study of 128 children in Yogyakarta Indonesia observed that children with chronic constipation have a 3.77 times higher risk of UTI compared to those without constipation. Similarly, [59] in another case-control study involving 105 children aged one to fifteen years with chronic constipation and 104 children as control group in Iran noted that constipated children were 6.8 times more likely to have a lower urinary tract infection than those not constipated. In Sri Lanka, [44] in a study of 79 children aged one month to fourteen years with febrile UTI found constipation to be the third most common contributing factor to UTI in their study. Furthermore, [60] in Bangladesh also documented constipation as a significant risk factor for the development of UTI.

Neuropathic Bladder

Neuropathic bladder increases the risk of UTI due to the non-coordination between the detrusor muscle and the external urethral sphincter. This leads to inability to empty the bladder completely, high void pressure, increased amount of post void urine and inability to properly wash the urethra of commensal bacteria [8]. Neuropathic bladder increases the risk of UTI due to the inability to empty the bladder completely due to the non-coordination between the detrussor and external urethral sphincter [8]. In Iran, [60] in a study of 183 children with symptomatic UTI

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observed that neuropathic bladder was significantly associated with UTI among the study participants, while [61] in India documented that neurogenic bladder was not significantly associated with UTI.

Urethral Catheterisation

It has been documented that urethral catheterization predisposes to increased rates of UTI as the use of urinary catheter disrupts the body's natural defence against bacterial infections, as well as, provides easy access for bacteria to enter the bladder [61-62]. The longer the duration of catheterization the higher the risk of UTI [62].
[44], in a study of 79 children with febrile UTI in Sri Lanka and Esteghamati [63] in Iran documented a significant association between urethral catheterization and UTI in their study subjects. In contrast, [61] in a prospective case-control study of 214 children aged two to twelve years did not observe a significant relationship between urethral catheterization and UTI, and this could be as a result of the fact that fewer participants had a history of urethral catheterization.

Dysfunctional Voiding

Dysfunctional voiding in children due uncoordinated contraction of the urethral sphincter and detrusor muscle spasm result in incomplete bladder emptying increasing residual bladder urine which facilitates multiplication of uropathogens, possibly resulting in UTI. [62-64], in a urodynamic study involving 52 children with febrile UTI found uncoordinated voiding in 93% of the study population. However, in studies carried out by the American Academy of Pediatrics (AAP) among children less than six years with a first or second UTI and followed up for two years, [65] documented bowel and bladder dysfunction (BBD) in 54% of the 181 toilet trained children and 35% of those with BBD experienced recurrent UTIs. [66], in another study of 109 children evaluated for urinary tract infections or for voiding dysfunction without infections, observed that 40.6% of females with infections had voiding dysfunction while 66% of the females with voiding dysfunction also developed infections. Although the relationship was only evaluated in females as the number of males in the study was too small for statistical analysis, the observation is similar to what was noted by [65]. There were no available Nigerian studies assessing dysfunctional voiding as a risk factor for UTI in children.

Pathophysiology of UTI

The pathophysiology of UTI is complex and involves many factors such as aetiologic agents, anatomical, immunological, urodynamic and genetic which may influence its location, course and prognosis [1,2,8]. The majority of urinary tract infections are ascending infections and the bacteria usually arise from faecal flora [8]. These pathogens usually colonize the periurethral area and there is an upward migration towards the bladder [1,8]. The short urethra in the female child means the bacteria is more likely to reach the bladder faster than in the male child [8]. The ability of microorganisms to achieve adherence to the uroepithelial cells is the major cause of the initial colonization of the bladder mucosa and subsequent ascent of the bacteria to the upper urinary tract [2,8]. The adherence to the uroepithelial cells is normally achieved by means of specialized filamentous structures called pili or fimbriae located on the bacterial capsule [2,8]. These fimbriae are of two types; type I and type II. Type I fimbriae are found on most strains of *Escherichia. coli* (*E. coli*) and are responsible for mostly cystitis and asymptomatic bacteriuria and rarely cause pyelonephritis [2,8]. Their attachment to target cells can be blocked by mannose hence they are referred to as mannose-sensitive [8]. However, type II fimbriae are the main cause of pyelonephritis, their attachment is not inhibited by mannose hence they are known as mannose –resistant and are usually expressed by only certain strains of E. coli [2,8]. Other virulence factors of uropathogenic *E.coli* include capsule and lipopolysaccharide. The capsule is predominantly a polysaccharide covering that protects the bacteria from the host immune system. The capsule also provides protection against phagocytic engulfment and complement –mediated bactericidal effect in the host. Certain types of capsule example K1 and K5, show molecular mimicry to tissue components, preventing a proper humoral immune response of the infected host [10]. Other secretory virulence factors include some toxins ; alpha hemolysin (HlyA), cytoxic necrotizing factor 1 and secreted autotransporter toxin(SAT) which have all been implicated in the pathogenesis of UTI [67]. In the bladder, regular and complete emptying of the bladder urine ensures that the bacteria count is significantly depopulated [2,3,8]. However, when this regular emptying of the bladder is impaired as seen in children with posterior urethral valve, constipation , neuropathic bladder or dysfunctional voiding, this important defence mechanism is lost predisposing the children to repeated UTI [2,8]. As soon as sufficient colonization occurs, bacteria may ascend to the ureters towards the kidneys [2,3,8]. Infection of the renal parenchyma gives rise to an inflammatory response called pyelonephritis [2,3,8]. Most infections of the renal parenchyma are as a result of bacterial ascension although, haematogenous spread can occur [3,8]. Progression of the inflammatory cascade can cause tubular obstruction and damage leading to interstitial oedema which may manifest as acute kidney injury [3].

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Clinical Forms of UTI

It is important to always distinguish the clinical forms of UTI, because the short and long-term effects and intensity of treatment depend on the clinical forms involved [2,8]. Involvement of the renal parenchyma is termed acute pyelonephritis (APN) while limitation of the infection to bladder is called cystitis [2,8].

Pyelonephritis

This refers to infection affecting the upper urinary tract (ureters, collecting system, renal parenchyma) [2,3,8]. Involvement of the renal parenchyma is referred to as acute pyelonephritis (APN) whereas if there is no parenchymal involvement it is termed pyelitis [8]. The most important symptom is fever, other symptoms include abdominal, back or flank pain, malaise, nausea, vomiting and occasionally diarrhoea [2,3,8]. Newborns can present with non-specific symptoms such as poor feeding, irritability, jaundice and weight loss [2,8]. Because of the frequent association of high-grade fever in pyelonephritis, it is also known as febrile UTI. However, the gold standard for the diagnosis of a UTI as acute pyelonephritis is by dimercaptosuccinic acid (DMSA) scan[8]. This involves the intravenous administration of radioisotopes through a gamma camera, the uptake and concentration of the radioisotope is recorded in two dimensional images [68]. The isotope is taken up in the proximal convoluted tubule accumulating in functioning cortex. DMSA scan reveals renal parenchyma and can demonstrate areas of filling defect (photopenic areas) which are areas of diminished or absent function referred to as renal scars [68]. This is not required for routine clinical practice [8]. Acute pyelonephritis requires more aggressive treatment, further investigations and longer follow-up because it can have significant consequences such as renal scaring [2,8].

Cystitis

This is a form of lower urinary tract infection with limitation of the infection to the bladder only [2,3,8]. The most prominent symptoms are dysuria, urgency, urinary incontinence, haematuria, suprapubic pain ,sensation of incomplete emptying [2,3,8]. Non-specific symptoms include vomiting, diarrhoea, ill-appearance and abdominal distension [2,3,8]. Cystitis is usually a benign condition without complications such as renal injury [2,8]. Though, not commonly, cystitis may progress to acute pyelonephritis. Most children with UTI present with non-specific symptoms as outlined above hence in clinical practice differentiating between these two types of UTI may be difficult especially in younger children [2]. Despite the outlined clinical forms of UTI, most of the studies in Nigeria did not specify the clinical forms of UTI in their studies [9-12].

CONCLUSION

The historical trajectory of UTIs showcases a transition from ancient interpretations rooted in humoral imbalances to modern insights grounded in microbiology. The study underlines the significance of distinguishing asymptomatic bacteriuria from clinical UTIs, particularly in vulnerable populations. Epidemiological variations across regions and demographics shed light on the multifaceted nature of UTI prevalence. Identified risk factors elucidate the complex interplay of biological, anatomical, and behavioral elements contributing to UTI susceptibility. The intricate pathophysiological mechanisms involving aetiologic agents and host factors provide a comprehensive understanding of UTI progression, influencing diagnosis and treatment approaches. Furthermore, recognizing distinct clinical forms, acute pyelonephritis and cystitis, and understanding their respective implications is crucial for tailored management and long-term outcomes. This review amalgamates historical insights, epidemiological trends, risk factors, pathophysiological mechanisms, and clinical manifestations, emphasizing the need for multifaceted approaches in UTI management and future research endeavors.

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