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Review Article

Overview of the causes and types of recurrent cystitis

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ABSTRACT

Bacterial cystitis accounts for the majority of urinary tract infection (UTI). It is frequently found in young, otherwise healthy females showing no signs of anatomical or physiological urinary tract defects. Among young women who have experienced an episode of acute bacterial cystitis, 25% to 50% develop recurrent episodes. Individuals with recurrent cystitis episodes have a greater susceptibility to urogenital colonization with uropathogens that thrive by adhering to uroepithelial cells. Further, there is an increased likelihood of infection with an antibiotic resistant uropathogen due to previous antimicrobial therapy for recurring infections. At each step of the pathogenesis, different host genetic, biologic, and behavioral factors, and bacterial factors interact and influence susceptibility to recurrent cystitis. Behavioral factors like sexual intercourse, use of spermicidal contraceptives and history of recurrent cystitis are major independent risk factors for recurrent cystitis infections. In post-menopausal women without comorbidities, estrogen depletion is mainly responsible for increased susceptibility to recurrent cystitis. Certain strain-specific bacterial virulence determinants may also contribute to recurrent cystitis by providing a selective advantage. Phenotypically, recurrent cystitis is categorized as reinfection or bacterial persistence. Majority of recurrent cystitis cases seen in men occur due to structural or functional abnormalities of the urinary bladder which allows same pathogens from the same site in the bladder to cause recurrences due to bacterial persistence. The concept of 'uncomplicated' and 'complicated' recurrent cystitis is used for classification of recurrent cystitis cases, similar to UTIs. Uncomplicated recurrent cystitis comprises cases occurring in young, healthy, nonpregnant women, mainly due to uropathogenic *Escherichia coli.* Due to the unique spectrum of host-bacterial interactions in the urinary tract, the distinction between complicated and uncomplicated recurrent cystitis is not straightforward. 'Complicating' factors such as structural, obstructive, neoplastic, functional, and neurological abnormalities of the urinary tract, systemic conditions including pregnancy, and certain demographic factors are attributed in the development of complicated recurrent bacterial cystitis.

Keywords: UTI, Recurrent, Cystitis, Uropathogen, *Escherichia coli*

INTRODUCTION

Cystitis refers to inflammation of the urinary bladder and is caused by diverse and often, unknown etiology. The most frequent type of cystitis is bacterial cystitis caused by uropathogenic bacteria, although it may also arise from noninfectious causes like bladder stone, bladder cancer, carcinoma in situ, radiational, chemical or unknown etiologies as in the case of interstitial cystitis.[1] Clinically, the infectious and non-infectious etiologies are managed distinctly. Bacterial cystitis accounts for the majority of UTI and predominantly affects women. Pyuria and bacteriuria are the most common presentations which may or may not be accompanied by dysuria, frequency, urgency, hematuria or suprapubic pain.[2] It is frequently found in young, otherwise healthy females showing no signs of anatomical or physiological urinary tract defects.

The annual incidence of acute uncomplicated cystitis in women is estimated at between 4% to 12%. Among young women who have experienced an episode of acute bacterial cystitis, 25% to 50% develop recurrent episodes.[3] Recurrent bacterial cystitis is defined as ≥2 episodes of symptomatic infection in six months or ≥3 episodes in one year. The incidence of recurrent cystitis among young women has been reported as 0.5 to 0.7 episodes per year.[4] For women above age sixty years, frequent recurrences have been reported to occur in an estimated 10% to 15% of cystitis cases.[5] Around one-third of the female patients encounter their first recurrence, caused either due to relapse or reinfection, within three months, and seventy five percentages to eighty percentages within two years after the initial episode.[4] In roughly ninety percentages of the cases, recurrence is due to reinfection rather than relapse, including reinfection caused by identical or new bacterial strains. Persistence of infectious foci following incomplete resolution of earlier infection may cause relapse occasionally.[2]

It has been observed that women with recurrent cystitis episodes have a greater susceptibility to urogenital colonization with uropathogens that thrive by adhering to uroepithelial cells.[5] In most cases, the management of recurrent cystitis is similar to that for sporadic cystitis. However, there is an increased likelihood of infection with an antibiotic resistant uropathogen due to previous antimicrobial therapy.[5] In rare cases, disease progression may result in patients developing significant complications such as pyelonephritis and sepsis.[6] Recurrent cystitis imposes a substantial burden on the health care system due to associated clinic visits, urologic evaluation, antimicrobial therapy, and health counseling. Moreover, it impacts the patient's quality of life and renders them socially and functionally handicapped due to physical discomfort, psychological distress, medical costs, time lost from work as well as the impaired sexual life.[7]

LITERATURE SEARCH

A literature search for articles published between January 1, 1990 and up to and including August 4, 2022 was carried out the national library of medicine (http://www.ncbi.nlm.nih.gov/PubMed) database to identify publications concerning the diagnosis, etiology, pathophysiology and classification criteria for recurrent bacterial cystitis and recurrent lower UTIs. Only articles in the English language were included. The search strategy used was (cystitis [Title]) or (UTI [Title]) and (recurrent [Title]). Randomized, controlled trials and systemic reviews were included. A limit to "human" studies and "full text" availability was put in the search query. A total of 287 potentially relevant titles were found by the electronic search. At the first phase of selection, 213 publications were excluded based on the title and keywords. At the second phase, 49 titles were excluded based on abstract evaluation. The reference lists of identified publications and relevant texts were also scanned. An additional nine articles were included after evaluation of references and texts.

DISCUSSION

At each step of the pathogenesis, different host genetic, biologic, and behavioral factors, and bacterial factors interact and influence susceptibility to recurrent cystitis. Uropathogenic *Escherichia coli* (UPEC) accounts for the majority of recurrent cystitis episodes, but infections can occur infrequently due to other pathogens like *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Enterococcus faecalis*, and may even involve polymicrobial etiologies.

Bacterial factors

Bacterial cystitis occurs due to colonization of the vaginal and periurethral openings due to frequent and/or prolonged exposure to uropathogenic bacteria residing in the rectal flora. These bacteria, UPEC in most cases, display a greater propensity for adhesion to cells of the urothelium.[5] By doing so, these coliforms avoid normal clearance during bladder emptying, which later leads to recurrences.[8] Most cases are believed to be a result of recolonization of vaginal introitus and lower urinary tract caused by a reinfection of fecal origin.[5]

Virulence factors

Certain strain-specific virulence determinants may contribute to recurrent cystitis by providing a selective advantage. For instance, virulence factors like hemolysin and type 1 fimbriae are more often encountered in acute cystitis strains as compared to other UTIs.[9] However, it should be noted that, so far, no 'cystitogenic' UPEC strains have been identified in the literature. These factors facilitate survival of the uropathogens in spite of a nutrient-limited environment, and aid in adhesion, colonization, compromise and invasion of host

urothelium, in addition to bypassing immunological defenses, thereby increasing their potential to persist in the urinary tract.[9,10]

Morphological alterations

Some uropathogens have demonstrated the ability to change their morphological structure allowing evasion of the host's immune response and recolonization of urinary tract.[11] For instance, UPEC cell filamentation is a mechanism by which the uropathogen transforms into a filamentous form which prevents its phagocytosis and possibly potentiates its adhesive abilities.[12]

Bacterial resistance and resilience

Antibiotic overuse has resulted in positive selection for pathogenic strains with particular genetic traits allowing their survival and proliferation. The majority of uropathogens possess the required machinery for transmission of genetic information among themselves and across species, thereby aiding in the rapid transfer of selected pathologic traits and emergence of multi-drug resistant bacteria.[13] Resilience behaviors that aid in transient evasion of antimicrobial agents in selected bacterial cells have also been observed. The rise of resilient strains has been implicated in the selection of uropathogens with more tolerant, persistent and heteroresistant phenotypic features.[14] This has been seen in the case of certain polymicrobial infections where uropathogens have demonstrated mutually protective behaviors against pharmacologically relevant antibiotic therapy by increased generation of tolerant or resistant phenotypic strains.[15]

Bacterial resistance is believed to be involved in the development of recurrent active infections, whereas bacterial resilience is mainly implicated in chronic cystitis cases.[16]

Host factors

Genetic factors

Differences in urogenital cell-receptor availability and binding potential are responsible for the enhanced propensity of uropathogens to adhere to uroepithelium in certain individuals more than others.[3] Recurrent UTIs are three to four times more likely to be found in female patients who are nonsecretors of ABH blood-group antigens, and are, therefore, considered to be genetically determined.[17] The epithelial cells of nonsecretor phenotypes, unlike secretors, express unique globoseries glycolipid receptors that bind uropathogenic coliforms.[5] Studies have shown that inherited factors may be important in some cases of recurrent cystitis.[5,18,19] One such study reported that having a mother with history of recurrent UTI and history of childhood cystitis onset raised the risk by two to four times in women.[19] However, it is speculated that common environmental and behavioral factors also contribute to disease development in both cases.

Immunological factors

Literature on the influence of host immune status on susceptibility to recurrent cystitis is sparse. Interleukin-6 and interleukin-8 are presumed to be released by the uroepithelium during acute illness, while the systemic response of the immune system is usually feeble and transient.[17] Expression of a defective version of interleukin-8 receptor, CXCR1 has been implicated in increasing predisposition to recurrent UTIs.[5] There is limited understanding of the role of antimicrobial peptides that are present in the urogenital tissues on acute or recurrent cystitis.[3] Further research is needed to understand the immunological drivers of the disease which may facilitate vaccine designing for recurrent cystitis.

Hormonal factors

In post-menopausal women without comorbidities, estrogen depletion is mainly responsible for increased susceptibility to recurrent cystitis.[20] Gradual decline in estrogen secretion after menopause causes atrophy of the urogenital tract and connective tissue as estrogen stimulates the proliferation of urogenital epithelium.[8] Moreover, deficiency of estrogen after menopause causes a depletion in the glycogen content of the uroepithelial cells. This glycogen insufficiency alters the vaginal microbiome by reducing the presence of glycogen-dependent lactobacilli and subsequently facilitating colonization by UPEC and other fecal origin Gram-negative bacteria, thereby creating a reservoir for future UTI occurrences.[3]

Microbial factors

The floral composition of the vaginal ecology determines the potential of the uropathogens to persist and cause recurrences. The dominance of some lactobacilli strains has been found to offer protection to the vaginal milieu from UPEC colonization.[3] Certain hydrogen peroxide producing lactobacilli strains have an inhibitory effect on uropathogens. One study found an inverse association of hydrogen peroxide releasing strains and introital UPEC colonization in female patients with UTI recurrences.[21] Other factors which alter vaginal flora such as the use of spermicides for contraception and antimicrobial agents like beta-lactams also increase susceptibility to recurrences by causing the microbiome to shift towards UPEC dominance due to their inhibitory effects on commensal bacteria.[22]

Anatomical factors

Urogenital anomalies like distal urethral stenosis as well as prolapse of uterus and bladder are certain anatomical defects that predispose to recurrent cystitis. Further,

functional defects such as poor bladder emptying or increased post-void residual, also present in case of certain pregnant women, may increase chances of recurrent cystitis episodes.[3] Majority of recurrent cystitis cases seen in men occur due to structural or functional abnormalities of the urinary bladder which allows same pathogens from the same site in the bladder to cause recurrences due to bacterial persistence.[1]

Behavioral factors

Sexual intercourse is a major, independent risk factor for the development of both, sporadic and recurrent cystitis.[23] One study found that a positive history of intercourse, frequency of episodes, new partners near the first recurrent episode reported after trial onset, and multiple lifetime partners magnified the risk for recurrent cystitis with odds ratio ranging from 1.6 to 6.2.[18] Certain contraceptives including foam and condom, diaphragm-spermicide and spermicidal condom have also shown to increase the risk of bacteriuria and periurethral colonization.[22,24] Alteration of the normal urogenital flora due to these contraceptive methods is believed to be responsible for the increased susceptibility to recurrent cystitis in their users.

For the purpose of diagnosis, management, research and drug development, recurrent cystitis, like UTIs in general, is classified into different categories using classification criteria developed for UTI by the center for disease control and prevention in the USA (CDC), infectious diseases society of America (IDSA) and European society of clinical microbiology and infectious diseases (ESCMID).[25] Lastly, phenotypically, recurrent cystitis is categorized as reinfection or bacterial persistence.[1] The latter falls under the category of complicated recurrent cystitis which is discussed below in detail.

The CDC's criteria provided guidelines for defining and reporting health care-associated (nosocomial) UTI.[26] It categorized UTIs into symptomatic UTIs, asymptomatic bacteriuria and other UTIs. For a diagnosis of symptomatic recurrent cystitis under CDC's criteria, the patient should present the associated symptom(s) and clinical evidence of infection via one or more forms of evidence including culture, dipstick, microscopic evaluation, medical diagnosis, or relevant antimicrobial therapy. It is unclear if asymptomatic bacteriuria (two positive cultures in cases without catheterization in the previous seven days before culture) is regarded as an infection or a potential risk factor.[26] Although complex for application in clinical practice, this classification system may serve a purpose in prevalence and incidence studies involving recurrent cystitis.[25]

According to IDSA and ESCMID guidelines, the concept of 'uncomplicated' and 'complicated' recurrent cystitis is used for classification of UTIs. IDSA established the concept of complicated and uncomplicated UTIs to create more homogeneous groups for research studies.[27,28] Uncomplicated recurrent cystitis research mainly involves the study of infections by *E. coli* while complicated recurrent cystitis research usually involves the study of other pathogens.[29]

Based on this criteria, uncomplicated recurrent cystitis comprises only those cases occurring in young, healthy, premenopausal, nonpregnant women with predisposing uropathogens.[30] The most frequent cause of acute uncomplicated cystitis is UPEC, causing 70% to 95% of recurrent cystitis cases.[31] 'Complicated' implies the presence of susceptibility factors that render the individual at an increased risk for developing recurrent cystitis.[32]

Due to the unique spectrum of host-bacterial interactions in the urinary tract, the distinction between complicated and uncomplicated recurrent cystitis is not straightforward.[5] It involves considering several heterogenous factors including conditions predisposing to recurrent episodes, treatment failure and/or increased risk of clinical complications if not appropriately managed, like in childhood.[25] 'Complicating' factors generally implicated in the complicated recurrent cystitis are: structural abnormalities of the urinary tract including congenital abnormalities like vesicoureteral reflux, pelviureteric junction; obstructive abnormalities like urinary tract calculus, bladder outlet obstruction, ureteral/urethral stricture; neoplastic abnormalities like neoplastic bladder; functional abnormalities like urinary tract instrumentation, indwelling catheterization, urinary/fecal incontinence and poor bladder emptying/increased post-void residual; and neurological abnormalities like multiple sclerosis, Parkinson's disease, spinal cord injury, and diabetes, general conditions including pregnancy, diabetes, immunosuppression, renal failure, and lastly demographic factors including such as male gender and hospital-acquired infection.[29] Regarding gender differences, it is believed that, physiologically, the predominance of recurrent cystitis in women is due to anatomic factors such as shorter urethral length, lesser distance from the anus to urethral meatus, and crosstalk between the vaginal and perineal microbiomes.[33] However, males at both ends of the age spectrum (mainly infants <1 year of age and elderly men with prostatic hypertrophy) display an increased propensity for UTI compared to their counterparts in between the two age groups.[34]

CONCLUSION

Majority of the recurrent cystitis cases are uncomplicated infections. The most common pathogen involved in the etiology of recurrent cystitis is *Escherichia coli.* At every stage in the pathogenesis of recurrent cystitis, key host risk factors like genetic factors, behavioral factors, and acquired factors interact with the bacterial risk factors like immunogenic factors to influence susceptibility to the UTI. Further, regarding definition of the recurrent cystitis types, the heterogenous understanding of the term

'complicated' makes it difficult to apply the findings of clinical research on patients to other patients in clinical practice with a distinct set of complications. An updated classification with more categories for comprehensive description of individual risk factors for recurrent cystitis, and transferability across academia, regulatory bodies and medicine would be welcomed.

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