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Review article

Recurrent urinary tract infections in healthy and nonpregnant women☆

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ABSTRACT

Recurrent urinary tract infections (RUTI) are prevalent and pose significant clinical challenges. Although the term RUTI has long been vaguely defined, a consensus definition has emerged in recent years. The exact etiology behind RUTI remains under debate, with valid arguments for both ascending reinfections as well as persistent infection inside the bladder. These persistent infections exist in the form of quiescent intracellular reservoirs in the mouse model and may represent a novel concept to explain UTI recurrence in humans. Manageable risk factors such as behavioral patterns alongside nonmanageable risk factors including genetic susceptibility are growing fields of investigation. Acute UTI have been studied through two model bacterial strains: *Escherichia coli* UTI89 and CFT073. However, the clinical relevance to RUTI of these two strains has not been firmly established. Current treatment strategies for RUTI are limited and remain dominated by antibiotic usage despite variable efficacy. The majority of studies in humans have focused on younger groups of women with little information available about the postmenopausal population despite a heightened risk of RUTI in this age group.

1. Introduction

Urinary tract infections (UTI) are the most common adult bacterial infection in the world.[1] In 2000, an estimated $2.5 billion was spent on UTI treatment excluding outpatient prescriptions.[2] Considering that the majority of women presenting with UTI have a history of more than two previous infections, recurrence represents a substantial social cost.[3] Recurrence also poses significant clinical challenges and has a major impact on quality of life. Unfortunately, few long-term or follow-up studies of recurrent UTI (RUTI) have been published to guide in evaluation and treatment. Current evidence indicates that the rate of recurrence following an initial UTI is high. A 1990 study at the University of Michigan involving female students aged 17–39 years showed that after a single UTI event, 27% of women will experience a second recurrence in the following 6 months with a further 3% experiencing a third UTI within the same time period.[4] An older study from Denmark showed that for women aged 16–65 years, rate of recurrence is highest during the first 2 months post-treatment and between 25% and 35% of women will have recurrence within 3–6 months.[5] Studies of UTI recurrence that include older women are rarer still. The results of a single study on recurrence in Finnish women indicated that 44% of women aged 17–82 years will experience recurrence within 12 months.[6] Rates of infection have been found to be lowest in the winter months.[7] Interestingly, the majority of women experiencing recurrence do so despite culture directed antibiotic treatment, having no anatomical abnormalities in the lower and upper urinary tracts, and being otherwise healthy individuals.[8]

In this review, we have considered only women suffering from RUTI who are otherwise normal with no obvious causal factor. Subpopulations excluded include pregnant women, infants, diabetics, patients with neurogenic bladder-like multiple sclerosis or AIDS, and individuals with abnormal genitourinary anatomy. Current guidelines for the diagnosis and management of RUTI in women along with indications for specialist referrals are beyond the scope of this review, but can be found elsewhere.[9] Following a systematic review of RUTI literature, we present a current update on how UTIs are defined, animal models and strains to study RUTI, risk factors for recurrence among different age groups, relevant clinical studies, and therapeutic options.

2. Definition

Until 2000, there was no generally accepted and broadly used definition for RUTI in women. Since then, the majority of

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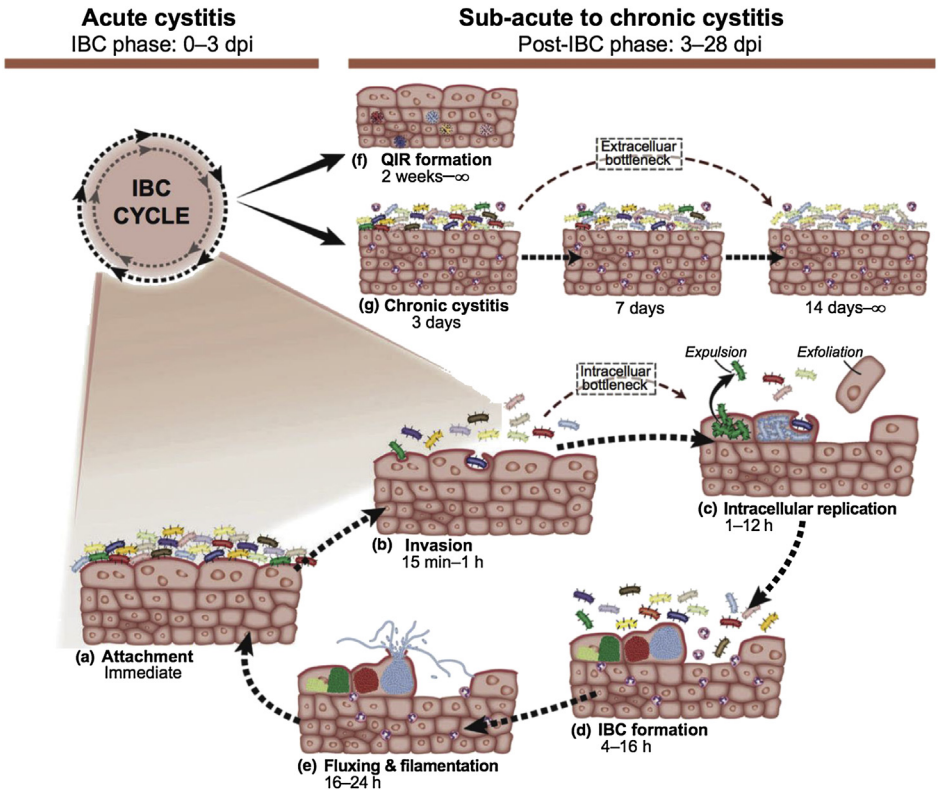

Fig. 1. Uropathogenic *Escherichia coli* model for acute cystitis, chronic cystitis, and quiescent intracellular reservoir formation: intracellular bacterial community (IBC) formation starts when bacteria attach onto the apical transitional epithelium of the bladder via type 1 pili. These bacteria are then enveloped and invade the epithelium — replicating and forming IBCs. As a host response to infection, the urothelium typically exfoliates, resulting in IBC liberation and IBC recreation in a clonal fashion. IBCs may also progress to quiescent intracellular reservoirs, which are not metabolically active and do not produce a measurable inflammatory response.
Note. From "Host-pathogen checkpoints and population bottlenecks in persistent and intracellular uropathogenic *Escherichia coli* bladder infection," by T.J. Hannan, M. Totsika, K.J. Mansfield, K.H. Moore, M.A. Schembri, and S.J. Hultgren, 2012, *FEMS Microbiol Rev, 3,* p. 616–48. Copyright 2012, Nature Publishing Group. Reprinted with permission.

publications on RUTI define the condition as "at least three episodes of urinary tract infections during the previous 12 months".[8,10–18] Additionally, six publications included a non-mutually exclusive alternative of "at least two episodes of UTI during the previous 6 months".[10,11,13,14,16,18] Proof of a positive urine culture was also frequently incorporated in the definition[8,11,15] with a specific concentration of $> 10^3$ colony forming units/mL mentioned in one instance.[15] Therefore, to define RUTI as "three episodes of urine culture positive UTI in the previous 12 months or two episodes within the 6 months" represents an acceptable compromise in contemporary studies.

3. Etiology

There is evidence to support that RUTIs may be caused by one of two mechanisms: repeated ascending infections or chronic/persistent infection in the bladder. Repeated ascending infections are thought to occur by the endogenous rectal flora via a fecal–perineal–urethral route. Bacteria migrate from the gastrointestinal tract into the periurethral area, ultimately ascending the urethra into the bladder. The finding that causative *Escherichia coli* strains are often detectable in a women's endogenous rectal flora during active UTIs as well as the fact that sexual intercourse is known to be a definitive risk factor for RUTI support this hypothesis.[19,20] In addition, women who suffer from RUTI have been found to have a higher frequency of infection with endogenous rectal flora, specifically *E. coli* and *Enterococcus faecalis*.[21]

However, several observations have countered this acceptable theory of ascending infections. First, following initial treatment with commonly used antibiotics, 77% of UTIs observed were due to a relapse with an *E. coli* strain identical to the primary infecting strain.[8] Second, antibiotics applied to the perineal area have been shown to be ineffective in reducing the risk of RUTI.[22] Finally, it has been noted that following antibiotic treatment, *E. coli* in the fecal flora are reduced in number.[23] That is to say, the fecal flora represents an unstable reservoir for recurrence. This evidence argues for an alternative source of infection.

One such plausible alternative is the survival of bacteria in the urinary bladder through the progression of transient intracellular bacterial communities (IBC) into persistent quiescent intracellular reservoirs (QIR). IBC formation and its relationship to bacterial colonization was first studied in the late 1970s with the support of data gathered from aquatic ecosystems. This theory was then applied to industrial water systems where bacterial biofilms represent a major concern.[24] To date, the majority of studies on RUTI-related IBC creation and subsequent QIR formation have been performed in murine models with *E. coli* strains UTI89 and CFT073.[25–28] Through the work of Hultgren et al,[29–33] the murine IBC/QIR pathogenic cycle has been gradually elucidated and is now largely understood.

IBCs are initially created when bacteria ascend the urethra and attach onto the bladder urothelium. In *E. coli*, luminal attachment is mediated via type 1 pili and results in urothelial envelopment.[30] Initial IBC formation is rapid and can be seen as early as 3 hours postinoculation.[31] By 12 hours postinfection, over half of all