

## Persistence or Reinfection for Recurrent Urinary Tract Infections in Women: Cloudy Boundaries When it comes to Management?

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### Abstract

**Objective:** To review current literature on the distinction between bacterial persistence or reinfection in recurrent urinary tract infections (RUTIs) in women and the resultant implications on evaluation and treatment.

**Methods:** A systematic literature review focusing on studies of non-pregnant women with cystitis was conducted. Studies not in English, not in full-text, and relating to children, men, and pregnant women were excluded.

**Results:** Between 1995 and 2012, 7 articles were identified from which the type of bacterial persistence/reinfection status could be clearly established. While some study findings suggest that bacterial reinfection prevails in RUTI, others have concluded that bacterial persistence is quite frequent or dominates (33% to 82%). Recent data on evaluation and treatment also suggest a shift towards less need to distinguish between these two categories.

**Conclusions:** While current RUTI management strategies hinge on delineating between bacterial persistence or reinfection, for women refractory to antibiotic therapy, one could argue that the boundary between the two groups may be irrelevant as optimal treatment may be the same regardless. Compared to simple urinary tract infections which are exceedingly common in women and relatively easy to treat, recurrent urinary tract infections (RUTIs) provoke treatment challenges, impact on quality of life, and substantial costs. Traditionally, RUTIs have been divided into two broad categories depending on urine culture findings: (1) Bacterial persistence refers to RUTIs caused by the same bacterial strain over and over again while (2) Bacterial reinfection implies a reinfection process from different bacterial strains. In this brief document, we reviewed the existing literature on the prevalence of these two forms of RUTI and briefly discussed the implications for their evaluation and treatment, while adding some newer information from our group and others. We will make the point that the boundaries between these 2 categories can sometimes be blurry and that their management may emerge as being similar in the end.

**Keywords:** Recurrent urinary tract Infection; Bladder fulguration; Female urology

### Introduction

Over the past decades, numerous studies on the prevalence of these two types of RUTIs have been published, and the results are divergent. For this review, we focused exclusively on non-pregnant women with cystitis and excluded studies not in English, not in full-text, or relating to children, men, and pregnant women [1,2]. We identified seven articles between 1995 and 2012 from which the type of bacterial persistence/reinfection status could be clearly established. As summarized in Table 1, the proportion of persistent RUTIs ranged from 33%-82%. Some study findings suggest that bacterial reinfection prevails in RUTI, [3-6] while others have concluded that bacterial persistence dominates [7-10]. There are many factors that can potentially contribute to such a wide percentage range for persistent RUTIs. Each study differed in their patient population demographics, urine collection technique, bacterial culturing methodology, duration of follow-up, and the method of strain analysis. The two main typing methods in bacterial strain identification were random amplified polymorphic DNA polymerase chain reaction (RAPD-PCR), where chromosomal DNA fragments are amplified by PCR and imaged by

Southern blotting, and pulsed-field gel electrophoresis (PFGE), where genomic DNA of bacterial strains are differentiated by migration patterns [5,8].

Despite the range of study parameters, the significant difference observed in persistent RUTI percentage is enough to question the accuracy of the clinical diagnoses of RUTIs. Based on a proposed theory by S.Hultgren in a mouse model, quiescent intracellular reservoirs (QIR) can develop in the bladder urothelium after an acute bacterial infection and those reservoirs can remain dormant for years until they get reactivated [1,8,11]. Therefore, regardless of intervening negative urine culture results, here is a process that can allow resurgence of a UTI months after the initial infection [1]. Based on culture results from trigonal biopsies obtained in women with recurrent UTIs, we have noticed some discrepancy between bladder wall bacterial findings and urine culture findings obtained at the same time. This observation suggests a differential clinical expression of bacterial populations niched in the bladder wall whereby one group of bacteria remains dormant while the other undergoes reactivation [12].

The current management strategy for RUTIs classically starts with determining whether the RUTI is caused by bacterial persistence or reinfection [2]. When dealing with reinfection, ie different bacterial strains identified in serial urine cultures, an upper tract imaging is not

recommended nor is a cystoscopy to look for the source of the bacteria in the urine since it is presumed to be happening through a re-ascending process via the urethra. For bacterial persistence, both lower urinary tract and upper urinary tract investigations have been recommended to determine the source of the persisting process [2]. In a recent study evaluating upper tract imaging findings in both groups of women with RUTIs, using ultrasound and/or CT scan, a very low yield (<2%) of upper tract anomalies was recorded in each category [13].

Office cystoscopy is typically recommended by major urology textbooks to exclude the presence of tumor or stone(s) in the bladder. In another study, we observed that many women with RUTI had inflammation of the trigone, known as trigonitis. The office procedure was done under local anesthesia with a flexible cystoscope to allow a retroflex view of the bladder neck and bladder base area in order to better detect trigonitis. Women treated for RUTIs with multiple rounds of antibiotics, who had trigonitis, and whose symptoms recurred soon after the discontinuation of several antibiotic courses, were offered endoscopic cauterization of this trigonitis area with the hope of potentially eradicating the source of bacterial persistence from inside the bladder wall. Long-term results were very encouraging with a marked reduction in secondary UTI rates or need for symptom-based antibiotic courses [14].

In summary, the yield of upper tract findings seems to be low and quite similar in both categories of RUTI. For cystoscopy, it might be beneficial to detect trigonitis as it could explain the persistence mechanism and be improved with a simple outpatient procedure, such as an endoscopic cauterization. However, for women refractory to multiple antibiotic therapy courses, one could argue that the boundary between bacterial persistence and reinfection RUTIs may be irrelevant as the optimal treatment may be the same regardless of RUTI subtype, including long-term antibiotic suppression, along with many additional therapies such as vaginal hormonal supplementation, cranberry products, probiotics, mannose, etc. [2]. A recent article proposed a nomogram to alert the internist treating patients with their first UTI on their risk for recurrence [15]. Such early detection, along with ongoing research on non-antibiotic based treatment strategies (vaccination, pilicides, anti-virulence factors) [16-18] may revolutionize the remaining challenging and somewhat frustrating field of RUTI management.

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