

DEFINITION OF CLASSICAL BACTERIAL CYSTITIS VERSUS "LOW COUNT BACTERIURIA"

This subject has been fully reviewed recently,²⁷ but a clear agreement has not been reached by the urologic scientific community. On one hand, the pioneering work of Kass, a Harvard nephrologist, established the time honored definition of significant bacteriuria as $\geq 10^5$ colony forming units (cfu) per ml (or $>10^8$ cfu/L), which was based on the differentiation of pyelonephritis from contaminated urine specimens. This work was done in the 1950s, when 20% of autopsies showed undiagnosed pyelonephritis as a contributor to death.²⁶ Stamm et al.²⁷ later re-evaluated the conventional criteria in 187 women, and found that such a strict cutoff for diagnosis of bacterial cystitis would miss about half of those who did have clinical features of bacterial cystitis. He concluded that the best diagnostic criterion was $\geq 10^4$ bacterial cfu/ml. In patients who void frequently (such as OAB), Kass himself noted that pooling of urine in the bladder may thus be reduced, with insufficient time to permit multiplication of bacteria to maximal numbers—therefore, such patients may be more likely to demonstrate "low count" bacteriuria. Kunin et al.²⁸ investigated the importance of "low count bacteriuria" in 639 gynecology outpatients and concluded that low count bacteriuria ($>10^2$ cfu/ml) was clinically relevant and probably was a manifestation of early bacterial cystitis that had not yet become fully established. Arav-Boger et al.²⁹ asked 113 women to postpone treatment of their cystitis symptoms for 2 days, and came to the same conclusion.

The Infectious Diseases Society of America (IDSA) and the European Association of Urology (EAU) revised their guidelines for the diagnosis of bacterial cystitis in normal women,²⁷ to include a diagnostic cutoff of 10^2 cfu/ml (or 10^5 cfu/L). The participants of this Think Tank session agreed with a cut off of at least 10^3 cfu/ml, but responded that most of their hospital laboratories would not provide diagnostic information at this level, as most laboratories persist with the diagnostic cutoff of Kass (10^5 cfu/ml). The discussants agreed that this was regrettable, and not appropriate for research studies of refractory OAB/DO and other LUTD. From an international perspective, hospital laboratories should consider revising their diagnostic criteria, allowing "low count bacteriuria" to be identified appropriately upon the request of the clinician, in keeping with IDSA and EAU guidelines.

RELEVANCE OF PYURIA

The diagnostic criteria for bacterial cystitis have traditionally required evidence of pyuria. As stated by Stamm,³⁰ once contamination is excluded, usually by presence of multiple epithelial cells, then "bacteriuria indicates either urinary colonization (replication of bacteria in urine without evidence of tissue invasion) or urinary tract infection (bacteriuria associated with clinical, histologic, or immunologic evidence of host injury). Practically speaking, measuring pyuria is the most readily available means of establishing the presence of host injury, thus differentiating colonization from infection. Careful studies have established the non-pathologic limits for pyuria as being less than 10 leukocytes mm^3 in uncentrifuged urine." However, the value of pyuria has been controversial and "its absence from any single specimen cannot be taken as evidence for the absence of bacteriuria."²⁶

Stamm³⁰ investigated different methods of measuring pyuria, and concluded that pyuria should be expressed as leukocytes per ml. Measuring pyuria per high power field in a centrifuged urine specimen did not correlate well with more

precise assays such as leukocyte excretion rate or hemocytometer chamber counts. Kunin et al.²⁸ established that the prevalence of pyuria rises with the level of bacteriuria, therefore, patients with low count bacteriuria do not always express pyuria, in keeping with the notion that low count bacteriuria is just an early phase of classical bacterial cystitis. The importance of pyuria was discussed by Think Tank participants, but no clear conclusion was reached as to whether the presence of pyuria is an essential diagnostic criterion for bacterial cystitis.

In general, catheter specimens of urine (CSU) are more likely to give a true representation of the presence of pyuria, compared with Mid Stream Urine (MSU) samples. The need for vigorous labial toilet, as opposed to a simple clean catch technique, was emphasized by participants. Although no direct comparison of labial toilet (washing the labia with sterile saline then opening the labia out laterally before commencing the clean catch MSU) versus simple clean catch technique has been published, anecdotal evidence suggests that the former method will reduce the likelihood of perineal organisms falling into the specimen pot (which may yield a "contamination" result). The argument regarding need for catheter urine specimens in the research context was briefly touched upon but not conclusively agreed upon. Consensus was not reached about the use of CSU versus MSU, because CSU is much more invasive for the patient, less agreeable to Ethics Committees and more time consuming/costly for the researcher. Therefore insistence upon CSU specimens generally limits recruitment into research studies. A comparison study of MSU by strict labial toilet versus CSU does not appear to have been published (but see Clinical Studies below for further discussion).

CLINICAL STUDIES IN PATIENTS WITH REFRACTORY OAB/DO

As mentioned above, part of the reason for this Think Tank being convened, is that several publications have appeared in the last 4 years regarding the topic. For example, Walsh et al.¹⁸ studied 50 women with refractory idiopathic DO over 2 years who were asked to provide an MSU whenever their OAB symptoms worsened—none of these patients had dysuria or foul smelling urine, just increased frequency/urgency/nocturia with or without urgency incontinence. Overall, 39% of their MSU samples revealed bacteriuria, compared to 6% of a control group of 50 women with no OAB symptoms. As regards only "low count bacteriuria," 17% of the Refractory IDO group versus 2% of the control group showed this finding. Pyuria occurred in 84% of traditional bacterial cystitis versus 23% of the low count bacteriuria specimens.

Because of the argument regarding the need for CSU, rather than MSU, the same authors³¹ went on to study CSUs, taken at urodynamic testing, from patients with newly diagnosed idiopathic DO versus other types of incontinence ($n=161$), compared with CSU taken from 75 continent women at the time of hysteroscopy or laparoscopy for routine gynecological conditions who had no OAB symptoms. This revealed an odds ratio of 5.2 for any bacteriuria in the incontinent group versus continent controls, which was particularly true for patients with pure DO (odds ratio 6.4). The same authors performed another study of catheter specimens of patients with refractory IDO (partly to measure levels of ATP after stretch by 50 ml of instilled fluid) which revealed bacteriuria $>10^3$ cfu/ml in 27% of these refractory patients.³²

Contemporaneously, another group in London was investigating the problem of refractory DO from the perspective of bladder biopsies. Digesu et al.¹⁰ studied 106 women with refractory IDO by bladder biopsy; histopathological analysis