

# Testing Men Who Have Sex With Men for Urethral Infection With *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Is Only Half the Job, and We Need the Right Tools

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Standard operating procedure in STD clinics commonly has been to test urethral specimens when evaluating males, whether they are heterosexual or men who have sex with men (MSM). Rectal or oropharyngeal specimens may be tested in MSM with symptoms, or in some clinics as screening tests if individuals report sexual practices that would indicate risk of infection at these sites. In a report in this issue of Sexually Transmitted Diseases, Marcus and colleagues studied the prevalence of infection with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) in the urethra, the oropharynx, and rectum in asymptomatic MSM visiting the San Francisco STD clinic.<sup>1</sup> A retrospective analysis of 3398 patient visits found CT or GC at 549 (16.2%) of those visits. The prevalence of infections among these asymptomatic men ranged from a high of 7.8% for rectal CT to a low of 0.4% for urethral GC. Strikingly, 83.8% of CT and GC infections would have been missed if only urethral screening was performed.

What was found in the Marcus study, and in others, as well, is that the majority of infections with CT/GC in MSM are not in the urethra. The first major study to make this point was performed by Kent and colleagues, in 2 clinics in San Francisco, where they found that >50% of chlamydial and gonococcal infections were extraurethral.<sup>2</sup> That finding has been confirmed by a number of approaches, including retrospective chart reviews and prospectively designed studies (Table 1). While these studies have focused on rectal and pharyngeal CT/GC infections in MSM, it must be noted that such infections are far from rare in women.<sup>12,13</sup> In many clinical settings, the infections in women will be seen more often than those in men. These extragenital infections should not be ignored now, and we need more research to better define their potential consequences.

Both CT and GC are recognized as causes of proctitis, and even asymptomatic infections have been associated with HIV transmission.<sup>14</sup> Current CDC recommendations call for routine screening of the oropharynx and rectum in MSM who may be exposed to GC or CT at those sites. It is not clear whether pharyngeal infections have a major direct impact on health. But evidence is emerging that infection can be transmitted from the oropharynx to the urethra of sex partners, thus continuing chains of infection.<sup>15</sup>

All of the cited studies have been made possible by the introduction and application of highly sensitive and specific nucleic acid amplification tests (NAATs) for the diagnosis of CT and GC infections. NAATs are recommended for routine diagnosis of CT/GC infections.<sup>15</sup> Where direct comparisons have been done, it has been shown that the increment in sensitivity for NAATs as compared to culture is greater with pharyngeal and rectal specimens than it is with cervical and urethral specimens. An approximate doubling of the number of infections detected has been obtained with NAATs.<sup>4,11</sup>

Alas, there remains a gap wherein the best tests are not readily available to the patients and providers who need them. Several NAATs are commercially available and have received FDA clearance for male and female urine specimens, urethral swabs from men, and cervical and vaginal swabs from women. Unfortunately, none have been cleared by the FDA for pharyngeal or rectal specimens. But the CDC, recognizing the superior performance of these tests used on these specimens, has taken an unusual step and recommended the use of NAATs for diagnosis of CT/GC in oropharyngeal and rectal specimens, even though such use has not received FDA clearance.<sup>16</sup> The

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**TABLE 1.** Percentage of Men With Rectal and/or Pharyngeal Infections With *Chlamydia trachomatis* or *Neisseria gonorrhoeae* That Would Not Be Treated if Only Urethral Infections Were Diagnosed

Author	Location	Clinic Type	n	Prevalence		% Infections Missed	
				CT	GC	CT	GC
Kent <sup>2</sup>	San Francisco, CA	MSM, STD	6434	13.3%	16.7%	53	64
Gunn <sup>3</sup>	San Diego, CA	STD	7333	ND	15.8%	ND	38
Schachter <sup>4</sup> , Moncada <sup>5</sup>	San Francisco, CA	STD	1089	12.4%	21.2%	46	38
Bachmann <sup>6</sup>	Birmingham, AL	HIV, STD	142	12.1%	7.9%	84	63
Annan <sup>7</sup>	Australia	HIV, STD	3076	13%	ND	62	ND
Manavi <sup>8</sup>	United Kingdom	STD	443	10%	ND	56	ND
Templeton <sup>9</sup>	Australia	STD	1417	1%	ND	68	ND
Moncada <sup>10</sup>	San Francisco, CA	STD	899	11.5%	16.5%	47	26
Ota <sup>11</sup>	Canada	MSM, STD	248	7.7%	11.7%	79	65

ND indicates not done; CT, *Chlamydia trachomatis*; GC, *Neisseria gonorrhoeae*; MSM, men who have sex with men.

FDA is not to be blamed for this; to our knowledge, no NAAT manufacturer has performed clinical trials and submitted the data to obtain clearance for these specimen types.

It is possible to use tests that have not received FDA clearance for patient management. Large laboratories have the capability of verifying the use of NAATs for rectal and pharyngeal specimens by following Clinical Laboratory Improvement Act (CLIA) guidelines. The 2 major commercial laboratories in the United States (Quest and LabCorp) have performed their own verification and offer NAAT testing on pharyngeal and rectal specimens. But use of these commercial labs by public health facilities is very expensive. Smaller public health labs and STD clinics cannot readily perform test verification. CDC is helping by using its resources to collect and distribute the specimen panels needed for verification, but most laboratories are not running multiple tests needed to verify an off-label use. Thus, while NAAT testing for extragenital infections in MSM is available to some clinics that serve MSM, it is not universal and often testing will be done by just GC culture as CT culture is not widely available.

We need NAATs with FDA clearance for use on oropharyngeal and rectal specimens to further expand clinical access to these tests. The CLIA verification approach is not appropriate for testing that should be universally available. The FDA would surely say that they need to have a submission, with appropriate supporting data to clear a specific usage. But from the companies' viewpoints, there is little to be gained by undergoing the expensive testing required to obtain the FDA clearance. The MSM testing market may not be large enough to justify the cost.

Thus, there are a number of very straight forward needs here. The first is that there must be a paradigm shift away from simply testing urethral specimens in MSM. The routine testing of oropharyngeal and rectal sites, as well as urethral specimens, must become the norm. To do less abrogates our responsibility to the client and may decrease effectiveness of our disease control efforts as these infections remain undiagnosed and untreated. Clearly, anatomical sites to be sampled can be directed by details concerning sexual practices. It is obvious that there are subsets of men whose exposures may be limited to only 1 or 2 of these 3 sites. If we are to deal with the public health problems that CT/GC provide, then we have to identify

and treat the infections to minimize their spread and reduce morbidity. Testing only for urethral infection when that site identifies <50% of the infected cannot be maximally effective.

Second, use of NAATs for these purposes should become routine. It is clear that culture for both organisms is, under the best of circumstances, inadequate. There is more variability in the performance of culture than there is in the performance of NAATs where procedures are highly standardized and automated. Both CT and GC culture are markedly affected by delays in processing specimens due to transportation to the laboratory, and optimal results can only be obtained in relatively large, experienced laboratories in proximity to clinics. Shipping of specimens degrades sensitivity. These limitations are not found with NAATs.

Given that NAATs are the tests of choice for these diagnoses, the question is "how can they be made universally available?" It is obvious that we have to get away from our current system of manufacturers performing clinical trials and submitting the data to the FDA for clearance. This is an issue that reaches beyond commercial interests. Given that so many laboratories and clinics are supported by the CDC, there are certainly sufficient resources to generate the data required to obtain clearance. Perhaps there could be a partnership between the CDC and the FDA (maybe even NIH, as a leading supporter of research), based on a public health imperative, to decide how NAATs could be evaluated in a postmarketing environment to allow extension of clearance to such specimens. This could be a model for other needs. The future here is clear, what is not, is how we get there.

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