Time for a Paradigm Shift: Testing MSM for Urethral Infection with *C. trachomatis* and *N. gonorrhoeae* Identifies Less than 60% of Infected Men

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INTRODUCTION: Men who have sex with men (MSM) may have a high prevalence of STDs. The CDC guidelines recommend routine screening of urethral and extra genital sites in MSM (pharyngeal and rectal) for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) to control for these infections. Nucleic acid amplification tests (NAATs) are highly sensitive and specific for the detection of CT and GC, but none are FDA cleared for use with extra genital specimens. Laboratories must perform in-house validations to use with pharyngeal and rectal specimens. Since the standard for testing extra genital sites is culture, multi-site testing in MSM is probably not performed in many clinics, and the most likely specimen collected is a urethral/first catch urine (FCU) for a CT or GC NAAT. Here we report how many CT and GC infections by either culture or NAAT (Gen-Probe Aptima Combo2, AC2) would be missed if only FCU was tested.

METHODS: Our study population consisted of MSM seen at the San Francisco City STD Clinic. We excluded subjects if antibiotics were used within 21 days or they have urinated within one hour. Verbal consent was obtained from all subjects. Each MSM provided approximately 25 ml of FCU, and three clinician-collected (1 for NAAT and 2 for cultures) pharyngeal and rectal swabs. The dacron swabs were placed into M4 medium for CT isolation and NAAT testing, and cotton swabs for GC culture were streaked onto Thayer Martin plates. Colonies with Gram negative, oxidase positive diplococci were confirmed as GC by carbohydrate utilization tests. Tissue culture isolation of *C. trachomatis* was done in cycloheximide-treated McCoy cells. All specimens had a second passage and coverslips were read after a species specific fluorescent antibody stain (MicroTrak *C. trachomatis* Culture Confirmation Reagent, Trinity Biotech Plc). FCU and aliquots of pharyngeal and rectal samples in M4 media were transferred into AC2 transport tubes. These specimens were then tested by AC2, according to package insert instructions. FCU true positives (TP) were defined as a positive AC2. Pharyngeal and rectal TPs were defined as a positive CT or GC culture, or an AC2 positive result confirmed by either repeat testing or an alternate target NAAT (using APTIMA CT or GC tests, stand alone tests with different targets than are used in the AC2).

RESULTS: 1089 men were enrolled; Of 664 (61%) symptomatic men 285 (43%) had urethral symptoms (32 (11.2%) had CT and 93 (32.6%) had GC). CT and GC prevalence was 12.4% (135/1089) and 21.2% (231/1089), respectively. 73 MSM had urethral CT infections. Testing only the FCU would miss 62 (46%) CT infected men (Table 1). Culture would have detected only 18 rectal, and 4 pharyngeal CT infections; 1 had a dual infection (AC2 detected 62 and 10, respectively; 4 had dual infection). There were 144 urethral GC infections. Testing only the FCU would miss 87 (38%) GC infected men. Culture would have detected 37 pharyngeal and 37 rectal GC infections (5 dual), while AC2 detected 79 pharyngeal and 84 rectal (26 dual) infections.

Table 1 – *C. trachomatis* and *N. gonorrhoeae* Infections in MSM by Site

		Pharynx		Rectum	
	n	Culture Pos	AC2 Pos	Culture Pos	AC2 Pos
FCU CT Pos (%)*	73	0 (0)	3 (30)	2 (11)	6 (10)
FCU CT Neg (%)**	1016	4 (100)	7 (70)	16 (89)	56 (90)
Total CT Pos	135	4	10	18	62
FCU GC Pos (%)*	144	15 (41)	34 (43)	18 (49)	34 (40)
FCU GC Neg (%)**	945	22 (59)	45 (57)	19 (51)	50 (60)
Total GC Pos	231	37	79	37	84

* % of men infected at this site who were FCU positive. ** % of men infected at this site who were FCU negative.

Table 2 - Percent of men with rectal and/or pharyngeal infections with *C. trachomatis* or *N. gonorrhoeae* that would not be treated if only urethral infections were diagnosed

				Prevalence		% Infections missed	
Author	**Location**	**Clinic type**	**n**	**CT**	**GC**	**CT**	**GC**
Kent *(CID. 2005; 41: 67-74)*	San Francisco	MSM, STD	6434	13.3%	16.7%	53	64
Gunn *(STD. 2008; 35: 845-8)*	San Diego	STD	7333	ND*	15.8%	ND	38
Bachmann *(JCM. 2010; 48: 1827-32)*	Birmingham, AL	HIV, STD	142	12.1%	7.9%	84	63
Annan *(STI. 2009; 85: 176-9)*	Australia	HIV STD	3076	13%	ND	62	ND
Manavi *(Int J STD AIDS. 2004; 15: 162-4)*	UK	STD	443	10%	ND	56	ND
Templeton *(STI. 2008; 84: 361-3)*	Australia	STD	1417	1%	ND	68	ND
Ota *(STI. 2009; 85: 182-6)*	Canada	MSM STD	248	7.7%	11.7%	79	65

CONCLUSIONS:

- In our study approximately 46% of CT and 38% of GC infected MSM would not be diagnosed if only urine specimens are screened with AC2.
- Most of the men with rectal or pharyngeal infections did not have urethral infections. This was more marked with CT than with GC.
- By testing FCU only, a larger number of CT rectal infections (~90%) are missed than are GC rectal infections (~55%).
- Culturing the oropharynx or rectum is inadequate as AC2 detected at least twice as many infections.
- Other studies using NAATs have also shown that the majority of infections with CT/GC in MSM are not in the urethra, but in the pharynx and rectum (Table 2).
- The current standard of just routine testing bfor urethral infection grossly underestimates the number of MSM with CT or GC infection.
- Clearly, multi-site testing in MSM is needed for CT and GC, and AC2 would improve our ability to diagnose these rectal and oropharyngeal infections.
- Having FDA cleared NAATs for detection of CT and GC in pharyngeal and rectal specimens will help us in efforts to control STDs in MSM.