

ORIGINAL ARTICLE

Comparative performance of culture using swabs transported in Amies medium and the Aptima Combo 2 nucleic acid amplification test in detection of *Neisseria gonorrhoeae* from genital and extra-genital sites: a retrospective study

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ABSTRACT

Background Nucleic acid amplification tests are being increasingly used for the routine diagnosis of *Neisseria gonorrhoeae* (GC), although culture remains essential for monitoring antimicrobial resistance. The authors investigated how symptoms and infection site influenced test sensitivity.

Methods This was a retrospective study at two centres of patients diagnosed as having GC by Aptima Combo 2 (AC2) confirmed with Aptima GC and/or culture.

Results The study included 251 men (71%) and 105 women (29%). The sensitivity for AC2 and culture in the lower genital tract of men with symptoms was 99% (95% CI 95% to 100%) and 79% (95% CI 71% to 85%) and for asymptomatic men was 94% (95% CI 69% to 100%) and 29% (95% CI 11% to 56%), respectively. At the rectum, the sensitivity in symptomatic men was 91% (95% CI 57% to 100%) and 55% (95% CI 25% to 82%) and in asymptomatic men 75% (95% CI 47% to 92%) and 44% (95% CI 21% to 69%) for AC2 and culture, respectively. In symptomatic women, the sensitivity from the genital site was 100% (95% CI 95% to 100%) and 53% (95% CI 38% to 68%) and for asymptomatic women 100% (95% CI 87% to 100%) and 47% (95% CI 30% to 65%) for AC2 and culture, respectively.

Conclusions The AC2 with AGC confirmation performs well at genital and extra-genital sites for detecting GC. Culture for GC using transport swabs performs poorly in asymptomatic men, symptomatic and asymptomatic women and at extra-genital sites. With the improved performance of nucleic acid amplification tests and the increase in GC antimicrobial resistance, research is needed into how best to optimise GC culture in settings where direct plating is not feasible.

INTRODUCTION

Gonorrhoea is the second most common bacterial sexually transmitted infection in England and Wales¹ and can be treated with appropriate antimicrobials. Dual detection of *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT) using a combined nucleic acid amplification test (NAAT) is being increasingly used in the UK.² NAATs have a number of advantages over culture including greater sensitivity^{3–6} particularly at extra-genital

sites, both invasive and non-invasive sampling, the ability to detect more than one organism in a single test and specimen stability.²

There are concerns regarding the use of NAATs for detecting GC, particularly at extra-genital sites. NAATs are not 100% specific, and in low-prevalence populations, the risk of false positives is increased.^{2,7,8} This may be more likely at extra-genital sites colonised by commensal *Neisseria* spp., which share genetic homology.² Thus, confirmation with another NAAT is recommended when the positive predictive value is <90%.² Furthermore, a NAAT sample does not provide a viable organism for culture and antibiotic sensitivity testing.^{2,9} The national surveillance programme in England and Wales, Gonococcal Resistance to Antimicrobials Surveillance Programme, has identified continued high levels of resistance to quinolones (previous first-line treatment) and emergence of decreased susceptibility to cefixime and ceftriaxone, the third-generation cephalosporins currently recommended for therapy.^{10,11} Culture is therefore recommended in patients with signs and symptoms compatible with GC and/or with a confirmed GC-positive NAAT result, so that susceptibility testing can be performed.²

Until recently, the gold standard for diagnosis of GC was conventional culture, which requires invasive sampling. Presumptive diagnoses are made with the detection of gram-negative intracellular diplococci on a gram-stained smear from appropriate sites.¹¹ Under optimum conditions, culture for GC from genital tract specimens may have a high sensitivity, although it performs less well with samples from extra-genital sites.^{2,12,13} Two approaches to culture are available: direct plating at time of specimen collection or use of transport media to transfer specimens to the laboratory where direct plating is subsequently performed, which under optimal conditions may have a similar sensitivity.^{12,14} However, a number of factors can adversely affect the latter approach which include transport swab type, failure to store at 4°C once taken and delay longer than 6 h before being plated out.^{14–16}

The Gen-Probe Aptima Combo 2 (AC2) Assay (San Diego, California, USA), detecting *N gonorrhoeae*

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and *C trachomatis* on a single sample, was introduced into the Bristol and Avon Sexual Health services in November 2005. All AC2 GC-positive samples are confirmed with a separate Aptima GC assay. This offered the opportunity to assess the performance of AC2 in a routine clinical setting compared with culture using transport swabs prior to plating. It also provided the opportunity to assess whether asymptomatic individuals with GC are more likely to be NAAT GC positive, culture negative.

METHODS

Study population

All new attendances at the Genitourinary (GU) Medicine clinic at Royal United Hospital Bath, NHS Trust and Bristol Sexual Health Centre, University Hospitals Bristol NHS Foundation Trust, between 1 April 2006 and 31 March 2008, were included.

Those diagnosed as having GC were identified using the local laboratory and clinical databases and their case notes reviewed. A GC-positive patient was defined as one who had at least one specimen with GC identified by AC2 and/or culture. The following data were recorded: gender, age, sexuality, ethnicity, sexual history, day of attendance, symptoms, signs and specimens taken. Symptoms of GC in women were defined as change in vaginal discharge, intermenstrual or postcoital bleeding, pelvic pain, rectal discharge or bleeding. Symptoms of GC in men were defined as urethral discharge or irritation, dysuria or rectal discharge, or bleeding. Signs recorded included urethral discharge in men, mucopurulent cervical discharge, contact bleeding and cervical excitation and/or adnexal tenderness in women.

Specimen collection

Asymptomatic women were offered a self or practitioner taken vulvovaginal swab for AC2 analysis, whereas symptomatic women underwent a speculum examination with endocervical swabs taken for both AC2 and culture. To diagnose GC in asymptomatic men, a first-catch urine specimen was taken for AC2 after holding urine for at least 1 h. Symptomatic men had a urethral culture specimen taken prior to their first-catch urine specimen. Men who have sex with men (MSM) were routinely offered rectal and throat culture swabs for GC if sexual history indicated these. Rectal swabs were taken at proctoscopy if rectal symptoms were present, otherwise they were taken 'blind'. Throat and rectal AC2 swabs were mainly (but not exclusively) taken from MSM at the clinician's discretion as, at the time of the study, these sites had not been validated for AC2 use. Symptomatic patients from whom invasive specimens had been obtained had a smear performed for gram staining and microscopy. Occasionally, swabs were taken for culture/microscopy in the absence of symptoms in a patient with a high-risk history. If an AC2 specimen from an asymptomatic patient was GC positive, patients were recalled to provide a specimen for culture prior to treatment.

Detection of GC

Specimens for culture were stored in Amies transport media (TRANSWAB®; Medical Wire & Equipment Co. Ltd., Corsham, UK). They were refrigerated at 0–4°C for 2–24 h except on a Friday when this could be up to 72 h. Collected AC2 samples were stored at room temperature 2–72 h before being sent to the Health Protection Agency testing laboratory. Detection of GC by the AC2 method was performed according to the standard manufacturer's instructions. Specimens found to be GC positive were confirmed by Aptima GC (AGC). Only those specimens positive on both assays were considered as positive for GC on AC2 testing.

Details of culture methodology, gram staining and microscopy are provided in the supplementary online file.

Ethical considerations and statistical analysis

This study was registered as a service evaluation with the UHBFT Research and Development department and ethical approval was not required. Data were collected onto a standardised data sheet and subsequently entered onto an Excel spreadsheet. For the purposes of this analysis, we assumed that all confirmed NAAT positives and culture positives were true positives and these tests identified all cases of GC at any anatomical site. Data analysis was undertaken using Epi Info V.6, and sensitivity with 95% CIs was calculated. Differences in test performance on different days of the week were described using χ^2 tests for independence.

RESULTS

Patient characteristics

A total of 20 908 new male attendances were seen at the two investigation sites. Of these, 251 (1.2%) were GC positive. Of 17 074 new female attendances seen, 105 (0.6%) were GC positive (see later). Epidemiological data and details of detection site are presented in tables 1 and 2 of the supplementary online file.

Clinical findings

Sensitivity of AC2 and culture in patients with both tests taken from the same site

Table 1 shows the relationship between the test sensitivities in the presence and absence of symptoms for a given anatomical site. The NAAT and culture sensitivities for detecting GC (see Methods) from the urogenital tract in 152 symptomatic men with urethral GC were 99% (95% CI 95% to 100%) and 79% (95% CI 71% to 85%), respectively. In 17 asymptomatic men, these were 94% (95% CI 69% to 100%) and 29% (95% CI 11% to 56%), respectively. Further analysis revealed that 8 of 60 (13%) MSM with urethral symptoms were negative by AC2 and culture at the urethra but positive elsewhere. Three men were urethral culture positive for GC but urine AC2 negative. One was an asymptomatic HIV-infected MSM who had more than two partners in the last 3 months. He was also GC positive on rectal AC2 and rectal culture. The other two men reported urethral symptoms. One was an MSM with more than two partners in the last 3 months and had gram-negative intracellular diplococci demonstrated on microscopy. The other male was heterosexual with two partners recorded in the last 3 months; one of these was Afro-Caribbean.

Ten men with rectal symptoms had both AC2 and culture specimens taken from the rectal site. Sensitivity was 100% (95% CI 66% to 100%) for AC2 and 60% (95% CI 27% to 86%) for culture. In 13 asymptomatic men who had both rectal AC2 and culture specimens collected, sensitivity of AC2 was 92% (95% CI 62% to 100%) and of culture was 54% (95% CI 26% to 80%).

The AC2 and culture sensitivities from the urogenital tract in 47 symptomatic women with GC were 100% (95% CI 95% to 100%) and 53% (95% CI 38% to 68%), respectively. In 32 asymptomatic women, AC2 and culture sensitivities were 100% (95% CI 87% to 100%) and 47% (95% CI 30% to 65%), respectively.

Neisseria gonorrhoeae detection in the rectum and throat from men and women

Fifty-four men (53 MSM) had rectal AC2 samples taken, of which 37 (69%) were AC2 GC positive. Of these, 14 (38%, 95% CI 23% to 55%) were GC culture positive. Of the remaining 23

Table 1 Comparison of AC2 and culture sensitivity by anatomical site and presence or absence of symptoms, for patients who had both tests taken from the specified site

Subgroup	GC culture	NAAT positive	NAAT negative	Total
Men with urethral symptoms	Urethra			
	Positive	118	2	120
	Negative	32	0	32
	Total	150	2	152
	AC2 sensitivity 99% (150/152) (95% CI 95% to 100%)			
	Culture sensitivity 79% (120/152) (95% CI 71% to 85%)			
Men without urethral symptoms	Urethra			
	Positive	4	1	5
	Negative	12	0	12
	Total	16	1	17
	AC2 sensitivity 94% (16/17) (95% CI 69% to 100%)			
	Culture sensitivity 29% (5/17) (95% CI 11% to 56%)			
Men with rectal symptoms	Rectal			
	Positive	6	0	6
	Negative	4	0	4
	Total	10	0	10
	AC2 sensitivity 100% (10/10) (95% CI 66% to 100%)			
	Culture sensitivity 60% (6/10) (95% CI 27% to 86%)			
Men without rectal symptoms	Rectal			
	Positive	6	1	7
	Negative	6	0	6
	Total	12	1	13
	AC2 sensitivity 92% (12/13) (95% CI 62% to 100%)			
	Culture sensitivity 54% (7/13) (95% CI 26% to 80%)			
Women with vulvovaginal symptoms	Cervical			
	Positive	25	0	25
	Negative	22	0	22
	Total	47	0	47
	AC2 sensitivity 100% (47/47) (95% CI 95% to 100%)			
	Culture sensitivity 53% (25/47) (95% CI 38% to 68%)			
Women without vulvovaginal symptoms	Cervical			
	Positive	15	0	15
	Negative	17	0	17
	Total	32	0	32
	AC2 sensitivity 100% (32/32) (95% CI 87% to 100%)			
	Culture sensitivity 47% (15/32) (95% CI 30% to 65%)			

NAAT, nucleic acid amplification tests.

men, two had no rectal culture sample taken. Of these 23, 12 (52%) were GC positive at another site. Of the remaining 11, two were GC contacts, nine had two or more partners in the last 3 months and two had sex abroad. Of the female patients, one of three with a rectal AC2 sample was GC positive; of these, one culture specimen was taken which was negative. In total, 10 women had rectal culture samples taken; of these, two were GC positive (20%).

Thirty-five men (33 MSM) had AC2 throat swabs taken. Seventeen (50%) were AC2 GC positive, and of these, two (12%, 95% CI -2% to 38%) had a GC-positive throat culture. Of the remaining 15, two had no throat culture sample taken, nine were GC positive at another site, a further two were contacts of GC and two had sex abroad. Of the 105 GC-positive women, seven (7%) had AC2 throat samples taken, of which four (57%) were positive. None of these women were positive on throat culture for GC. All four women were positive for GC in at least one other site. An additional 16 women (15%) had throat culture (no AC2 throat) performed, none of which were positive.

Influence of day of the week of sample collection on culture positivity rate

Specimens taken on Friday were significantly less likely to be GC positive when compared with those taken on other days of the

week ($p=0.005$) (see table 3 supplementary online file). Thus, 23/47 (49%) people were GC culture positive on Friday compared with 142/201 (71%) people attending Monday to Thursday. Specimens taken on a Wednesday were more likely to be culture positive compared with those taken during the rest of the week ($p=0.0004$). Thus, 46/53 (87%) people were GC culture positive on a Wednesday compared with 119/195 (61%) people attending on the other days of the week. There was no difference in proportion of symptomatic male patients diagnosed by day of the week (range 63%–70%).

DISCUSSION

One hundred and one (36%) of 283 samples of GC positive by confirmed NAAT were culture negative. We think that by far the more likely explanation for this discrepant finding is low sensitivity of culture rather than low specificity of the confirmed AC2 NAAT. On the basis of this assumption, sensitivity of culture appeared particularly low in asymptomatic men, symptomatic and asymptomatic women and at extra-genital sites. Thus, at the genital tract compared with AC2, culture sensitivity was 79% (95% CI 71% to 85%) in symptomatic men and 53% (95% CI 38% to 67%) in symptomatic women. In asymptomatic men and women, the respective figures for culture sensitivity

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compared with AC2 were 29% (95% CI 11% to 56%) and 47% (95% CI 30% to 65%). At the rectum and throat in men, the sensitivity of culture was 38% (95% CI 23% to 55%) and 12% (95% CI 2% to 38%), respectively. Culture sensitivity varied by day of the week, being less sensitive on a Friday 49% (95% CI 34% to 64%), when specimens may not be plated out for 72 h, compared with 71% (95% CI 64% to 77%) on other days.

This was a large study conducted in routine clinical settings in which GC-positive individuals were identified using the microbiology and genitourinary medicine databases. All patients attending were tested with AC2 and GC positives were confirmed by Aptima GC,² with the majority also being tested by culture. Weaknesses of this study include its retrospective nature with the result that some data were missing from the case notes. Finally, only one NAAT was used to detect GC, and, while it is likely that this approach may have overestimated AC2 sensitivity as no NAAT is 100% sensitive, the literature indicates that sensitivity of AC2 is high at >95%.^{17 18}

The study is in keeping with previous observations that the AC2 is more sensitive than culture for detecting GC at genital and extra-genital sites^{4 19–23} and in asymptomatic men, compared with symptomatic men, with urethral infection.³ We believe that this is unlikely to be due to false positives because all specimens were confirmed with AGC, which detects a different target sequence than AC2. This is consistent with the studies by Moss *et al* and Lavelle *et al* who concluded that those who were AC2 positive were likely to be true positives based on culture and partner data.^{22 23} However, in both studies, AC2 GC-positive samples were confirmed by repeating the same assay on the same specimen. False positives are more likely at extra-genital sites because of commensal *Neisseria* spp.² However, this does not seem to be the case with AC2, and is consistent with our observations that those who were AC2 positive, culture negative were either positive at another site, or were at high risk of acquiring GC and with other studies which have demonstrated a high specificity of AC2 for detecting GC.^{20 21} Only five tests (3%) positive on culture were NAAT negative, three from the urethral site and two from the rectal site. The reason for this is unclear. Of the samples with discrepant results from the urethra, one man was an MSM who was AC2 positive at the rectal site, which suggests that this may have been a processing problem and not related to an isolate and which the assay is unable to detect. It is, however, possible that some of these isolates may have lost the target site in the 16S rRNA genome used by the AC2 assay.²⁴ It has been previously reported that due to genetic exchange and recombination in the target genome, GC can become undetectable by NAATs, which detect that sequence.²⁵ This requires further investigation.

Few studies have looked at the performance of culture following time since specimen was obtained. These have either compared direct plating or the use of swab transport systems. The evidence suggests that storage for 6 h or longer results in a loss in sensitivity.^{15 16} This would explain the poor performance on a Friday when specimens may not be plated out for 72 h and possibly also the better performance on a Wednesday. Wednesday morning was traditionally a walk-in service at both centres, the busiest clinic of the week. There were two collections a day, early and late afternoon, with some specimens being stored overnight. As the better performance on Wednesday cannot be explained by a greater proportion of symptomatic men being diagnosed, one possible explanation is that, on Wednesdays, fewer specimens containing GC may have been stored overnight. In response to the findings of this study, we have instituted twice daily specimen collections and are in

the process of addressing training, operational and logistical issues, so that all specimens are processed within 6 h of collection. Ultimately we intend to introduce direct plating, and in the near future, we will trial its introduction prior to full implementation.

The use of a transport system is likely to explain the low sensitivity of culture reported in our study compared with others that used direct plating.^{26 27} However, direct plating may not necessarily be more sensitive than swabs. Human *et al*¹⁶ and Rishmawi *et al*¹⁵ used an in vitro approach which compared the ability of transport media to maintain GC viability over time, using the CLSI procedures M40-A (quality control of microbiological transport systems) for evaluating swabs.²⁸ The charcoal transport system of Medical Wire & Equipment was not able to maintain viability of GC beyond 6 h, whereas the Copan M40 Transystem Amies without charcoal was able to maintain viability for up to 48 h. Olsen *et al*¹⁴ observed a sensitivity of 98% and 95% after 6 and 24 h, respectively, for a Copan transport system compared with direct plating of clinical samples. In view of this, we intend to perform a comparison of different swab transport systems for use in the community.

Many of the individuals who were GC NAAT positive were asymptomatic, especially women who reported less high-risk behaviour. As AC2 performs better than culture in asymptomatic men and all women, it would seem sensible that all patients have dual NAAT testing performed, with culture being reserved for symptomatic men, women requiring a speculum examination and any patient who is NAAT GC positive prior to treatment. This has the advantage of eliminating invasive testing for initial GC diagnosis and reducing consultation costs in those not requiring examination. Isolates from patients who are NAAT GC negative, culture positive should be investigated for possible loss of the NAAT target genome site.

The AC2 with AGC confirmation performs well at genital and extra-genital sites for detecting *N gonorrhoeae*. Culture for GC using TRANSWAB® (Medical Wire & Equipment) performs poorly in asymptomatic men, symptomatic and asymptomatic women and at extra-genital sites. We believe that swabs taken in a community setting are likely to perform less well than those taken in our department due to greater chance of transport delays. If dual testing NAATs are available, routine culture should be limited to those individuals in whom treatment will be offered unless they are symptomatic and male. Those subsequently found to be NAAT GC positive should be advised to attend their local GU department for culture confirmation. If transport swabs are used, these need to be set up for culture

Key messages

- ▶ Aptima Combo 2 with Aptima GC confirmation performs well at genital and extra-genital sites for detecting *Neisseria gonorrhoeae*.
- ▶ Culture for gonorrhoea using swabs performs poorly in asymptomatic men, symptomatic and asymptomatic women and at extra-genital sites.
- ▶ If dual testing NAATs are available in a community setting, routine culture should be limited to those requiring immediate treatment unless symptomatic and male.
- ▶ In view of increasing GC antimicrobial resistance, research is needed into how best to optimise GC culture in settings where direct plating is not feasible.

within 6 h.²⁹ With the improved performance of NAATs and the propensity for GC to develop antimicrobial resistance, research is needed into how best to optimise GC culture in settings where direct plating is not feasible.

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Competing interests Dr Paddy Horner has been involved in a multi-centre evaluation of a new molecular diagnostic test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by Siemens Healthcare Diagnostics Inc., for which his department received funding. None declared for other authors.

Contributors PH, LH, SS and DC conceived the study. PH, LH, SC, JM and DC informed the study design. LH and SS collected the data with the support of PH and AF. LH, SS, PH and JM analysed the data and DC and OMW contributed to data interpretation. LH and SS prepared the first draft of the manuscript with support of PH. All authors were involved in reviewing and revising subsequent drafts.

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