Assessing the Frequency of Spontaneous Clearance of Gonococcal Infection in the Absence of Antibiotic Therapy: a review of the literature

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Background

- In the last few decades, *Neisseria gonorrhoeae* has developed resistance against many different antimicrobials. Internationally there is increasing concern regarding the potential of "untreatable" gonorrhoea [1].
- Despite many countries employing dual antimicrobial therapy as first line treatment, cases with resistance to both ceftriaxone and azithromycin have been identified [2].
- Antimicrobial stewardship is essential for the control of antimicrobial resistance and includes the avoidance of antibiotics when not required
- Clearance of gonorrhoea without treatment has been reported, yet there is little information regarding
  - How often this occurs
  - The timescale within which it occurs
  - Whether it varies by site of infection
  - If other factors, such as previous gonococcal infection, play a role
- We undertook a review of the literature
  - To estimate the frequency of spontaneous clearance of gonococcal infection
  - To identify potentially important mediating factors
  - To inform priorities for future research

Methods

- Following initial scoping to establish terminologies, a literature search was performed using Medline, EMBASE, CINAHL and Cochrane databases.
- Conference posters, oral presentations and letters to editor were included in addition to randomised controlled trials, non-randomised trials, cohort studies and case series

Figure 1: Search terms

((“Neisseria gonorrh*” OR gonorrh* OR gonococc*) AND (“natural clearance” OR clearance” OR “natural resolution” OR “spontaneous clearance” OR “spontaneous resolution” OR “resolv* infection” OR “self-clear*” OR “repeat* sampling “))

in Title or Abstract for publications in English between 01/01/1975 and 01/06/2018

The search identified 186 relevant papers – Figure 2

- 79 duplicates were removed and 98 papers excluded after review of title and abstract
- Full text of 9 papers was reviewed

  Of these 9 papers:
  - 2 were excluded because they did not specifically provide original data on spontaneous clearance. One paper used mathematical modelling and epidemiological measures to describe the short duration of pharyngeal gonorrhoea [3], the other referred to difficulties in confirming spontaneous clearance given the discrepancies in sensitivity and specificity of testing methodologies available. [4]
- An additional scoping exercise (this included cross checking references and wider reading on testing and test of cure timing at genital and extra genital sites)identified three other papers not identified by the literature search; two because publication was over 30 years ago and an electronic search of abstracts was unavailable

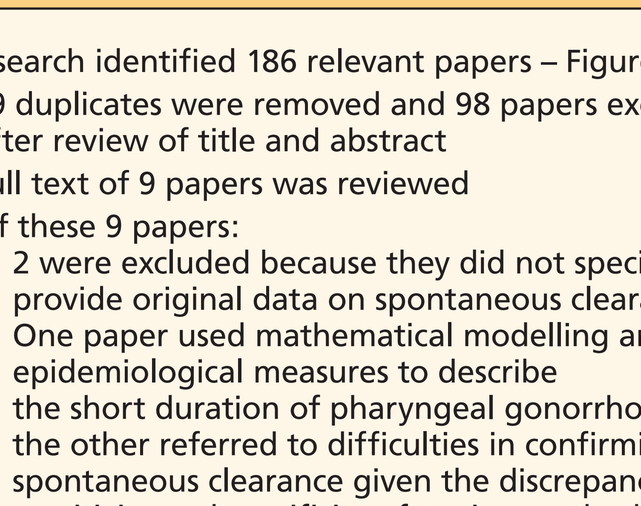


Figure 2. Flow chart for selection of studies

	Study design and publication type	Gonorrhoea diagnostic test	Site(s) of infection	Time between initial and repeat testing	Proportion of negative tests on repeat testing before treatment
Chow *et al 2016 [5]*	cohort short report	NAAT* and culture	pharynx	7 days (culture) 14days (culture) 14 days (NAAT*)	40% (13/33) on culture on day 7 57% (19/33) on culture on day 14 6% (2/33) on NAAT*
Apewokin *et al 2010 [6]*	cohort letter to editor	NAAT*	pharynx	median 11 days	27% (3/11)
van Liere *et al 2013 [7]*	cohort conference poster abstract	NAAT*	vulvovaginal extra-genital (pharynx and rectal)	median 11 days	20% (5/25) vulvovaginal 12% (2/9) extra-genital 19% (3/16)
Wallin *et al 1979 [8]*	cohort letter to editor	culture	pharynx	up to 12 weeks	100% (17/17)
Hutt *et al 1986 [9]*	cohort published paper	culture	pharynx	up to 7 days	55% (33/60)
Bissessor *et al 2013 [10]*	cohort conference poster abstract	culture	pharynx	median 7 days	31% (20/61) tonsils 48% (29/61) oropharynx 30% (18/61) both sites combined
Wind *et al 2016 [11]*	cohort published cohort study	NAAT*	sites not specified	not specified	6% (5/77)
Hantana *et al 2017 [12]*	cohort short report	NAAT*	pharynx	not specified	6% (139/2204)
Nguyen *et al 2015 [13]*	cohort conference poster abstract	NAAT*	sites not specified	not specified	24% (11/46)
Sultan *et al 2016 [14]*	cohort conference poster abstract	NAAT*	sites not specified	not specified	24% (20/84)

Figure 3. Summary of studies included in review *NAAT – nucleic acid amplification Test

Results

- The search overall identified:
  - 10 cohort studies, with a of total of 2618 patients
- There was considerable heterogeneity between the studies and none was specifically designed to assess spontaneous infection clearance
  - A variety of testing methods were used to detect *N.gonorrheae*; 6 studies used NAAT, 3 used culture and 1 used both.
- Populations included men and women with infection at a variety of anatomical sites
- Timescales between initial and repeat testing were variable (Figure 3)
  - 1 study demonstrated an increase in clearance rate at 14 days compared to 7 days after initial testing [5].
  - 2 studies performed sequential pharyngeal cultures; in 1 study all samples were negative by 12 weeks [8] and in the other 55% of samples were negative by 7 days [9].
- Overall spontaneous clearance rate was 9.7% (253/2618)
- Spontaneous clearance rates by test method
  - culture: 48%- 100%
  - NAAT 6%-27%
- Spontaneous clearance rates by site of infection is shown in Figure 5
  - 6 studies assessed spontaneous clearance at the Pharynx; 2 using NAAT, 3 culture and 1 both techniques. Average clearance rate was 32% (range 6% -100%)
  - 1 study assessed spontaneous clearance at the vulvovaginal site, using NAAT. The clearance rate was 20%.
  - 1 study grouped pharyngeal and rectal sites as “extra-genital” and used NAAT the clearance rate was 19%
  - No study reported on spontaneous clearance at urethral and rectal sites separately.

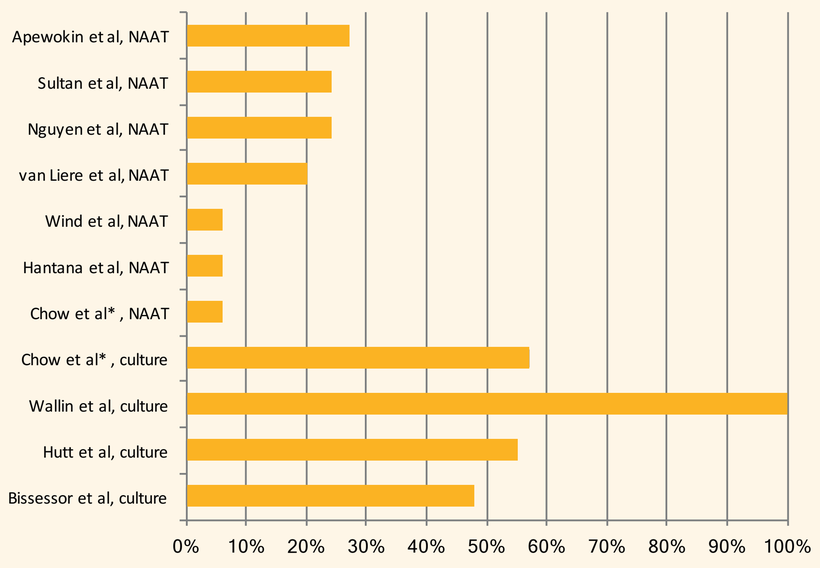
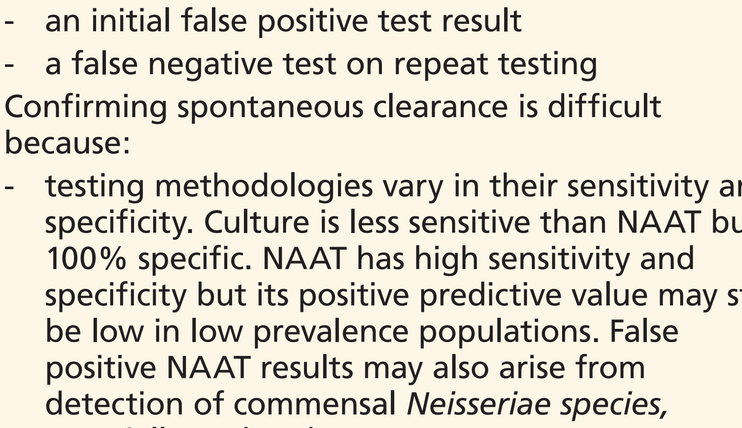


Figure 4. Spontaneous clearance rates in each study



Discussion

- Few available studies include information on how frequently spontaneous clearance of gonorrhoea occurs
- The majority of the studies reviewed were published as conference abstracts and lack methodological detail and in depth results on which to draw firm conclusions
- The reversion of an initially positive test result to negative (without treatment) could be due to:
  - ‘spontaneous’ clearance by the host immune system
  - an initial false positive test result
  - a false negative test on repeat testing
- Confirming spontaneous clearance is difficult because:
  - testing methodologies vary in their sensitivity and specificity. Culture is less sensitive than NAAT but 100% specific. NAAT has high sensitivity and specificity but its positive predictive value may still be low in low prevalence populations. False positive NAAT results may also arise from detection of commensal *Neisseriae species,* especially at the pharynx.
  - using a combination of test approaches (e.g. culture and NAAT) will help to identify how frequently spontaneous clearance of infection occurs.
- The majority of studies have evaluated pharyngeal clearance, there is little data on rectal, urethral, vulvovaginal and endocervical sites.
- There is insufficient evidence at present to accurately estimate how quickly spontaneous clearance might occur
  - One study from 1979 [8] reported spontaneous clearance of pharyngeal gonorrhoea (using culture) in all patients by 12 weeks. Although this has not been replicated using the more sensitive NAAT, epidemiological evidence suggests that pharyngeal gonorrhoea persists for an average of 4 months and that untreated rectal gonorrhoea may persist for around 1 year [15].
- This current review identifies important gaps in our knowledge regarding spontaneous clearance of gonorrhoea, especially at sites other than the pharynx.
- The available literature suggests that 6-27% of those with gonorrhoea will clear their infection without treatment over a period of several weeks. This is a significant proportion and, if confirmed, suggests that use of a point of care test to confirm infection before treatment may be useful to avoid inappropriate antimicrobial use.

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