



## Global view

# In vitro activity of several antimicrobial agents against *Neisseria gonorrhoeae* in the western region of the Kingdom of Saudi Arabia

### Introduction

The causative organism of gonorrhoea, the gonococcus *Neisseria gonorrhoeae* was discovered by Neisser in 1879. Leistikow in 1882 and Bumm in 1885 grew the organism on culture medium and the latter also successfully inoculated the male urethra, producing characteristic symptoms and signs of gonorrhoea. Considerable changes have occurred over the last century in the incidence of gonorrhoea and other sexually transmitted diseases (STDs) worldwide. Penicillin has been used as first line of therapy for gonorrhoea for over 40 years, but increased resistance of *N gonorrhoeae* to penicillin has been reported from many centres around the world. At present, the World Health Organisation guidelines recommend one of the following single dose drugs as the first line of therapy: ciprofloxacin, 500 mg orally; ceftriaxone, 250 mg intramuscularly; or spectinomycin, 2 g intramuscularly. Penicillin is only recommended where resistance is rare.<sup>1</sup> The aim of this study was to determine the antibiotic susceptibility of all *N gonorrhoeae* organisms isolated during a period of 3 years, and to compare the finding with similar published studies.

### Materials and methods

To assess the *N gonorrhoeae* antibiotic susceptibility patterns, we reviewed the records and microbiology results of all cases associated with positive cultures for *N gonorrhoeae* at our institution from January 1994 through to February 1997. The strains of *N gonorrhoeae* isolated were examined for susceptibility to

penicillin, ampicillin/amoxicillin, spectinomycin, ciprofloxacin, and ceftriaxone by single disc diffusion technique.

### Results

We identified 67 patients; 58 (86.6%) male and nine (13.4%) female. All female patients were referred by the gynaecology clinic. The mean age was 25.5 years. Only 38.8% of the isolates were sensitive to penicillin, whereas all isolates were sensitive to spectinomycin, ciprofloxacin, and ceftriaxone. Screening for other STDs including a chlamydia test in both sexes and testing for *Trichomonas vaginalis* in females was carried out routinely. Patients were also tested for syphilis and HIV serology. All patients were treated successfully with spectinomycin. Routine follow up in all patients revealed excellent clinical and microbiological cure.

### Discussion

The genitourinary medicine clinic at King Khalid National Guard Hospital serves a local patient population including national guard personnel and their dependants (60%) and non-national guard patients (40%). All patients had acquired *N gonorrhoeae* infection in the Jeddah area. Of the 67 isolated cases, the majority (58) were male; this may be because the asymptomatic nature of gonorrhoea in some women which may account for non-attendance at a clinic, the nature of the studied groups (national guard soldiers), and the unavailability of a contact tracing programme. There has been no similar study in the Kingdom of Saudi Arabia, but a study from

the region (Dubai<sup>2</sup>) showed that the penicillin resistant *N gonorrhoeae* rate to be 67%. In a study from Indonesia,<sup>3</sup> the penicillin resistant rate was 89% and in the Philippines it was 55%.<sup>4</sup> Our report, as well as others, confirms that gonococcal infections caused by antimicrobial resistant strains of *N gonorrhoeae* have spread into many geographic areas and have increased in prevalence in the past 20 years. These data support the use of spectinomycin as first line therapy. The drug is cheap and available in Saudi Arabia. Ciprofloxacin and ceftriaxone appear to be effective alternates.

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## Antimicrobial susceptibility of *Neisseria gonorrhoeae* isolates from men with urethritis in Kenya

### Introduction, materials, and methods

Periodic monitoring of the susceptibility profiles of *Neisseria gonorrhoeae* strains is important in order to adapt empirical treatment strategies. The recommended, cumbersome technique is determination of the minimal inhibitory concentration (MIC) by the agar dilution technique. The Etest is a recently developed technique, easy to use, and also validated for gonococci.<sup>1,2</sup>

During a study in 1995-6 on urethritis in male patients in Nairobi, Kenya, *N gonorrhoeae* isolates were identified. No selection of isolates was done and 177 strains were available for testing. Identification of the isolates was confirmed using a rapid carbohydrate degradation test.<sup>3</sup>

β Lactamase production was detected with

nitrocefine solution. Susceptibility testing was conducted with Etest (AB Biodisk, Solna, Sweden) on supplemented gonococcal agar, incubated in 5% carbon dioxide for 24 hours at 36°C. Quality control was done with *N gonorrhoeae* ATCC 49226. Antibiotics tested are listed in table 1.

The susceptibility for trimethoprim-sulphamethoxazole (1/19) of the strains categorised as resistant with the first method were retested using a second medium: diagnostic sensitivity test (DST) agar, supplemented with 5% lysed horse blood and 1% Kellogg's supplement.<sup>1</sup>

### Results

The results of the MIC determinations for the antibiotics tested are presented in table 1.

Breakpoints were used according to the National Committee for Clinical Laboratory Standards (NCCLS)<sup>4</sup> or suggested by other sources.

One hundred and two (56%) of the isolates are β lactamase producing isolates (PPNGs) and thus considered resistant to treatment with penicillin and amoxicillin.<sup>4</sup> MICs for penicillin were performed on non-PPNGs only. Of 75 non-PPNG strains five were susceptible to penicillin, 63 had reduced susceptibility, and seven were fully resistant. The overall complete resistance to penicillin G is 63%.

Clavulanic acid neutralises the activity of gonococcal β lactamase and restores the MICs of amoxicillin to values similar to non-PPNGs. All isolates have very low MICs for ceftriaxone and are all susceptible. None of the isolates is

Table 1 Susceptibility data on 177 recent cases of *N gonorrhoeae* in Kenya

	Criteria for susceptibility* † ‡	MIC <sub>50</sub> †	MIC <sub>90</sub> †	MIC range†	% Resistant isolates	Ref
Penicillin G						
PPNG§ (n=102)		NT	NT	NT		
non-PPNG (n=75)		0.125	0.38	0.012-1		
all (n=177)	low level resistance: 0.06-0.25 high level resistance: MIC ≥0.5 or PPNG				low level resistance: 34.5% high level resistance: 63%	4
Amoxicillin + clavulanate (2/1) (MICs are given for amoxicillin only)	S if ≤2	0.38	0.75	0.38-1	0%	9
Ceftriaxone	S if ≤0.25	≤0.002	0.004	≤0.002-0.032	0%	4
Tetracycline	low level resistance 0.25-8 high level resistance ≥16	32	64	0.32-96	Moderately resistant 14% fully resistant 86%	4
Erythromycin	R if ≥8	0.190	0.25	0.023-1	0% (see discussion)	12
Azithromycin	R if ≥2	0.023	0.047	≤0.016-0.19	0%	10
Trimethoprim-sulphamethoxazole (1/19) (MICs are given for trimethoprim only) tested on GC agar (n=177)	R if ≥4					1
tested on supplemented DST agar (n=24)¶		1	4	0.064-≥32	(14%)	
Chloramphenicol	R if ≥2	0.5¶	1¶	0.064-4¶	0%	
Spectinomycin	S if ≤32, R if ≥128	0.38	0.5	0.1-1	0%	1
Norfloxacin	decreased susceptibility: ≥0.25	4	8	3-12	0%	4
Ofloxacin	decreased susceptibility: ≥0.25	≤0.016	0.016	0.016-0.125	0%	5
		0.008	0.012	0.004-0.032	Decreased susceptibility: 0%	4

\*S = susceptible, R = resistant.

†MIC and breakpoint values are in µg/ml.

‡Criteria = according to NCCLS or as in reference.

§PPNG = penicillinase producing *N gonorrhoeae*.

¶Tested on strains with MICs >2 µg/ml on GC agar.

fully susceptible to tetracycline; 86% display high level resistance. All isolates have low MICs for erythromycin and even lower MICs to the azalide azithromycin.

Strains with MIC ≥4/76 µg/ml to trimethoprim-sulphamethoxazole are considered resistant.<sup>1</sup> Fourteen per cent of the studied gonococci fulfilled this criterion. We retested all resistant strains on the more reliable, supplemented DST agar<sup>1</sup> and all isolates were considered susceptible. All strains were also susceptible to spectinomycin,<sup>4</sup> and chloramphenicol and none of the isolates was resistant to fluoroquinolones or had reduced susceptibility to quinolones.<sup>5</sup>

## Discussion

In the past gonococci were susceptible to penicillins and tetracyclines, and responded to fairly low doses of these antibiotics. Selected by the use of antibiotics very susceptible isolates were replaced by isolates with higher MICs: infections with these gonococci were still treatable, although higher doses are required. Recently, isolates appeared fully resistant to penicillin and tetracycline. The frequency of this resistance varies. Because of the increasing resistance new treatment strategies are being advocated. The Centers for Disease Control (CDC) had recommended new treatment regimens for gonococcal infections. Ofloxacin, ciprofloxacin, cefixime, or ceftriaxone were chosen for the treatment of uncomplicated gonococcal infection, because of their proved efficacy and safety when used in single dose regimens.<sup>6</sup>

In our study we did not find resistance to ceftriaxone. Quinolone resistance recently emerged in the Far East<sup>7</sup> but was not present in the population under study. Hence, the recommendations made by the CDC are valid for the treatment of gonorrhoea in Kenya.

Norfloxacin, to which we did not find any resistance, is a less expensive fluoroquinolone, only used for treatment of gastrointestinal and genital infections. It has been proposed as an alternative for the treatment of gonorrhoea.<sup>8</sup>

Amoxicillin + clavulanic acid is not selected as a drug of choice by the CDC.<sup>6</sup> Unacceptably low cure rates were reported in early studies when low doses of clavulanate were

used; in a study where a 2:1 ratio was used a cure rate of 100% was obtained.<sup>9,10</sup>

We found that erythromycin and the azalide azithromycin were effective. Single dose treatment with erythromycin has only been advised in combination with rifampicin. Single dose treatment with azithromycin, 1 or 2 g,<sup>11,12</sup> has been demonstrated to be effective for uncomplicated gonorrhoea and *C trachomatis* infection. This is however an expensive drug. Spectinomycin, trimethoprim-sulphamethoxazole, and chloramphenicol (or thiamphenicol) also showed high activity in this study.

In summary, we documented very high resistance rates to tetracycline and penicillin in recent Kenyan gonococcal isolates. As a consequence these antibiotics are useless for the treatment of gonorrhoea. There was no resistance to a number of antibiotics that have been advocated recently as first choice regimens (ofloxacin, ceftriaxone) or as alternatives (norfloxacin, amoxicillin+clavulanic acid, and azithromycin). However, a major drawback for the use of these antibiotics in developing countries is their high cost. An interesting finding of our study is the good in vitro susceptibility of the isolates to less expensive drugs—spectinomycin, which is not available for oral use, and the orally available trimethoprim-sulphamethoxazole, chloramphenicol, and erythromycin.

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