

## The Return of Gonorrhea

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In March 2000 a committee was appointed by the Israel Ministry of Health to re-examine the need for ocular prophylaxis at birth, because many neonatologists were questioning the relevance of preventive measures against gonococcal conjunctivitis, stating that ophthalmia neonatorum had not been observed in Israel “for years.”

At the same time, data began to accumulate alluding to what would later be recognized as an evolving epidemic of gonorrhea. The incidence of gonococcal infection in Israel began to increase in 1998: while the mean annual incidence during most of the 1990s was 0.97 per 100,000 population, it sharply increased to 8.37 per 100,000 in 2000, and 14.5 per 100,000 in 2001 [1]. Similar rates were reported during the 1950s and mid-1960s (approximately 17 per 100,000). This was followed by a steep increase beginning in 1967, leading to a peak of 40.48 per 100,000 in 1970 and coinciding with the “Belle Epoque” that followed the 1967 Six Day War. During the 1970s and early 1980s a slow decline in the incidence was registered, followed by a marked fall in the annual rates to the nadir observed in the 1990s.

A similar trend of resurgence of gonorrhea in recent years is also being observed in several European countries, such as Sweden [2], Denmark [3], the United Kingdom [4] and France [5]. However, the available data on the prevalence and incidence of gonorrhea are far from reflecting the real disease burden. Under-diagnosis is a significant problem because *Neisseria gonorrhoeae* infection in women is very often asymptomatic or produces non-specific, mild symptoms that do not promote health-seeking action. It is not surprising, therefore, that male patients account for 96% of the reported cases in the present epidemic. Another problem is the under-reporting of the infection even when it is accurately diagnosed, so that notified disease may represent only a fraction of the actual morbidity. According to some estimates, as few as 10% of diagnosed cases are reported in developed countries [6]. The reasons include privacy/stigmatization concerns, flaws in reporting systems, a perception by patients and practitioners that little is to be gained from the notification process, and general lack of interest [7]. The problem of under-diagnosis and under-reporting can be resolved by the use of laboratory diagnosis and screening programs. In one such survey, gonorrhea was diagnosed by polymerase chain reaction testing of urine in 1.1% of 708 Israeli female soldiers [8].

One of the major aspects of the ongoing epidemic is the high rate of gonococcal resistance to fluoroquinolones: among 100 clinical isolates studied, 61 were fully resistant to ciprofloxacin (minimal inhibitory concentration  $\geq 1.0$  mg/L) [Table 1] [9]. This is in sharp contrast to the situation in the pre-epidemic years, during

**Table 1.** Antimicrobial susceptibility of 100 gonococcal strains isolated in Israel

Agent	Susceptible	Intermediate	Resistant
Penicillin	11	73	16
Tetracycline	26	66	8
Ciprofloxacin	36	3	61
Ceftriaxone	100	0	0
Spectinomycin	100	0	0

Source: Dan et al. [9]

**Table 2.** Recommended regimens for the empiric treatment of urethritis/cervicitis in Israel

Target	Agent	Dosage
Gonorrhea	Cefixime (Supran®)	400 mg orally, single dose
	or	
	Ceftriaxone (Rocephin®)	125–250 mg i.m., single dose
Chlamydia	Spectinomycin (Togamycin®)	2.0 g i.m., single dose
	plus	
Chlamydia	Azithromycin (Azenil®)	1.0 g orally, single dose
	or	
	Doxycycline (Doxilyn®)	100 mg orally twice a day for 7 days

Source: Centers for Disease Control [12], modified.

which no case of fluoroquinolone resistance was documented [10]. Consequently, fluoroquinolones such as ciprofloxacin, ofloxacin and levofloxacin should no longer be used in Israel for the empiric treatment of (gonococcal) urethritis/cervicitis [Table 2] and other gonococcal infections. The present prevalence of fluoroquinolone resistance in Israel is similar to the rates observed in the Far East, and much higher than the figures reported in Western Europe and North America, although there, too, resistance is increasing [7]. Analysis of the fluoroquinolone-resistant gonococci in Israel disclosed that resistant strains were grouped within a narrow range of MICs (2.0–8.0 mg/L) [9]. Moreover, unlike susceptible strains, all resistant isolates had the same pulsed field gel electrophoresis pattern [10]. This uniformity of the resistant isolates was recently confirmed by PIB porin typing and DNA sequencing studies: resistant isolates represented two subtypes, while one PIB type predominated; all ciprofloxacin-resistant strains showed identical

MIC = minimal inhibitory concentration

mutations in amino acids [11]. These findings suggest an outbreak by a single clone that developed or was introduced over a short period.

What is the contribution of the high fluoroquinolone resistance to the spread of gonorrhoea in Israel? Since effective treatment of infected persons is one of the most important components of prevention [12], the impact of antibiotic resistance on the expansion of the epidemic seems evident yet difficult to quantify.

What has caused the recent resurgence of gonorrhoea in Israel and some European countries? There is more than one possible explanation. An important factor is the increase in travel: there has been an exponential rise in travel for pleasure in the past few decades. The amount and speed of travel favors transmission of strains from one country to another [13]. Individual travelers spread new strains of gonococci upon returning to their country of origin, as was documented in Sweden [14], Finland [15] and the UK [16]. There is no evidence, however, that this factor has been involved in the Israeli epidemic. Although the high rate of resistance to fluoroquinolones is reminiscent of the situation in the Far East, most of our cases (97%) contracted the infection within Israel (unpublished data). Another possible cause relates to the core-group theory, according to which the spread of gonorrhoea is facilitated through high risk groups such as sex workers. Indeed, about half the Israeli gonorrhoea patients interviewed admitted having paid for sex. The sex-worker population in Israel has been augmented in the past few years by foreign workers from the former Soviet Union (mainly Russia, Ukraine and Moldova), where gonorrhoea prevalence is substantially higher. High rates of gonococcal carriage in the pharynx (9%) and genital tract (3.1%) were documented in this group [17]. However, information on the prevalence of gonococcal resistance to fluoroquinolones in their countries of origin is very limited.

Gonorrhoea may have very hazardous consequences, particularly in women and newborns. The complications of the genital infection include pelvic inflammatory disease with possible sequelae such as tubal infertility, ectopic pregnancy, and chronic pelvic pain. Gonococcal infection among neonates most often results from exposure to infected cervical exudates at delivery. It is usually an acute illness that starts 2–5 days after birth. The most severe manifestations of *N. gonorrhoeae* infection in newborns are ophthalmia neonatorum and sepsis, including arthritis and meningitis. Up to 30% of infants born to women who have gonorrhoea at the time of delivery will develop ophthalmia neonatorum. If not treated there is a risk of disease progression, with corneal involvement, perforation of the globe of the eye and blindness. Gonococcal conjunctivitis is strongly suspected when intracellular Gram-negative diplococci are identified in conjunctival exudates, justifying presumptive treatment after appropriate cultures are obtained; chlamydial testing should be done concomitantly. A definitive diagnosis is important because of the public health and social consequences of a diagnosis of a sexually transmitted infection. The patient should be hospitalized, evaluated for signs of disseminated infection, and receive daily eye care by a specialist. One dose of ceftriaxone (25–50 mg/kg intravenously or

intramuscularly, not to exceed 125 mg) is adequate therapy for gonococcal conjunctivitis (topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is administered) [12].

One of the mainstays in the management of sexually transmitted infections is action to limit the spread of infection. Prevention is based on the following concepts: a) education and counseling on safe sexual behavior; b) identification of asymptotically infected persons and symptomatic patients unlikely to seek diagnosis and treatment; c) effective diagnosis and treatment of infected persons; d) evaluation, treatment, and counseling of sex partners of persons with a sexually transmitted infection; and e) pre-exposure vaccination of persons at risk [12]. If a person chooses to have sex with a partner whose infection status is unknown, a new condom should be used for each act of insertive intercourse (e.g., vaginal, anal, and oral). In fact, in the present gonorrhoea outbreak in Israel, the majority of patients acquired the infection following unprotected oral sex (fellatio). When used consistently and correctly, male latex condoms are effective in preventing the sexual transmission of infections, particularly those transmitted by fluids from mucosal surfaces (e.g., gonorrhoea, chlamydial infection, trichomoniasis, and human immunodeficiency virus). The best method of preventing neonatal gonococcal (and chlamydial) infections is to diagnose and treat these infections in pregnant women. However, since not all women are screened for gonorrhoea and chlamydial infection during prenatal care, ocular prophylaxis is recommended: it can prevent sight-threatening gonococcal ophthalmia, and is safe, easy to administer and inexpensive. The U.S. Centers for Disease Control and Prevention recommend one of three preparations to be used in a single application: a) silver nitrate (1%) aqueous solution (can cause local irritation), b) erythromycin (0.5%) ophthalmic ointment, and c) tetracycline (1%) ophthalmic ointment. One of these preparations should be instilled into both eyes of every neonate as soon as possible after birth [12]. More recently, povidone-iodine (2.5%) solution was found to be as effective as silver nitrate or erythromycin in preventing gonococcal ophthalmia [18]. Most experts feel, however, that more experience is needed before this preparation can be recommended for prophylaxis of ophthalmia neonatorum.

The case of gonococcal ophthalmia neonatorum reported by Fruchtman et al. in this issue of *IMAJ* [19] reflects the main aspects of the present situation in Israel regarding gonorrhoea: it is here again with its complications but is more resistant to antimicrobial agents. At the start of the 21st century we should remain vigilant to the threat of sexually transmitted infections in general, and gonorrhoea in particular, with emphasis on all aspects of prevention – the cornerstone of modern medicine.

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