

# Uterine Cervical Non-Gonococcal and Non-Chlamydial Bacterial Flora and its Antibiotic Sensitivity in Women with Pelvic Inflammatory Disease: Did it Vary over 20 Years?

Samuel Lurie MD<sup>1,3</sup>, Halla Asaala MA<sup>3</sup>, Orna Schwartz Harari MA<sup>2</sup>, Abraham Golan MD FRCOG<sup>1,3</sup> and Oscar Sadan MD<sup>1,3</sup>

<sup>1</sup>Department of Obstetrics and Gynecology and <sup>2</sup>Microbiology Laboratory, Wolfson Medical Center, Holon, Israel

<sup>3</sup>Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

**ABSTRACT:** **Background:** Although the presence of bacteria in the cervix is not a sign of disease, the majority of pathogens involved in pelvic inflammatory disease originate from this "normal" flora.

**Objectives:** To assess the distribution of cervical non-gonococcal and non-chlamydial bacteria in hospitalized women with PID and the bacteria's antibiotic sensitivity.

**Methods:** We retrospectively evaluated the cultures obtained from the uterine cervix over a 1 year period (2008) at Wolfson Medical Center, Holon. The distribution of cervical non-gonococcal and non-chlamydial bacteria in women with PID and the bacteria's antibiotic sensitivity was compared to that in our previous 1 year study that was performed at Kaplan Medical Center, Rehovot (1988–89).

**Results:** In 2008, a total of 412 cultures were obtained of which 126 (30.5%) were sterile. The prevalence of negative cultures was similar in 2008 and in 1988, namely, 30.5% and 33.7%, respectively ( $P = 0.23$ ). PID was finally diagnosed in 116 patients with positive cultures. The most prevalent bacteria in the 2008 study were *Enterococcus* species and *Escherichia coli* – 24.0% and 26.4% respectively compared to 18.0% and 38.1% in the 1988 study, with the decrease in *E. coli* isolates being significant ( $P = 0.0003$ ). In 2008 the antimicrobial sensitivity for various antibiotics ranged from 44.3% to 100.0% (median 90.2%) while in 1988 it ranged from 2.9% to 80.1% (median 51.9%).

**Conclusions:** The cervical bacterial flora in hospitalized women with PID did not vary significantly between 1988 and 2008. However, antimicrobial sensitivity of the isolated bacteria increased dramatically, probably due to a decrease in resistance to antibiotics.

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**KEY WORDS:** bacterial flora, pelvic inflammatory disease, antimicrobial sensitivity, uterine cervix, cultures

The presence of bacteria in the cervix, as in the vagina, is not necessarily evidence of disease [1]. Basically, the normal cervical flora resembles the normal vaginal flora, comprising both aerobic and anaerobic organisms [2,3]. Nevertheless, cervicitis or even colonization of the cervix by certain bacteria may antecede pelvic infection [4]. Indeed, most of the pathogens involved in pelvic inflammatory disease originate from this "normal" flora, whereas *Neisseria gonorrhoeae* or *Chlamydia trachomatis* are isolated less often [5–7].

Ongoing surveillance of local epidemiology and of antimicrobial resistance is essential for empirically treating infections and controlling resistant microorganisms [8,9]. About 20 years ago one of the present authors (S.L.) investigated the distribution of cervical non-gonococcal and non-chlamydial bacteria in women with suspected PID and the bacteria's antibiotic sensitivities in a typical Israeli hospital (Kaplan Medical Center, Rehovot) [1]. In an attempt to explore any change in distribution of cervical non-gonococcal and non-chlamydial bacteria in women with suspected PID and the bacteria's antibiotic sensitivities over these 20 years, we embarked on a similar analysis during the same length of time (12 months). Even though the current study was carried out in a different hospital (Wolfson Medical Center, Holon), the proximity of the two facilities (about 20 kilometers) implies a similar population. Accordingly, this comparison may elucidate a secondary question: which antibiotic should be used before the results of the cultures are received?

## MATERIALS AND METHODS

The study protocol was approved by the Wolfson Institutional Review Board Committee (protocol number 973-2008). We performed a retrospective analysis of the cultures obtained from the uterine cervix over a 1 year period (2008) at Wolfson Medical Center. The cultures were routinely obtained in symptomatic patients. These cultures were sent to the medical center's microbiology laboratory for routine culturing for non-sexually transmitted pathogens. The isolated bacteria were identified and checked for antimicrobial sensitivity. The charts

PID = pelvic inflammatory disease

**Table 1.** Prevalence of non-sexually transmitted pathogens among cultures taken in 2008

	Cultures in 2008 (n=257)
<i>Escherichia coli</i>	60 (23.3%)
<i>Enterococcus</i> spp	46 (17.9%)
<i>Staphylococcus</i> coagulase negative	42 (16.3%)
<i>Streptococcus viridians</i>	24 (9.4%)
<i>Streptococcus</i> Group B	24 (9.4%)
<i>Klebsiella pneumoniae</i>	12 (4.7%)
<i>Bacteroides fragilis</i>	10 (3.9%)
<i>Staphylococcus aureus</i>	7 (2.7%)
<i>Bacillus</i> spp	6 (2.3%)
<i>Citrobacter koseri</i>	5 (1.9%)
<i>Enterobacter</i> spp	5 (1.9%)
<i>Haemophilus</i> spp	5 (1.9%)
<i>Proteus mirabilis</i>	4 (1.6%)
<i>Corynebacterium</i> spp	2 (0.8%)
<i>Streptococcus pasteurianus</i>	2 (0.8%)
<i>Streptococcus</i> Group G	1 (0.4%)
<i>Streptococcus</i> Group A	1 (0.4%)
<i>Streptococcus salivarius</i>	1 (0.4%)

**Table 2.** Prevalence of non-sexually transmitted pathogens among patients with PID with positive cultures taken in 2008 compared to 1988

	Cultures in 2008 (n=100)	Cultures in 1988 (n=582)	P value
<i>Enterococcus</i> spp	24 (24.0%)	154 (26.4%)	NS
<i>Escherichia coli</i>	18 (18.0%)	222 (38.1%)	0.0003
<i>Staphylococcus</i> coagulase negative	16 (16.0%)	0 (0.0%)	0.0001
<i>Streptococcus viridans</i>	8 (8.0%)	0 (0.0%)	0.0001
<i>Streptococcus</i> Group B	8 (8.0%)	48 (8.2%)	NS
<i>Klebsiella pneumoniae</i>	6 (6.0%)	44 (7.5%)	NS
<i>Staphylococcus aureus</i>	4 (4.0%)	10 (1.7%)	NS
<i>Enterobacter</i> spp	4 (4.0%)	16 (2.8%)	NS
<i>Bacteroides fragilis</i>	3 (3.0%)	7 (1.2%)	NS
<i>Bacillus</i> spp	3 (3.0%)	0 (0.0%)	NS
<i>Streptococcus pasteurianus</i>	2 (2.0%)	0 (0.0%)	NS
<i>Haemophilus</i> spp	1 (1.0%)	10 (1.7%)	NS
<i>Corynebacterium</i> spp	1 (1.0%)	0 (0.0%)	NS
<i>Citrobacter koseri</i>	1 (1.0%)	4 (0.6%)	NS
<i>Streptococcus salivarius</i>	1 (1.0%)	0 (0.0%)	NS
<i>Proteus mirabilis</i>	0 (0.0%)	53 (9.1%)	0.004
<i>Acinobacter calcoaceticus</i>	0 (0.0%)	10 (1.7%)	NS
<i>Pseudomonas</i> spp	0 (0.0%)	6 (1.0%)	NS

The data for 1988 were derived from Lurie et al., 1990 [1]

of the patients with the cultures were checked for the final diagnosis and were categorized as PID and non-PID groups.

The distribution of cervical non-gonococcal and non-chlamydial bacteria in women with PID and the bacteria's antibiotic sensitivity was compared to that in our previous study that was performed in Kaplan Medical Center, Rehovot also over 1 year period (1988–1989) [1].

#### STATISTICAL ANALYSIS

Proportions were compared using the chi-square test. The test was two sided and considered significant at  $P < 0.05$ .

#### RESULTS

In 2008, a total of 412 cultures were obtained: 126 (30.5%) were sterile and 286 (69.5%) were positive, of which 257 (89.9%) were positive for non-sexually transmitted pathogens; 27 (9.4%) contained *Candida* species, and in 2 (0.7%) *Lactobacillus* species was identified. The prevalence of negative cultures was similar in 2008 and in 1988, i.e., 30.5% and 33.7% respectively ( $P = 0.23$ ) [1]. The prevalence of the non-sexually transmitted pathogens in cultures obtained in 2008 is summarized in Table 1. PID was finally diagnosed in 116 patients with positive cultures. Of those, 100 cultures (86.2%) were positive for non-sexually transmitted pathogens, 14 (12.1%) contained *Candida* species, and in 2 (1.7%) *Lactobacillus* species was identified. Table 2 summarizes the prevalence of the non-sexually transmitted pathogens in patients with PID and compares it to that obtained in 1988 [1]. The statistically significant differences were a reduced prevalence of *Escherichia coli* (from 38.1% to 18.0%) and *Proteus mirabilis* (from 9.1% to 0.0%) and increased prevalence of *Staphylococcus* coagulase negative (from 0.0% to 16.0%) and *Streptococcus viridans* (from 0.0% to 8.0%).

A comparison of antimicrobial sensitivity of the non-sexually transmitted pathogen in patients with PID between 2008 and 1988 is presented in Table 3. In general, with the exception of chloramphenicol and cefotaxime, the rate of antimicrobial sensitivity was higher in 2008 than in 1988. In 1988 the antimicrobial sensitivity for various antibiotics ranged from 2.9% to 80.1% (median 51.9%) [1], as compared to 44.3% to 100.0% (median 90.2%) in 2008.

#### DISCUSSION

The prevalence of negative cultures in women with PID was 33% in the study performed in 1988 [1], and 30% in the current study 20 years later (2008). Since the cultures were not analyzed for sexually transmitted pathogens (i.e., *Neisseria gonorrhoeae* or *Chlamydia trachomatis*), it is possible that those cultures were not entirely sterile. Another unusual pathogen that was not sought but might be considered is

*Entamoeba histolytica* [10]. The question regarding the incidence of positive cultures in women suspected of having PID was recently addressed in a retrospective study that included cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* [11]. In that study the rate of negative cultures in women with PID was roughly around 58%. Therefore, the incidence of 30–33% negative cervical cultures in women with PID in our study is acceptable and not necessarily associated with the fact that cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were not included.

Most of the isolated bacteria in women with PID were facultative anaerobic (i.e., *E. coli*) or obligate anaerobic [12] (e.g., *Bacteroides fragilis*) in the current (2008) as well as previous studies (1988) [1]. The finding of a predominance of anaerobic bacteria in the origin of PID is in agreement with a previously published study [6]. This is not surprising since the anaerobic bacteria are abundantly present in normal vaginal flora, with a concentration of approximately 1 million organisms per gram of secretion [12]. The most prevalent bacterium in the 1988 study was *E. coli* [1], while 20 years later, in the current study, the most prevalent bacterium was *Enterococcus* species [Table 2]. This could be explained by the decrease in the rate of *E. coli* isolates (from 38.1% to 18.0%,  $P = 0.0003$ ) rather than an increase of *Enterococcus* species isolates (26.4% to 24.0%, respectively). Still, the two most prevalent isolates were *E. coli* and *Enterococcus* species that were isolated from 64.5% and 42.0% of women with PID in 1988 and 2008, respectively.

The antimicrobial sensitivity for various antibiotics in the current study (2008) ranged from 44.3% to 100.0% with a median of 90.2%. Good results (high sensitivity) were obtained for frequently used antibiotics such as ciprofloxacin (91.9%), gentamicin (90.4%), clindamycin (87.5%), cefuroxime (79.1%) and co-trimoxazole (79.1%). In 1988 [1], the results were much less sensitive: the antimicrobial sensitivity ranged from 2.9% to 80.1% with a median of 51.9%. This decreased rate of resistance to antibiotics could be attributed to a more restrictive strategy of antibiotic use [13,14]. This strategy is also based on optimal empiric antibiotic choice [12], which should be based on the prevalence of the pathogens involved in certain infection sites and on their antibiotic sensitivity. Based on our study, it appears that the optimal first-line empiric antibiotic choice in hospitalized women with suspected PID would be a combination of cefuroxime, ciprofloxacin and gentamicin. This suggestion of ciprofloxacin is in agreement with previously published data which revealed that ciprofloxacin is superior to a combination of doxycycline and metronidazole in the treatment of PID, resulting in a 94% and 70% cure rate, respectively [15]. The limitation of this suggestion is that the study did not address cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

**Table 3.** Distribution of sensitivity to antibiotics of non-sexually transmitted pathogens among patients with PID with positive cultures taken in 2008 compared to 1988

		Cultures in 2008		Cultures in 1988		P value
		n (%) sensitive	n tested for	n (%) sensitive	n tested for	
Oral or Oral/parenteral	Ampicilin	47 (44.3%)	106	335 (57.6%)	582	0.012
	Augmentin	4 (66.6%)	6	–	–	–
	Cefuroxime (oral)	57 (79.1%)	72	–	–	–
	Ciprofloxacin	68 (91.9%)	74	–	–	–
	Chloramphenicol	5 (100.0%)	5	469 (80.5%)	582	NS
	Clindamycin	7 (87.5%)	8	–	–	–
	Co-trimoxazole	69 (79.1%)	87	397 (68.2%)	582	0.033
	Erythromycin	8 (100.0%)	8	198 (34.0%)	582	0.001
	Minocycline	8 (72.1%)	11	–	–	–
	Moxifloxacin	5 (100.0%)	5	–	–	–
	Rifampin	10 (76.9%)	13	–	–	–
	Tetracycline	–	–	244 (41.9%)	582	–
Parenteral only	Amikacin	74 (100.0%)	74	56 (53.8%)	104	p=0.001
	Ampicillin/sulbactam	41 (56.1%)	73	–	–	–
	Aztreonam	66 (89.2%)	74	–	–	–
	Cefalexin	–	–	372(63.9%)	582	–
	Cefazolin	54 (72.9%)	74	–	–	–
	Cefepime	65 (90.2%)	72	–	–	–
	Cefotaxime	5 (100.0%)	5	62 (59.6%)	104	NS
	Cefoxitin	–	–	49 (47.1%)	104	–
	Ceftriaxone	72 (91.1%)	79	302 (51.9%)	582	0.001
	Cefuroxime (parenteral)	57 (79.1%)	72	–	–	–
	Ertapenem	73 (100.0%)	73	–	–	–
	Gentamicin	95 (90.4%)	105	353 (60.7%)	582	0.001
	Imipenem	67 (98.5%)	68	–	–	–
	Meropenem	78 (98.7%)	79	–	–	–
	Penicillin-G	28 (80.0%)	35	194 (33.3%)	582	0.001
Piperacillin	69 (92.7%)	75	57 (54.8%)	104	0.001	
Tobramycin	–	–	66 (63.5%)	104	–	
Vancomycin	35 (100.0%)	35	–	–	–	

The data for 1988 were derived from Lurie et al., 1990 [1]

In summary, it appears that the cervical bacterial flora in hospitalized women with PID did not vary significantly between 1988 and 2008. However, the antimicrobial sensitivity of the isolated bacteria changed dramatically, resulting in a decreased rate in resistance to antibiotics.

**Corresponding author:**

**Dr. S. Lurie**

Dept. of Obstetrics & Gynecology, Wolfson Medical Center, Holon 58100, Israel

Phone: (972-3) 502-8329, Fax: (972-8) 936-6259

email: drslurie@hotmail.com

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