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Стаття надійшла 12.03.2020 р.

DOI 10.26724/2079-8334-2021-1-75-95-100

UDC 618.13-002:616-022.7

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### TRENDS IN CHANGES OF LEADING BACTERIAL CAUSATIVE AGENTS OF PELVIC INFLAMMATORY DISEASES IN WOMEN DURING 2013-2017

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Over the last decade, both in the world and in Ukraine, there has been a significant increase in the incidence of pelvic inflammatory disease in women. The purpose of the study was to evaluate the trends in the leading bacterial causative agents of pelvic inflammatory diseases during 2013-2017 in 554 women in the disease exacerbation. The results of the examination of patients for the period from 2013 to 2017 indicate: inoculation rate fluctuations of individual bacterial inflammatory factors in different years of the study, increasing vaginal contamination of patients with opportunistic pathogens and a significant frequency of contamination with fungi of the genus *Candida* on the background of protective bacteria deficiency. The structure of vaginal bacteriological flora in women was dominated by *S. epidermidis* (haem+), *E. faecalis*, *S. haemolyticus*, *E. coli* and *Kl. pneumoniae*, which frequency and quantitative indices of inoculation in the observation trends tended to increase. The obtained data indicate the need for microbiological monitoring of changes in pathogens of pelvic inflammatory diseases in order to timely identify violations of microecology and prescribe rational therapy regimens.

**Key words:** trends in changes, bacterial causative agents, pelvic inflammatory diseases.

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#### ДИНАМІКА ЗМІН ПРОВІДНИХ БАКТЕРІАЛЬНИХ ЗБУДНИКІВ ЗАПАЛЬНИХ ЗАХВОРЮВАНЬ ОРГАНІВ МАЛОГО ТАЗА У ЖІНОК ЗА ПЕРІОД 2013-2017 рр.

За останнє десятиріччя, як у світі, так і в Україні, реєструється суттєве зростання частоти запальних захворювань органів малого тазу у жінок. В задачі роботи входило вивчення динаміки провідних бактеріальних збудників запальних захворювань статевих органів на протязі 2013-2017рр у 554 жінок в гострій фазі захворювання. Результати обстеження хворих за період з 2013 року по 2017 рік свідчать про коливання показників висіву окремих бактеріальних чинників запалення в різні роки дослідження, зростання рівня контамінації піхви хворих умовно-патогенною мікрофлорою та значну частоту обсіменіння гр. р. *Candida* на фоні дефіциту захисної мікрофлори. В структурі бактеріологічної флори піхви у жінок переважали *S. epidermidis* (гем+), *E. faecalis*, *S. haemolyticus*, *E. coli* та *Kl. pneumoniae*, частота та кількісні показники висіву яких в динаміці спостереження мали тенденцію до збільшення. Одержані дані свідчать про необхідність мікробіологічного моніторингу за зміною збудників запальних захворювань органів малого тазу з метою своєчасного виявлення порушень мікроекології та призначення раціональних схем терапії.

**Ключові слова:** динаміка змін, бактеріальні збудники, запальні захворювання органів малого тазу.

*The article is a fragment of the research project “To study the possibilities of optimizing cervical erosion treatment in women of childbearing age with chronic inflammatory diseases of the genital organs”, state registration No. 0117U002900.*

Over the last decade, both in the world and in Ukraine, there has been a significant increase in the incidence of pelvic inflammatory diseases (PID) in women, which is associated with the deterioration of social-economic and environmental living conditions, migration, sexual behavior of young people, the use of contraception and invasive gynecological methods, the widespread use of antibacterial and hormonal drugs [2, 5].

The relevance of this problem is due not only to the high frequency of PID, but also to their negative impact on the reproductive, menstrual and sexual functions of the female body [6, 8].

The opportunistic pathogenic bacteria of exogenous or endogenous origin, which can be found in associations with viruses, fungi and infectious agents of the “new generation” [1, 12], plays a significant role in the etiology of PID.

In particular, microorganisms take part in the occurrence of the inflammatory process, which due to their biological properties are capable of long-term persistence [3, 11]. Active proliferation of opportunistic pathogens is accompanied by the emergence of genital dysbiosis, changes in homeostasis and microcirculation, which contributes to the inflammatory process chronicity [9, 15].

Literature data of recent years indicate that in patients with a mixed nature of infection, the biological properties of causative agents have changed: competition for nutrients, the ability to antagonize and adhere, and metabolism of pathogenicity factors (hemolytic and lecithinase activity), the production of antibiotic substances, and antibiotic resistance [4, 7].

These processes can change the composition of bacterial flora (monoculture, associations) in the genital tract, both during treatment and in the remote follow-up periods [13, 14]. At the heart of the vaginal microecology violations are changes in living conditions in the biotope – microecological imbalance. As a result, the population of one or more autoflora species, or species introduced from other biotopes, or the external environment gain an advantage in growth and reproduction over competitors and acquire a non-inherent dominant state in the microbiocenosis. Information on changes in the dominant representatives of opportunistic vaginal pathogens in patients with PID in different years of follow-up is important to increase the effectiveness of anti-epidemiological and therapeutic measures to reduce the incidence of this pathology [10].

**The purpose** of the study was to identify the leading bacterial causative agents that contaminate the vagina of women with pelvic inflammatory diseases and analyze the trends in the inoculation rates of opportunistic and protective bacterial populations from the genital tract of women during 2013-2017.

**Materials and methods.** The study included women with acute PID, who were hospitalized in the gynecological departments of the SI “Institute of Pediatrics, Obstetrics and Gynecology named after Academician O. Lukyanova of the NAMS of Ukraine” during 2013-2017. No patients received antibacterial therapy before and at the time of examination. No TORCH infections and extragenital diseases in the decompensation stage were reported in women during the examination, patients did not differ in their psychoemotional state and social status.

The contents of the posterior vaginal wall were used as a material for bacteriological examination. A total of 554 patients were examined: in 2013 – 96 women, in 2014 – 180 women, in 2015 – 122 women, in 2016 – 86 women and in 2017 – 70 women. The age of patients was 26-39 years. Clinical and laboratory examination of patients (ultrasonography, ECG, colposcopy) was performed. Most patients have chronic inflammatory diseases: salpingitis, coelitis and vaginitis. For comparison, we examined 30 healthy women.

Analysis of the vaginal bacterial composition and the results calculation were carried out in accordance with Order No. 535 of the Ministry of Health of the USSR of 1985 and Order No. 234 of the Ministry of Health of Ukraine of 2005.

The following differential diagnostic nutrient media were used for the genital mucus inoculation: blood agar, egg yolk high salt agar, “chocolate” agar, Endo, Ploskirev, Saburo media, Mueller Hinton broth, De Man, Rogosa and Sharpe medium for lactobacilli (produced by HiMedia, India and State Research Enterprise of the Institute of Food Resources of the National Academy of Agrarian Sciences of Ukraine). Inoculation was carried out by the method of sectoral inoculation on the dense nutrient media, which allows to determine the degree of microbial contamination and to identify the maximum possible composition of aerobic and facultative anaerobic bacteria.

The taxonomic position of microorganisms was determined according to the “Bergey's Manual of Systematic Bacteriology”. Identification of microorganisms was carried out by their cultural and morphological characteristics.

The number of microbial cells was calculated after counting the colonies and converting the data to decimal logarithms (lg CFU/mL).

Statistical analysis of the obtained research data was performed using standard computer packages “Data Analysis” Microsoft Excel for Windows 2007. The arithmetic mean value was calculated – arithmetic mean (M), arithmetic mean error (m), and probability of differences (p). Evaluation of the obtained data reliability was performed by the conventional parametric method using the Student's t-test. Reliability was considered established if its probability was at least 95 % (0.05).

**Results of the study and their discussion.** The study objective was to identify changes in the leading bacterial causative agents in women with PID during 2013-2017. Examination results in patients for the period from 2013 to 2017 indicate fluctuations in the inoculation rates of some bacterial inflammatory factors in different years of the study.

The species composition of the vaginal microflora in women surveyed in 2013-2017, included mainly 8 facultative anaerobic species of bacteria: representatives of the protective microflora – lactobacilli and fungi of the genus *Candida* (fig. 1).

Among the microorganisms belonging to the phylum Firmicutes, which were isolated from the genital tract of patients, epidermal staphylococcus with hemolytic properties (*S. epidermidis* haem+) had a significant share. In 2013, the frequency of its registration in women's vaginal plating was 14.6 %. Quantitative indices of registration exceeded the diagnostic level – lg 4.2±0.02 CFU/mL.

During 2014, there was an increase in vaginal contamination of patients with *S. epidermidis* with hemolytic properties. In particular, the plating rate was 26.7 %, and the concentration was lg 4.6±0.01 CFU/mL. In 2015, there was a slight decrease in the plating rate of *S. epidermidis* haem+. The frequency of its registration decreased to 23.0 %, the quantitative indices were lg 4.4±0.03 CFU/mL. In 2016, compared to 2015, there was an upward trend in the plating frequency of *S. epidermidis* with hemolysis (27.9 %), as well as an increase in concentration to the level of lg 4.8±0.04 CFU/mL. In 2017, the frequency and quantitative indicators of isolation from patients with *S. epidermidis* haem+ did not change significantly and remained at a significant level (25.7 % and lg 5.2±0.02 CFU/mL).

Thus, it should be noted that during the study period, in general, there was an increase in the frequency of *S. epidermidis* with hemolysis from 14.6 % in 2013 to 25.7 % in 2017.

The significant *S. epidermidis* (haem+) proportion in the bacterial populations isolated from the vagina of women with PID is associated with a wide range of colonization factors: the ability to adhere, biofilm formation, persistence, survival due to a dense cell wall.

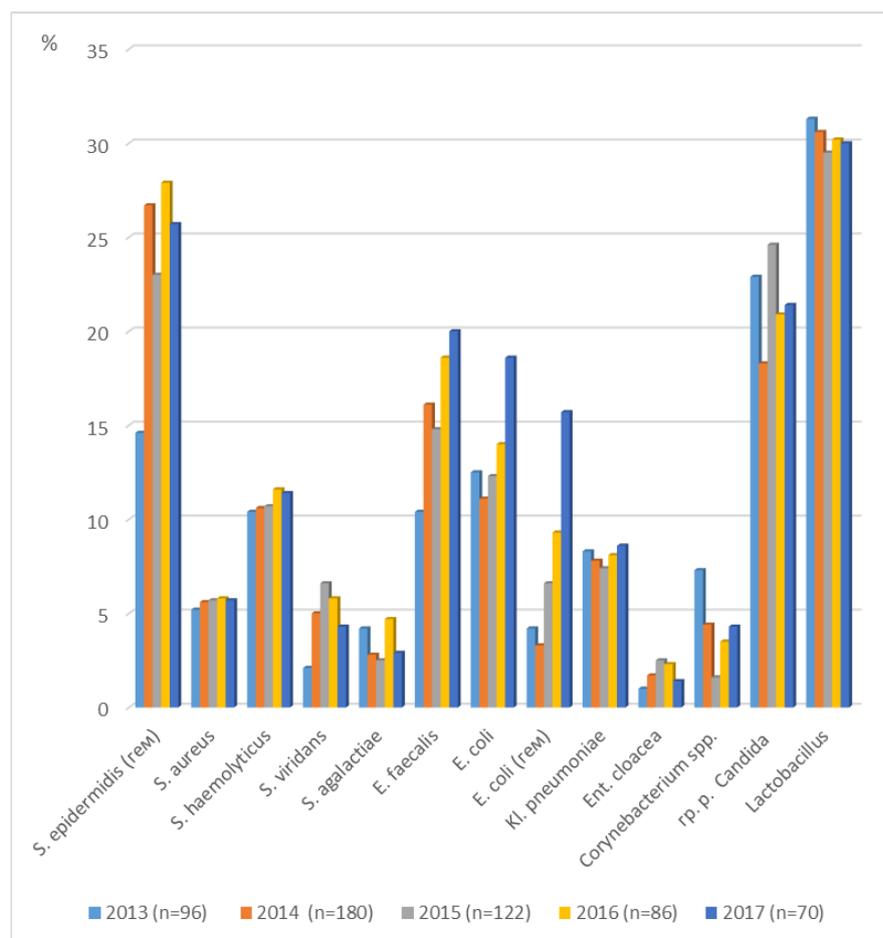


Fig. 1. Changes in the leading bacterial causative agents in women with PID during 2013-2017.

Analysis of the spectrum of other representatives of gram-positive bacteria in vaginal cultures of women with pelvic inflammatory diseases revealed a significant frequency of the *E. faecalis* enterococci registration.

In 2013, the frequency of *E. faecalis* isolation from patients was 10.4 %, and its quantitative level was lg 4.0±0.03 CFU/mL. During 2014, there was an increase in *E. faecalis* registration rate compared to the data obtained in 2013. The plating rate was 16.1 %, and the quantitative indicators were lg 4.4±0.04 CFU/mL. In 2015, there was a slight decrease in the detection rate of *E. faecalis* from patients up to 14.8 %, and the quantitative level was lg 4.2±0.02 CFU/mL. In 2016, a further increase

was registered in both the isolation frequency (18.6 %) and the concentration this bacterial population – lg 4.6±0.01 CFU/mL. In 2017, there was an upward trend in *E. faecalis* plating in patients. The

frequency of its registration was 20.0 %, and quantitative indices increased to the level of  $\lg 5.0 \pm 0.03$  CFU/mL.

Hemolytic staphylococcus (*S. haemolyticus*) was on the third place on frequency of isolation from sick representatives of gram-positive cocci bacteria. From 2013 to 2015, no significant fluctuations in its qualitative and quantitative indices were detected.

In 2013, *S. haemolyticus* was isolated from the vagina of 10.4 % of sick women. Its concentration was  $\lg 3.8 \pm 0.05$  CFU/mL. In 2014 and 2015, the frequency of its registration did not change significantly (10.6 % and 10.7 %, respectively), and quantitative indices reached diagnostic indices ( $\lg 4.0 \pm 0.03$  CFU/mL and  $\lg 4.2 \pm 0.02$  CFU/mL, respectively). Further analysis performed from 2016 to 2017 indicates a slight increase in its level. The isolation frequency from the patients' vagina was 11.6 % in 2016, and 11.4 % in 2017. Quantitative plating indices of *S. haemolyticus* in the last two years exceeded the diagnostic level (2016 –  $\lg 4.6 \pm 0.02$  CFU/mL, 2017 –  $\lg 4.4 \pm 0.03$  CFU/mL).

In women with sexually transmitted infections (STIs) for the period from 2013 to 2017, there was no significant increase in the level of *S. aureus* isolation (respectively, from 5.2 % to 5.7 % during the study period).

Proteobacteria type culture had a significant share in the vaginal microflora in patients with PID. In women with pelvic inflammatory diseases, examined in 2013, the composition of enterobacteria isolated from the vagina was dominated by *Escherichia coli* (*E. coli*). Their plating frequency was 12.5 %, and the quantitative level reached diagnostic indices ( $\lg 4.2 \pm 0.02$  CFU/mL).

In 2014, *E. coli* isolation rates from the vagina of patients did not change significantly. *E. coli* isolation rates was 11.1 %, and the quantitative level was  $\lg 4.0 \pm 0.03$  CFU/mL. During 2015, there was a tendency to increase both the frequency and quantitative indices of *Escherichia coli* isolation from patients. Its plating frequency was 12.3 %, and the concentration was  $\lg 4.4 \pm 0.03$  CFU/mL. In 2016, plating rates of *E. coli* from the genital tract of women tended to increase: frequency – 14.0 %, concentration –  $\lg 4.6 \pm 0.02$  CFU/mL. In 2017, there was a further increase in vaginal contamination of patients with *E. coli*. Its presence was detected in 18.6 % of patients, and the quantitative indices were  $\lg 5.2 \pm 0.03$  CFU/mL.

It should also be noted the gradual increase from 2013 to 2017 in the indices of vaginal contamination with *Escherichia coli* with hemolytic properties (*E. coli* haem+) from 4.2 % in 2013 to 15.7 % in 2017.

During the study period, in the spectrum of gram-negative rods isolated from the vagina of patients with STIs, in addition to *Escherichia*, we also found *Kl. pneumoniae*, but no significant changes in its registration were observed.

In 2013, the isolation frequency of this Enterobacteria representative was 8.3 %, and the quantitative level was  $\lg 4.2 \pm 0.02$  CFU/mL. In 2014, compared to 2013, the indices of *Kl. pneumoniae* vaginal isolation in patients have not changed significantly. The registration rate was 7.8 %, and the  $\lg$  concentration was  $4.0 \pm 0.03$  CFU/mL. During 2015–2017, there was also no upward trend in plating this type of bacteria. The frequency of *Kl. pneumoniae* vaginal isolation in patients in 2015 was 7.4 %, in 2016 – 8.1 %, in 2017 – 8.6 %. During 2015–2017, *Kl. pneumoniae* concentration exceeded the diagnostic values ( $\lg 4.2 \pm 0.02$  CFU/mL -  $\lg 4.6 \pm 0.03$  CFU/mL).

The data obtained in patients regarding opportunistic pathogens plating differed significantly from the corresponding indices registered in healthy women. In healthy women, plating rates of facultative anaerobic opportunistic bacteria were in the range of  $\lg < 4.0 \pm 0.01$  CFU/mL and the frequency was insignificant – 3.3–13.3 %. Quantitative indices of protective bacteria (*Lactobacillus* spp.) plating amounted  $\lg 5.2 \pm 0.07$  CFU/mL, and their presence was detected in 100 % of the examined women.

When examining patients with STIs at different stages, the high frequency of vaginal contamination with *Candida* fungi attracts attention. The frequency of their registration in 2013 was 22.9 %, and in 2015, it increased to 24.6 %. The quantitative plating rate of fungi of the genus *Candida* gradually increased from  $\lg 4.2 \pm 0.02$  CFU/mL in 2013 to  $\lg 4.8 \pm 0.04$  CFU/mL in 2015. During 2016–2017, the registration frequency of the genus *Candida* fungi did not change significantly and remained at a high level (20.9 %–21.4 %).

Fungi of the genus *Candida* are able to produce gliotoxin, which disrupts the viability and function of white blood cells. Under gliotoxin influence, the geometry of neutrophils changes, the superoxidation production decreases, and absorption and digestion bacterial activity decreases.

During the study period, vaginal microecology violations were manifested not only by the active proliferation of certain members of the facultative anaerobic bacteria, but also, to a large extent, the deficiency or absence of lactobacilli.

In contrast to the data obtained on the upward trend in plating rates of opportunistic pathogens in different years of observation, the frequency and quantitative level of protective bacteria did not reach normal levels during the study.

The deficiency of protective bacteria identified by us during observation process is of negative importance. During 2013–2017, changes in the plating rates of protective bacteria were not significant. There were no significant fluctuations in both the frequency of registration (68-71 %) and the quantitative level of lactobacilli plating in some years of the study. Thus, in 2017, the quantitative indices of lactobacilli registration did not exceed  $\lg 3.8 \pm 0.02$  CFU/mL

Stable deficiency of lactobacilli may be the result of the negative impact of biologically active substances due to the inflammatory process, hormonal disorders, inadequate methods of therapy, and environmental factors. It is known that vaginal protective bacteria *Lactobacillus* spp., effectively inhibits the growth of *Gardnerella vaginalis*, *Staphylococcus* spp., bacteria of the genera *Klebsiella*, *Escherichia*, fungi of the genus *Candida* and other microorganisms due to the production of lactic acid, hydrogen peroxide, lysozyme, antibiotic substances, and lactocin. Lactobacilli regulate the basic metabolism, maintain the optimal pH value, and take an active part in the formation and stabilization of the microbial ecology of the genital tract.

The results of the study of the vaginal bacterial composition of patients with PID indicate an upward trend in the opportunistic bacteria contamination levels during 2013-2017, and a significant frequency of vaginal contamination with fungi of the genus *Candida* on the background of protective bacteria deficiency.

Long-term monitoring of fluctuations in the leading bacterial pathogens of PID in patients is of epidemiological importance. This allows you to control the frequency of accumulation of gram-positive or gram-negative bacteria with pathogenic properties, to identify imbalances between stabilizing and transient microflora in the vaginal microbiocenosis, to choose rational antibacterial therapy regimens aimed at reducing the incidence of inflammatory diseases in women.

Because of study, it was found that during 2013–2017, the structure of vaginal bacteriological flora in women was dominated by *S. epidermidis* (haem+), *E. faecalis*, *S. haemolyticus*, *E. coli* and *Kl. pneumoniae*, which frequency and quantitative indices of inoculation in the observation trends tended to increase.

Other scientists have also shown in their studies the increasing role of opportunistic pathogens in the development of pelvic inflammatory diseases. According to their data, the predominant pathogens were: Enterobacteriaceae (*E. coli*), enterococci and staphylococci, both in monoculture and in associations with other microorganisms [3, 12].

The development and formation of PID is based on most of the interrelated processes that begin with acute inflammation and end with severe destructive tissue changes. The main trigger for the development of inflammation is bacterial invasion, which often associated with the activation of endogenous microflora.

The inflammatory reaction consists of damaged cells, altered vascular reactions with exudation, release of biologically active substances, phagocytosis, physicochemical changes in the inflammatory focus and proliferative processes aimed at eliminating the inflammatory agent and restoring damaged tissues. The infectious inflammation consequence is a violation of the normal structure of the internal reproductive organs at the macro and micro levels.

The leading role of staphylococcus as a causative agent of PID is evidenced by the results of studies in which staphylococcus with hemolytic properties in pure culture was isolated with the highest frequency.

Proteobacteria type culture has a significant share in the vaginal microflora in patients with PID. In the examined women with pelvic inflammatory diseases, enterobacteria composition isolated from the vagina was dominated by *Escherichia coli* (*E. coli*), which plating frequency increased during the study. Other researchers have shown that there is an increase in the microbial density of such opportunistic bacteria as *S. aureus*, *Enterococcus* spp. and fungi of the genus *Candida* against the background of increasing enterobacteria number, which is confirmed by our studies [4].

Studies show that PID is a serious medical problem that affects the health of women with childbearing potential. PID is a polyetiologic disease that leads to severe disorders of all organs and systems of the body [1, 6].

The obtained data indicate the need for microbiological monitoring of changes in pathogens of pelvic inflammatory diseases in order to timely identify violations of microecology and prescribe rational therapy regimens.

### Conclusions

1. In different years of observation (2013–2017), we found a change and upward trend in dominant bacterial inflammatory factors in vaginal plating of women, high plating level in fungi of the genus *Candida* and a stable deficiency of *Lactobacillus*.

2. During the study period, significant vaginal contamination by representatives of gram-positive cocci bacteria belonging to the phylum Firmicutes (*S. epidermidis* haem+ and *E. faecalis*), as well as representatives of gram-negative rod bacteria (*E. coli* and *Kl. pneumoniae*), was found in women with STIs.

3. The obtained data indicate the need to develop effective schemes for the vaginal microbiocenosis correction in women with STIs, taking into account changes in bacteriological inflammatory factors in different periods of the study.

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Стаття надійшла 14.02.2020 р.