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ORIGINAL ARTICLE

Clinical Situation, Species Distribution, and Antibiotic Resistance of Pathogenic Bacteria and Fungi in 626 Cases of Vulvovaginitis in Hangzhou, China

Xiaoxia Wang, Qin Song

Department of Obstetrics and Gynecology, Hangzhou Third People´s Hospital, Hangzhou, Zhejiang, China

SUMMARY

Background: **Female vulvovaginitis was one of the most common gynecological diseases. It had a great negative impact on their work and quality of life. This retrospective study evaluated the clinical and laboratory data of patients with vulvovaginitis in Hangzhou, China. To analyze the clinical situation, species distribution and antibiotic resistance of pathogenic fungi and bacteria in 626 cases of vulvovaginitis in Hangzhou. Microorganism culture, identification, and antibiotic susceptibility testing were conducted. The study aimed to provide a theoretical value for an effective treatment of vulvovaginitis.**

Methods: **In total, 626 outpatients and inpatients diagnosed with vulvovaginitis were selected from January 2018 to January 2023. Data of all the patients were collected from the hospital's electronic medical records. Vaginal secretion was collected for testing and SPSS 25.0 software was used to perform statistical analysis.**

Results: **A total of 626 strains of fungi, Gram-positive, and -negative bacteria were detected. Clinical situations of patients infected with the top five pathogenic fungi and bacteria were analyzed. Pathogenic fungi and bacteria were slightly different in each age group and in each onset time group. The results of antibiotic susceptibility testing showed that the resistance rates of itraconazole and fluconazole were high and Gram- negative and -positive bacteria were multidrug resistant. Gram-negative bacteria were more sensitive to carbenicillins and compound antibiotics, while Gram-positive bacteria were sensitive to rifampicin and daptomycin. MRSA and non vancomycin-resistant strains were detected.**

Conclusions: **Fungi and bacteria were usually detected as pathogenes in patients with vulvovaginitis in Hangzhou. Some factors, such as age and onset time, often affected the incidence. Pathogenic fungi and bacteria were resistant to some common antibiotics, and clinical treatments should be carried out in a timely and reasonable manner according to the results of antibiotic susceptibility testing.**

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Correspondence:
Qin Song, BD
Department of Obstetrics and Gynecology
Hangzhou Third People´s Hospital
No. 38 Xihu Avenue, Hangzhou, Zhejiang
China
Email: songqin0214@163.com

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KEYWORDS

Hangzhou, vulvovaginitis, vaginal secretion, pathogenic fungi and bacteria, antibiotic resistance

INTRODUCTION

Vulvovaginitis, an inflammatory state that mainly includes increased vaginal secretion, itching, pain, dysuria, dyspareunia, and other symptoms, is one of the most common gynecological diseases [1-4]. Women of almost every age can be affected by the disease, the probability of infection is high, and it can be caught

more than just once [5-7]. Fungal and bacterial infections are the most common causes of vulvovaginitis [8-10]. In recent years, antibiotics have become one of the most widely used drugs for the clinical treatment of an inflammation. A timely application of the necessary antibiotics has saved the lives of many patients, but at the same time, there are also adverse consequences caused by an unreasonable usage of antibiotics, among which antibiotic resistance is the most prominent problem [11-13]. In this study, culture identification and antibiotic susceptibility testing were conducted for the pathogenic fungi and bacteria of 626 outpatients and inpatients with vulvovaginitis in Department of Obstetrics and Gynecology in our hospital from January 2018 to January 2023. Clinical situation, species distribution, and antibiotic resistance of pathogenic fungi and bacteria of 626 outpatients and inpatients with vulvovaginitis in Hangzhou were analyzed. Our study aimed to provide value for the clinical treatment, enhance antibiotic safety, and reduce antibiotic resistance.

MATERIALS AND METHODS

Study population

A total of 626 outpatients and inpatients diagnosed with vulvovaginitis in Hangzhou Third People's Hospital were selected from January 2018 to January 2023, and the diagnostic criteria used were referred to the Guidelines for Diagnosis and Treatment of Gynecological Inflammation in 2021. Data of all patients were collected from the hospital's electronic medical records. Approximately 668 patients were enrolled in the study, with 626 patients being selected. Patients with congenital and acquired immune deficiency or other body site infection were excluded, and so were those who had been treated with antibiotics.

Instruments and reagents

Matrix-assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) and original reagents were purchased from Bruker (Germany) (production batch number: 0000401249), VITEK® 2 Compact automatic microbial identification and antibiotic susceptibility analysis system and original reagents (production batch number: 7742317403) were purchased from Biomerieux (France), fungal and bacterial culture medium plates and AGAR medium plates used for antibiotic susceptibility testing with the disk diffusion method were both purchased from Zhengzhou Antu Company, and KB paper was purchased from Oxoid Company (production lot number: 3439891, 3454894, 3454850, 3443628, etc.). Quality control strains were respectively *Candida albicans* ATCC90028, *Escherichia coli* ATCC25922, *Staphylococcus aureus* ATCC-25923, *Pseudomonas aeruginosa* ATCC27853, *Enterococcus faecalis* ATCC29212, and *Streptococcus pneumoniae* ATCC49619 which were purchased from National Center for Clinical Laboratories.

Specimen collection and microorganism culture

A sterile cotton swab was used for specimen collection. Vaginal secretion was selected at 1 cm to 2 cm of the inner side of the female cervix. After rotating twice or three times and after remaining inside the cervix for about 30 seconds, the sterile cotton swab was placed inside a sterile test tube. Secretions were inoculated into fungal and bacterial medium plates within 30 to 60 minutes, and then cultured in an incubator at 37℃ with 5% CO_2 for 24 to 48 hours.

Identification of bacteria and fungi

A single fungal or bacterial colony was picked up with a toothpick and put into a sterile EP tube, and then 10 μL of formic acid (70%) was added and vortexed. After that, 1 μL of the sample suspension was smeared on the target plate and 0.5 μL of matrix solution was added to it. Software automatically matched the sample mass spectrogram to the standard mass spectrogram in the database.

Antibiotic susceptibility testing

Fungal susceptibility testing was performed with ATB Fungus3 susceptibility strip, and bacterial susceptibility testing was performed with VITEK® 2 Compact automatic microbial identification and susceptibility analysis system, supplemented with the KB paper method. Sensitivity and resistance criteria were based on Document M100-S29 compiled by Clinical and Laboratory Standards Research Institute (CLSI) in 2019.

Statistical analysis

SPSS 25.0 software was used for statistical analysis. Data of the categorical variables were expressed as rate (%) and analyzed with the chi-squared test. A p-value < 0.05 was considered statistically significant.

RESULTS

Distribution of pathogenic bacteria and fungi

A total of 626 strains of pathogenic fungi and bacteria were detected. It included 306 strains of fungi, 187 strains of Gram-negative bacteria, and 133 strains of Gram-positive bacteria. All 22 species of pathogenic fungi and bacteria were detected, including 7 species of fungi, 8 species of Gram-negative bacteria, and 7 species of Gram-positive bacteria. The top five pathogens were *Candida albicans* (171 strains, 27.3%), *Candida glabrata* (83 strains, 13.3%), *Escherichia coli* (76 strains, 12.1%), *Neisseria gonorrhoeae* (43 strains, 6.9%), and *Staphylococcus aureus* (41 strains, 6.5%), as shown in Table 1.

Distribution of pathogenic fungi and bacteria in different age groups

The age of 626 patients ranged from 16 to 72, with most of them being older than 55. There were significant differences between the age groups ($\chi^2 = 13.26$, $p < 0.05$).

Table 1. Overall analysis of 626 strains of pathogenic bacteria and fungi.

Pathogenic fungi and bacteria	Number of strains (strains)	Composition ratio (%)
Candida albicans	171	27.3
Candida glabrata	83	13.3
Candida tropicalis	23	3.7
Candida krusei	14	2.2
Candida parapsilosis	10	1.6
Candida innominate	4	0.6
Candida pseudotropicalis	1	0.2
Escherichia coli	76	12.1
Neisseria gonorrhoeae	43	6.9
Klebsiella pneumoniae	26	4.2
Enterobacter cloacae	21	3.4
Pseudomonas aeruginosa	9	1.4
Proteus mirabilis	8	1.3
Acinetobacter juneensis	3	0.5
Acinetobacter baumannii	1	0.2
Staphylococcus aureus	41	6.5
Coagulase-negative staphylococci	27	4.3
Enterococcus faecium	26	4.2
Enterococcus faecalis	21	3.4
Streptococcus agalactiae	11	1.8
Staphylococcus saprophyticus	6	1.0
Staphylococcus haemolyticus	1	0.2
Total	626	100

Table 2. Analysis of the top five pathogens in different age groups.

Age group	*Candida albicans*	*Candida glabrata*	*Escherichia coli*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*
< 25 years (n = 96, 23.2%)	33	19	14	18	12
25 - 55 years (n = 141, 34.1%)	61	26	27	14	13
> 55 years (n = 177, 42.8%)	77	38	35	11	16

Table 3. Analysis of the top five pathogens in different month groups.

Month group	*Candida albicans*	*Candida glabrata*	*Escherichia coli*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*
Jan to Mar (n = 72)	31	15	12	8	6
Apr to Jun (n = 118)	41	22	27	12	16
Jul to Sep (n = 142)	62	29	21	16	14
Oct to Dec (n = 82)	37	17	16	7	5

Table 4. Antibiotic resistance of fungi isolates.

Antibiotic	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida krusei*	*Candida parapsilosis*	*Candida innominate*
5-flucytosine	**7 (4.1)**	**5 (6.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Amphotericin B	**9 (5.3)**	**3 (3.6)**	**2 (8.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Fluconazole	**51 (29.8)**	**28 (33.4)**	**5 (21.7)**	**14 (100.0)**	**4 (40.0)**	**2 (50.0)**
Itraconazole	**62 (36.3)**	**33 (39.8)**	**12 (52.2)**	**8 (57.1)**	**2 (20.0)**	**0 (0.0)**
Voriconazole	**42 (24.6)**	**14 (16.9)**	**4 (17.4)**	**6 (42.9)**	**0 (0.0)**	**0 (0.0)**

Table 5. Antibiotic resistance of Gram-negative bacteria isolates.

Antibiotic	*Escherichia coli*	*Klebsiella pneumoniae*	*Enterobacter cloacae*
Amoxicillin/clavulanic acid	**4 (5.3)**	**3 (11.5)**	**3 (14.3)**
Piperacillin/tazobactam	**2 (2.6)**	**2 (7.7)**	**2 (9.5)**
Cefuroxime	**56 (73.7)**	**20 (76.9)**	**17 (81.0)**
Cefuroxime axetil	**56 (73.7)**	**20 (76.9)**	**17 (81.0)**
Cefoxitin	**39 (51.3)**	**14 (53.8)**	**19 (90.5)**
Ceftazidime	**27 (35.6)**	**10 (38.5)**	**9 (42.9)**
Ceftriaxone	**27 (35.6)**	**10 (38.5)**	**9 (42.9)**
Cefoperazone/sulbactam	**7 (9.2)**	**3 (11.5)**	**3 (14.3)**
Cefpirome	**4 (5.3)**	**2 (7.7)**	**2 (9.5)**
Ertapenem	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Imipenem	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Amikacin	**16 (21.1)**	**5 (19.2)**	**8 (38.1)**
Levofloxacin	**16 (21.1)**	**5 (19.2)**	**8 (38.1)**
Tigecycline	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Compound sulfamethoxazole	**10 (13.2)**	**6 (23.1)**	**9 (42.9)**

Candida albicans and *Candida glabrata* were detected in > 55 age group, while *Escherichia coli* and *Staphylococcus aureus* were more common in 25 to 55 age group. *Neisseria gonorrhoeae* was found more in patients < 25 age group, as listed in Table 2.

Distribution of pathogenic fungi and bacteria in different month groups

From July to September, 142 strains (34.3%) of pathogenic fungi and bacteria were detected, which had the highest incidence. The incidence of pathogenic fungi and bacteria in different months was statistically significant ($\chi^2 = 15.37$, $p < 0.05$), as listed in Table 3.

Antibiotic resistance of pathogenic fungi and bacteria

Most of pathogenic fungi were sensitive to 5-flucytosine and amphotericin B, and less were sensitive to itraconazole and fluconazole. Antibiotic resistance of fungi was shown in Table 4. Most of pathogenic Gram-negative bacteria were sensitive to carbapenems antibiotics, such as meropenem and imipenem. Its resistance rate was shown in Table 5. 19 strains of ESBLs-producing *Escherichia coli* were detected. Pathogenic Gram-positive bacteria were highly resistant to antibiotics, such as clindamycin and erythromycin. Also, 15 strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and non vancomycin-resistant enterococci were detected.

DISCUSSION

Vulvovaginitis was a common infection that plagued many women and had a great negative impact on their work and their quality of life. An incorrect antibiotic use and the emergence of antibiotic resistant microorganism might delay the treatment of the disease and in

Table 6. Antibiotic resistance of Gram-positive bacteria isolates.

Antibiotic	*Staphylococcus aureus*	*Coagulase-negative staphylococci*	*Enterococcus faecium*
Penicillin	**37 (90.2)**	**23 (85.2)**	**22 (84.6)**
Oxacillin	**21 (51.2)**	**14 (51.9)**	**2 (7.7)**
Gentamicin	**10 (24.4)**	**7 (25.9)**	**7 (26.9)**
Levofloxacin	**14 (34.1)**	**10 (37.0)**	**9 (34.6)**
Moxifloxacin	**14 (34.1)**	**8 (29.6)**	**8 (30.1)**
Erythrocin	**41 (100)**	**25 (92.6)**	**24 (92.3)**
Clindamycin	**38 (92.7)**	**23 (85.2)**	**23 (88.5)**
Linezolid	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Daptomycin	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Teicoplanin	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Vancomycin	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Tigecycline	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Rifampicin	**5 (12.2)**	**6 (25.9)**	**10 (38.5)**
Compound sulfamethoxazole	**6 (14.6)**	**14 (51.9)**	**15 (57.7)**

crease the economic burden.

Among 626 strains of pathogenic fungi and bacteria isolates in this study, *Candida albicans, Candida glabrata, Escherichia coli,* and *Staphylococcus aureus* were the most important pathogenic fungi and Gram-negative and -positive bacteria, which was consistent with the reports of other related studies [14-16]. In the distribution of age groups, the majority of the elderly were over 55 years old. One of the reasons for that might be that aged women generally had ovarian atrophy and could not continuously secrete estrogen. The low level of estrogen led them to a decreased vulvovaginal immunity and inflammation. It was consistent with the results of Hainer et al. [17], who reported that symptoms of vaginal dryness, itching, irritation, discharge, and dyspareunia caused by estrogen deficiency. A normal vagina often had *lactobacillus* and other beneficial bacteria. *Lactobacillus* could reduce the adhesion of the pathogens to the vagina and stimulate the body's immune function to produce antibacterial substances to kill pathogens which ultimately resisted the invasion of foreign pathogenic fungi and bacteria and maintained the balance of the vaginal flora [18,19]. A large amount of glycogen was distributed on the surface of the vaginal mucosal epithelial cells, which was one of the nutrients for the proliferation and the growth of the *Lactobacillus*. The level of estrogen affected the rate at which the vaginal epithelial cells shed. When age increased, the level of estrogen decreased, and the vaginal mucosal epithelial cells shed faster. Due to the imbalance, the *Lactobacillus* lost its dominance and the vaginal local immunity got impaired. Therefore, changes in estrogen had an important impact on maintaining the health of vaginal environment [20-21]. Another reason might be that the older women were more willing to seek medical care in the hospital, and most women over 55 were retired having more time than the younger women who struggled to work. The younger women chose to seek medical treatment online and chose to buy drugs at the pharmacy instead. In terms of the distribution in onset months, the incidence was the highest from July to September which might be related to the hot weather. In summer, microorganisms grew more easily and women were more susceptible to infection. The results of fungal antibiotic sensitivity testing showed that common pathogenic fungi such as *Candida albicans* and *Candida glabrata* were resistant to itraconazole and fluconazole, up to more than 20%, which was consistent with the reports of other related studies [22-23]. In the results of antibiotic sensitivity testing of Gram-negative bacteria, 19 strains of *Escherichia coli* producing extended-spectrum β-lactamases (ESBLs) accounted for 25.0%. *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* were more sensitive to carbapenems (imipenem and ertapenem) and compound agents (piperacillin/tazobactam, cefoperazone/sulbactam). The results could provide a reference for clinical medication. In addition, the results of antibiotic susceptibility testing of Gram-positive bacteria showed that there were 15 strains of MRSA, accounting for 36.6%. *Staphylococcus aureus* and *coagulase-negative Staphylococcus* were susceptive to rifampicin, teicoplanin, and vancomycin which had low antibiotic resistance ratios and were resistant to penicillin and erythromycin which had high antibiotic resistance ratios. Antibiotics should be used according to the results and then selected for treatment [24].

The primary outcome of our study was that species distribution and antibiotic resistance of pathogenic bacteria

and fungi were analyzed in 626 cases of vulvovaginitis. The secondary outcome was that clinical situation of all the patients was analyzed. The statistical reports on pathogenic bacteria and fungi of vaginitis in Hangzhou were limited, and the study made up for the deficiency. One strength of the study was based on the statistics of data in the past five years which was different from previous studies, and another was that it was a relatively new study. A third strength lied in the fact that antibiotic resistances of the pathogens were statistically analyzed and summarized, which played an important role in the clinical antibiotic treatment.

CONCLUSION

More and more attention had been paid to monitoring distribution and antibiotic resistance of pathogenic fungi and bacteria in patients with vulvovaginitis. More sensitive antibiotics should be selected according to actual clinical situation of patients and the results of antibiotic susceptibility testing. The emergence of antibiotic resistant strains should be avoided as much as possible to enhance the rationality of the clinical medication.

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Data Availability Statement:
The datasets used and/or analyzed during the study are available from the corresponding author on reasonable request.

Ethical Approval:
The research was reviewed and approved by the Ethics Committee of Hangzhou Third People´s Hospital in accordance with the Declaration of Helsinki (reference number: 2023KA040). Informed consents were obtained from the patients.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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