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Microbial Culture Characteristics and Antimicrobial Susceptibility Patterns Associated with Vesicovaginal Fistula

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Abstract

Vesicovaginal fistula (VVF) is commonly linked with recurrent urinary tract infection (UTI). Thus, the patterns of the pathogenic microorganism becomes important consideration in the management of this disease. This study aimed to describe patient profiles, disease etiology, and antimicrobial susceptibility patterns of microorganisms in VVF patients. This retrospective study was conducted on 49 medical records of vesicovaginal fistula patients seen from January 2016 to December 2020. The most prevalent age group of the patients was 40-50 years old. Analysis demonstrated that the leading etiology for VVF among these patients was malignancy (73.47%). The antimicrobial susceptibility was tested using the disc diffusion method and *Escherichia coli* (44.90%) and *Proteus mirabilis* (14.29%) were identified as the bacterial pathogens most frequently isolated from urine samples. Of the 39 patients with significant growth of organism cases, 29 (74.35%) had symptomatic UTIs. The isolated gram-negative bacteria had excellent sensitivity to aztreonam, ertapenem, and meropenem, with a more than 90% susceptibility rate, while the gram-positive bacteria had good sensitivity to amikacin, cefepime, tigecycline, aztreonam, ertapenem, and meropenem, with a more than 90% susceptibility. In conclusion, bacterial culture and antibiotic susceptibility test (AST) remains an essential part of managing VVF and their results can be used as a reference for empirical therapy. Amikacin, cefepime, tigecycline, aztreonam, ertapenem, and meropenem should be considered for treatment of UTIs associated with VVF.

Keywords: Antimicrobial, culture, sensitivity, vesicovaginal fistula

Introduction

A vesicovaginal fistula (VVF) is a pathological anatomical junction between the dorsal bladder wall and the anterior vagina. The pathophysiological mechanism underlying VVF is mainly caused by ischemia, leading to necrosis of both organ walls. The clinical manifestation of women with VVF is persistent urinary leakage through the vagina. Usually, the size of the fistula is directly responsible for the degree of incontinence caused.[1]

On estimate, the incidence of these procedures is around 0.3–2% in developed countries.[1] Meanwhile, in developing countries, the primary etiology of VVF is obstruction due to continuous labor (97%). In contrast, in industrialized countries, drug-induced injury to the urinary tract is the most often cause of VVF and most of the consequences of gynecological surgery.[2] Other causes of VVF are radiation therapy for malignant disease or accidental surgical injury to the bladder during procedures such as hysterectomy, malignant neoplasms, and pelvic irradiation.[3] VVF can often be found in developed countries with a yearly incidence of 50,000–100,000 cases and more than 2 million women being affected worldwide. VVF is a weakening condition that could cause a persistent bad-smelling odor combined with urinary discharge that would, later on, lead to the excoriation of the vulva and vagina. In developing countries such as India, where culturally, there are a lot of religious beliefs in their society, VVF could result in a plethora of social taboos that would cause social isolation as well as physical and emotional distress amongst patients.[4]

VVF should always be treated because it can cause the vagina to be inflamed and ulcerated.[1] Social stigma could be created as a result of

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VVF, which would affect women and hinder their overall development. These women, which should have been in their prime, would then lose various opportunities and could not fulfill their maximum potential in society.[5]

Therefore, we would like to investigate the characteristic of VVF patients at Hasan Sadikin Hospital, Bandung, to learn their demographic profile, etiology, type of microorganism through culture, clinical manifestation and characteristic of VVF, the sensitivity of each patient's response to antimicrobial, management received by the VVF patients in order to deliver appropriate treatment.

Methods

A descriptive retrospective analysis of 49 patients admitted to the Department of Urology, Hasan Sadikin Hospital, Bandung, for five years, January 2016–December 2020, was included in the study. Extensive medical record data were reviewed, including patient's demographic profile, etiology, type of microorganism through culture, clinical manifestation and characteristic of VVF, the sensitivity of each patient's response to antimicrobial, management received by the VVF patients, and success rate of treatment also included in this study. Antimicrobial susceptibility was tested with a disc diffusion method. Urine samples were taken from midstream urine preparation. The inclusion criteria were: 1) patients were diagnosed with VVF and treated in the Urology Department, Hasan Sadikin Hospital during the study period, and 2) the exclusion criteria were that the medical record data were incomplete, missing, or not identified. Data were analyzed with descriptive analysis using SPSS v20 for windows. After receiving ethical approval from The Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung No. LB.02.01/X.6.5/283/2021, the study was carried out.

Results

There were 49 patients for the last five years collected in this study. The VVF patients included in this study were in the age range of 19–73 years. The mean age of 47.98±10.23 years.

Initial urine cultures taken at the time of first reporting showed significant growth of the organism in 39 (80%) of the cases. The organisms' growth mostly was *E. coli,* as shown in Figure 1. *Escherichia coli* (44.90%) and *Proteus mirabilis* (14.29%) are both the most often isolated bacterial pathogen from a urine sample, continued with *Staphylococcus aureus* (12.24%)*, Pseudomonas* (10.20%), *Enterococcus* (8.16%)*, Klebsiella pneumonia* (6.12%)*, and Citrobacter freundii* (2.04%)*.* UTI became the main complication in cases of VVF. Of the total 39 significant growth of organism cases, 29 (74.35%) of them were symptomatic UTIs (dysuria, suprapubic pain or tenderness, frequency, and urgency), and 10 (25.65%) of them were asymptomatic UTIs.

The leading factor in the etiology of the fistula was malignancy (73.47%), followed by surgical and obstructed labor. The possibility of unrecognized intraoperative injury to the urinary tract, and hence an impending fistula, should be considered in any patient with prolonged ileus, excessive pain, or hematuria following pelvic surgery.

All 36 (73.47%) patients with malignancy were cervical cancer cases, with 13 patients receiving radiation therapy. Hysterectomy procedure became the second most common etiology of VVF. Two VVF patients with a history of obstructed labor underwent surgery by an obstetrician. Two patients with VVF had a

Table 1 Sociodemographic Characteristics of Patients

	Etiology and History of Radiation	Frequency	Percentage
Etiology	Malignancy	36	73%
	Obstructed labor	5	10%
	Surgical	8	16%
	Hysterectomy (total and subtotal)	9	18%
	Prolonged obstructed labor	2	4%
	Cesarean section	2	4%
History of radiation		13	36%

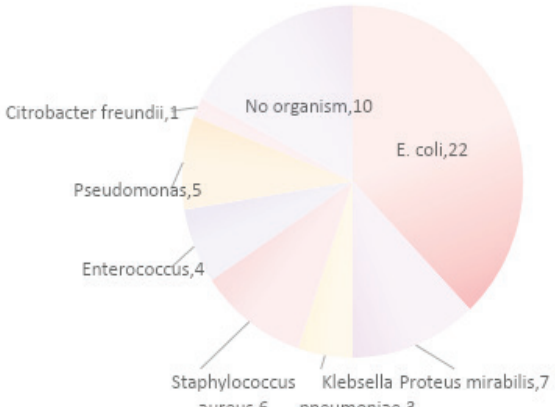

Figure Type of Microorganism Growth In Culture

Table 2 Antimicrobial Susceptibility Patterns of Gram-Positive Bacteria Isolated from VVF Cases

Bacterial Isolates		Antimicrobial tested														
		AMS	CFT	GNT	AMI	AMP	PRT	CFO	CTA	CFP	CPR	COT	TIG	AZT	ERT	MER
Staphylococcus	S	3	4	5	6	3	2	4	4	5	4	3	5	5	6	6
(n=6)	%	50	66.7	83.3	100	50	33.3	66.7	66.7	83.3	66.7	50	83.3	83.3	100	100
Enterococcus	S	2	3	3	4	2	2	3	3	4	4	3	4	4	4	4
(n=4)	%	50	75	75	100	50	50	75	75	100	100	75	100	100	100	100
Total	S	5	7	8	10	5	4	7	7	9	8	6	9	9	10	10
(n=10) %		50	70	80	100	50	40	70	70	90	80	60	90	90	100	100

AMS: Ampicillin/sulbactam, CFT: Ceftriaxone, GNT: Gentamicin, AMI: Amikacin, AMP: Ampicillin, PRT: Piperacillin/Tazobactam, CFO: Cefotaxime, CTA: Ceftazidime, CFP: Cefepime, CPR: Ciprofloxacin, COT: Cotrimoxazole, TIG: Tigecycline, AZT: Aztreonam, ERT: Ertapenem, MER: Meropenem

Table 3 Antimicrobial Susceptibility Patterns of Gram Negative Bacteria Isolated from VVF Cases

Bacterial isolates		Antimicrobial tested														
		AMS	CFT	GNT	AMI	AMP	PRT	CFO	CTA	CFP	CPR	COT	TIG	AZT	ERT	MER
E. coli	S	3	6	18	20	3	5	6	8	9	7	5	20	21	22	22
(n=22)	%	13.6	27.3	81.8	90.9	13.6	22.7	27.3	36.4	40.9	31.8	22.7	90.9	95.5	100	100
P. mirabilis	S	1	0	1	4	1	3	0	5	6	1	0	2	6	7	7
(n=7)	%	14.3	0	14.3	57.1	14.3	42.9	0	71.4	85.7	14.3	0	28.6	85.7	100	100
Klebsiella spp	S	0	3	2	1	0	1	2	3	3	1	1	3	3	3	3
(n=3)	%	0	100	66.7	33.3	0	33.3	66.7	100	100	33.3	33.3	100	100	100	100
Pseudomonas spp	S	0	0	4	4	0	3	0	2	4	2	0	1	4	4	5
(n=5)	%	0	0	80	80	0	60	0	40	80	40	0	20	80	80	100
Citrobacter	S	1	0	0	1	1	0	0	0	1	0	0	1	1	1	1
freundii (n=1)	%	100	0	0	100	100	0	0	0	100	0	0	100	100	100	100
Total	S	5	9	25	30	5	12	8	18	23	11	6	27	35	37	38
(n=38)	%	13.2	23.7	65.8	78.9	13.2	31.6	21.1	47.4	60.5	28.9	15.8	71.1	92.1	97.4	100

AMS: Ampicillin/sulbactam, CFT: Ceftriaxone, GNT: Gentamicin, AMI: Amikacin, AMP: Ampicillin, PRT: Piperacillin/Tazobactam, CFO: Cefotaxime, CTA: Ceftazidime, CFP: Cefepime, CPR: Ciprofloxacin, COT: Cotrimoxazole, TIG: Tigecycline, AZT: Aztreonam, ERT: Ertapenem, MER: Meropenem

history of cesarean section operations. As part of management, antimicrobial therapy was given after an antibacterial susceptibility test. There were ten types of bacteria that grew from culture. Susceptibility tests were performed using 15 antimicrobial agents in a panel at our center.

All the isolated gram-positive bacteria were 100% sensitive to meropenem and ertapenem. Most gram-positive bacteria were also sensitive to aztreonam, tigecycline, cefepime, ciprofloxacin, gentamicin, ceftriaxone, cefotaxime, and ceftazidime (Table 2).

The antimicrobial susceptibility patterns of gram-negative bacteria (n=38) against 15 antimicrobial agents are shown in Table 3.

All gram-negative bacteria isolates, most *E. coli* (>50%) isolates were sensitive to meropenem, ertapenem, aztreonam, tigecycline, amikacin, and gentamycin. Both *P. mirabillis* and *Klebsiella* were sensitive to meropenem, ertapenem, aztreonam, cefepime and ceftazidime. On the other hand, the last 2 isolate (*Pseudomonas*, and *Citrobacter freudii*) were both shown only good sensitivity to meropenem, ertapenem, aztreonam, cefepime, and amikacin.

Discussion

Hillary et al. reported that 83.2% of VVF cases in developed countries were caused by surgery-related actions, such as simple abdominal hysterectomy and other types of pelvic surgery, which include benign and malignant colorectal, urological and gynecological procedures. On the other hand, only 4.8% were caused by surgery-related actions in less developed countries. 75% of all fistulae were due to VVFs following abdominal hysterectomy. The main causative factor is primarily due to the bladder's injuries that were unnoticed during surgery or a placement of a suture or a clamp into the bladder wall. It is estimated that the value for VVFs as a complication towards hysterectomies was around 0.5–2%.[7]

These fistulas are most commonly related to obstetric complications worldwide, with prolonged labor being a predominant contributing factor. VVF is more often a consequence of pelvic surgery or cancer therapy in nations with better obstetric care, with pelvic surgery most typically preceded by accidental bladder or ureteral damage during abdominal hysterectomy.[8] In this study, the most common etiology is malignancy, which is in accordance with previous studies.

Urinary tract infections are the most common infections in the world. Microorganisms that cause urinary tract infections are most often caused by bacteria. It is an emergency condition because it can cause the progression of urinary tract infections which will cause complications, one of which is sepsis and septic shock. Urinary tract infection is the most common complication in patients with vesicovaginal fistula. The prevalence of urinary tract infections in patients with vesicovaginal fistula is estimated at 58.1% of the population, which is most common in developing countries. Germs that cause urinary tract infections in patients with vesicovaginal fistulas are germs that come from enteropathogenic bacteria.[13]

Management of urinary tract infections in patients with vesicovaginal fistula must be considered from various aspects, such as the pattern of germs of infection and sensitivity to antibiotics. Before examining the type of bacteria and testing for sensitivity to antibiotics, vesicovaginal fistula patients with urinary tract infections should immediately be given broad-spectrum antibiotic therapy based on the pattern of bacteria and sensitivity to antibiotics. It is done to prevent the progression of urinary tract infections.[13,14] The importance of choosing antibiotics according to the type of bacteria is to prevent bacterial resistance to one or more types of antibiotics. The pattern of germs from each hospital center is different. In our study, the most identified microorganisms causing urinary tract infections were *E. coli* (22%), *Proteus mirabilis* (7%), *Staphylococcus aureus* (6%), and *Pseudomonas aeruginosa* (5%). This is in line with previous studies where the bacteria most frequently identified in patients with vesicovaginal fistulas were *Escherichia coli*, *Proteus spp.*, *Pseudomonas*, and *Staphylococcus aureus*. However, research by Wondimeneh, et al. (2014) identified that the most common bacteria found was *Citrobacter*, while in our study, only one specimen was identified.

The antibiotic susceptibility test in our study showed different patterns. In this study, we tested the susceptibility of antibiotics to gram-positive and gram-negative bacteria. The antibiotics we used in this test were amoxicillin, ceftriaxone, gentamicin, amikacin, ampicillin, piperacillin/tazobactam, cefotaxime, ceftazidime, cefepime, ciprofloxacin, cotrimoxazole, tigecycline, aztreonam, ertapenem, and meropenem. Antibiotic sensitivity test on ten specimens that were confirmed to be gram-positive bacteria types *Staphylococcus* and *Enterococcus* from

the culture results that we found in the study showed different patterns. The resistance pattern was found in the antibiotics amoxicillin, ampicillin, and piperacillin/tazobactam with less than 50% susceptibility. In contrast, the sensitivity pattern was found in the antibiotics amikacin, ertapenem, and meropenem with more than 90% susceptibility. The pattern of isolated bacteria has similarities, but the pattern of antibiotic resistance is different from several previous studies. Research by Ugbo et al.[3] isolated gram-positive bacteria such as *Staphylococcus aureus* and *Enterococcus faecalis*, where the most resistant pattern was found to amoxicillin, tetracycline, and cotrimoxazole antibiotics.Research by Dereje et al.[14] the isolated gram-positive bacteria were *Staphylococcus spp*. where the pattern of antibiotic resistance was commonly found in the type of gentamicin antibiotic.Another study by Marami et al.[15] showed the pattern of resistance of gram-positive bacteria was mostly found in amoxicillin, gentamicin, and ciprofloxacin. In the pattern of resistance of gram-positive bacteria in the study of Ngozi et al. the most common were resistant to cotrimoxazole, chloramphenicol, sparfloxacin, amoxicillin, gentamicin, pefloxacin, and ofloxacin. The pattern of sensitivity against gram-positive bacteria in our study was found in amikacin, ertapenem, and meropenem antibiotics susceptibility tests that reached more than 80%.[16] In contrast, four previous studies, including research by Ugbo et al. showed a high sensitivity pattern found in the antibiotics gentamicin, ciprofloxacin, nitrofurantoin, ofloxacin, and imipenem.[3] Research by Dereje et al. (2017), a pattern of high sensitivity was found for the antibiotics amoxicillin and ciprofloxacin.[14] Research by Marami et al. (2022), a pattern of high sensitivity was found for the antibiotics penicillin and cefoxitin.[15] As well as research by Ngozi et al. (2021), a high sensitivity pattern was not found.[16] Thus, in our study, antibiotics that could be considered for urinary tract infections caused by gram-positive bacterial infections (*Staphylococcus spp*. and *Enterococcus spp.*) in patients with vesicovaginal fistulas were amikacin, cefepime, tigecycline, aztreonam, ertapenem, and meropenem. They have a susceptibility rate of more than 90%. Patients with vesicovaginal fistulas need to be screened for urinary tract infections before antibiotic therapy considering the pattern of resistance of *Staphylococcus spp.* and *Enterococcus spp.*, which is relatively high.

Antibiotic sensitivity tests on 38 confirmed specimens were gram-negative bacteria identified as *Escherichia coli*, *Proteus mirabilis*, *Klebsiella spp*. *Pseudomonas spp*. and *Citrobacter freundii*. In our study, a fair resistance pattern was found in *Proteus mirabilis* and *Pseudomonas spp*. Aztreonam, ertapenem, and meropenem have more than 90% of susceptibility rate, while ampicillin/sulbactam, ceftriaxone, ampicillin, piperacillin/tazobactam, cefotaxime, ceftazidime, ciprofloxacin, and cotrimoxazole have less than 50% of susceptibility. This is different from previous studies where research by Ngozi et al. (2021) revealed that the most common bacterial patterns were *Escherichia coli*, *Klebsiella spp*., and *Pseudomonas spp*., where the resistance pattern reached 100% of isolate bacteria was found in antibiotics cotrimoxazole, chloramphenicol, sparfloxacin, amoxicillin, gentamicin, streptomycin, and cefuroxime while the highest sensitivity pattern to antibiotics did not reach 50%.[16] Research by Marami et al. (2022) revealed that the pattern of isolated bacteria was *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus spp.*, *Enterobacter spp.*, *Citrobacter spp.*, and *Klebsiella spp.*, where the bacteria that had the highest resistance to antibiotics were *Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus spp*. The pattern of resistance reached more than 60% was found in trimethoprim-sulfamethoxazole, and the sensitivity pattern reached more than >70% was found in the antibiotics ceftazidime, cefoxitin, and ceftriaxone.[15] Research by Dereje et al. found that the patterns of isolated bacteria were *Escherichia coli*, *Klebsiella spp*., *Pseudomonas spp.*, *Proteus spp.*, and *Serratia spp*., where the bacteria that have the most resistance to antibiotics are *Escherichia coli*, *Klebsiella spp*., and *Pseudomonas spp*. The pattern of resistance reaching more than 50% was found with ciprofloxacin and gentamicin, while the sensitivity pattern reaching more than 70% was found in the antibiotics amoxicillin and ceftriaxone.[14] As well to research by Ugbo et al. isolated bacteria were *Klebsiella pneumonia*, *Proteus mirabilis*, and *E. coli*, whereas the bacteria that showed resistance to antibiotics were *Klebsiella pneumonia*. The highest resistance pattern, reaching more than 70%, was found in the antibiotics tetracycline, amoxicillin, and cotrimoxazole, while the sensitivity pattern reached up to 100% in imipenem antibiotics.[3] Thus, in our study, antibiotics that could be considered for urinary tract infections caused by gram-negative bacterial infections in vesicovaginal fistula patients were aztreonam, ertapenem, and meropenem, with susceptibility

rates reaching more than 90%. Patients with vesicovaginal fistulas need to be screened for urinary tract infections before antibiotic therapy, considering gram-negative bacteria's high resistance patterns such as *Escherichia coli*, *Klebsiella pneumonia*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. We found that the most etiology of VVF in our study was a malignancy. Examination of bacterial culture and antibiotic susceptibility test (AST) were not only for appropriate antibiotics treatment (definitive therapy) but also had the role of antibiogram as one consideration for empirical therapy decision. Based on the study, amikacin, cefepime, tigecycline, aztreonam, ertapenem, and meropenem should be considered in UTIs associated with VVF treatment.

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