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Patterns of Bacteria and Fungal and Their Antibiotic Sensitivitiesin Patients with Preterm Premature Rupture of Membrane: Study of Patients with PPROM ≤ 6 HoursAnd > 6 Hoursat General Hospital Kariadi Semarang

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ABSTRACT

Background: Preterm premature rupture of membranes (PPROM) has multifactorial causes. Ascending bacterial invasion can cause intrauterine infection in up to 60% of cases with PPROM. Giving antibiotics at inadequate concentrations causes bacteria to grow exponentially, which is characterized by very fast growth.
Objective: This study aims to determine bacteria patterns and antibiotic sensitivity in patients with PPROM at Dr. RSUP. Kariadi, Semarang.
Methods: Observational analytical research with a cross-sectional design. The research subjects were 46 pregnant women aged 20-36 weeks 6 days who experienced PPROM. The selection of research subjects was carried out using the consecutive sampling method, namely the selection of research subjects based on research criteria and the subjects signed an agreement to participate in the research. The independent variables in this study were preterm PPROM ≤ 6 hours and > 6 hours, the dependent variables in this study were bacteria patterns and antibiotic sensitivity. The data that has been obtained is analyzed using the SPSS program. Results are significant if $p<0.05$.
Results: *Escherichia coli* and *Candida albicans* are the most found pathogens. The antibiotics vancomycin, meropenem, and amphotericin B are effective in patients with PPROM. Women who experienced PPROM ≤ 6 hours and > 6 hours did not have significant differences in bacteria patterns and antibiotic sensitivity results.
Conclusion: The gram-negative rod-shaped bacteria Escherichia coli and the fungus Candida albicans are the main pathogens that cause PPROM. The administration of vancomycin, meropenem, and amphotericin B has high effectiveness in PPROM patients at RSUP dr. Kariadi Semarang.

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1. Introduction

Preterm Premature Rupture of Membranes (PPROM) is the rupture of the amniotic membranes before 37 weeks of gestation.[1] Preterm premature rupture of membranes is one of the important causes of premature birth with an incidence rate of 30-40% which can result in high perinatal morbidity and mortality along with maternal morbidity.[2] The incidence of PPROM worldwide ranges from 5-10% of all births.[3] Meanwhile in Indonesia the incidence of PPROM is 4.5% of all pregnancies.[4]

Premature rupture of membranes has multifactorial causes. Ascending bacterial invasion can cause intrauterine infection in up to 60% of cases with PROM. Bacteria can spread to the uterus and amniotic fluid, triggering inflammation and resulting in preterm labor and PPROM. Some pathogens that cause infections that are associated with PPROM include *Gardnerella vaginalis, Mycoplasma hominies, Chlamydia, Ureaplasma urealyticum, Fusobacterium, Trichomonas vaginalis, Klebsiella pneumoniae, Escherichia col*i and *Hemophilus vaginalis*.[5]

The most common bacteria found were coagulase negative *Staphylococcus*, namely 52.27% and *Escherichia coli*, namely 25%. *Coagulase negative Staphylococcus* bacteria are most sensitive to amoxicillin – clavulanate, fosfomycin, trimethoprim/sulfamethoxazole, and amikacin. *Escherichia coli* bacteria are most sensitive to amoxicillin – clavulanate.[6] A cohort study conducted in Iran reported a significant difference in the incidence of chorioamnionitis on the duration of preterm PPROM based on endocervical swab culture results and NICU admissions versus endocervical culture results with the predominance of culture results being *Escherichia coli*.[7] This shows that differences in causative pathogens can be found in different communities and demographics so that the therapy given can be adjusted to the predominance of the main pathogen in that area.

Prolonged premature rupture of membranes before the onset of labor increases the incidence of neonatal sepsis 2 – 10x due to infection ascending to the uterine cavity. The risk of sepsis can increase 4x if PPROM is accompanied by chorioamnionitis.[8] Research on the incidence of neonatal sepsis in Indonesia involving 2853 neonates reported an increase in the rate of neonatal sepsis in proportion to the increase in the duration of PPROM. In PPROM < 12 hours the incidence of sepsis is 1.6%, 1.3% in PPROM 12 – 23 hours, and 3.8% in PPROM ≥ 24 hours.[9] Research related to perinatal outcomes shows better APGAR scores in cases of PPROM ≤ 6 hours compared to cases of PPROM > 6 hours although this difference is not statistically significant.[10]

Giving antibiotics with inadequate concentrations causes bacteria to grow exponentially, which is characterized by very fast growth.[11,12] Thus, the duration of PPROM can be related to bacteria growth, however, there has been no research that specifically discusses differences in bacteria growth in groups with different duration of PPROM. The growth of different bacteria can be related to the accuracy of therapy in PPROM.

Therefore, researchers feel it is necessary to conduct research to determine the pattern of microorganisms and antibiotic sensitivity according to the population at RSUP Dr. Kariadi with PPROM duration ≤ 6 and > 6 hours. Currently, the PPROM protocol is being carried out at RSUP Dr. Kariadi more often gives 2g ampicillin as an initial prophylactic option, however, data regarding bacteria patterns and antibiotic sensitivity has never been carried out. Research data can be used as a consideration in preparing general guidelines for the use of antibiotics (PPAB) in PROM cases.

2. Methods

This research is an observational analytical study with a cross sectional design. The research subjects were 46 pregnant women aged 20-36 weeks 6 days who experienced PROM, obtained by means of consecutive sampling, namely selecting research subjects based on research criteria and subjects signing an agreement to participate in the research. The inclusion criteria in this study were 1) gestational age > 20 – 36 weeks 6 days a week with PROM, 2) singleton pregnancy, 3) had not been given antibiotics when vaginal swab samples were taken, 4) willing to be a research subject The exclusion criteria in this study were 1) pregnant patients with hypertension, 2) pregnant patients with chronic infectious diseases, 3) pregnant patients with diabetes mellitus, 4) pregnant patients with fetal congenital abnormalities, 5) pregnant patients with fetal death in the womb, 6) history of trauma in pregnancy. The data that was obtained was analyzed using the Statistical Package for the Social Sciences (SPSS) software program. Analysis was carried out using the Chi-square test. Results are significant if $p<0.05$. The research has obtained ethical permission from the Health Research Ethics Commission (KEPK) Dr Kariadi Hospital Semarang.

3. Result

Evaluations carried out on 46 pregnant women 20-36 months 6 days who experienced PPROM showed the following results.

Table 1. Association between demographic status and preterm premature rupture of membranes

Variable	PPROM Preterm	
	≤ 6 hours n(%)	> 6 hours n(%)
Age		
≤ 19 years old	4(17,4)	2(8,7)
20-34 years old	14(60,9)	16(69,6)
≥ 35 years old	5(21,7)	5(21,7)
BMI		
Normoweight	2(8,7)	2(8,7)
Overweight	19(82,6)	17(73,9)
Obese	2(8,7)	4(17,4)
Education		
Elementary	1(4,3)	2(8,7)
Junior high school	1(4,3)	2(8,7)
Senior high school	14(60,9)	14(60,9)
University	7(30.4)	5(21,7)
Parity		
P0	13(56,5)	13(56,5)
P1	6(26,1)	6(26,1)
P2	3(13,0)	4(17,4)
P3	1(4,3)	0(0,0)
Socioeconomic	2(8,7)	2(8.7)
Lower class		
Middle class	19(82,6)	17(73.9)
Upper class	2(8,7)	4(17.4)

Based on the likelihood ratio test above, it was found that the variables age, body mass index, education, and parity status were not significantly related to the onset of preterm premature rupture of membranes in pregnant female patients with gestational age > 20 – 36 weeks 6 days with PPROM in the treatment room. maternity hospital dr. Kariadi, Semarang.

Table 2. Bacteria patterns from vaginal swab culture results

Bacteria Pattern	PPROM ≤6 hours		PPROM >6 hours	
	n	%	n	%
GRAM POSITIVE				
Enterococcus faecalis	1	4,35	3	13,04
Enterococcus raffinosus	0	0,00	1	4,35
Staphylococcus aureus	1	4,35	1	4,35
Streptococcus agalactiae	2	8,70	0	0,00
Actinomyces urogenitalis	1	4,35	0	0,00
GRAM NEGATIVE				
Escherichia coli	1	4,35	5	21,74
Citrobacter koseri	1	4,35	1	4,35
Klebsiella pneumoniae	1	4,35	0	0,00
Haemophilus influenzae	1	4,35	0	0,00
Sphingomonas paucimobilis	1	4,35	0	0,00
FUNGUS				
Candida albicans	4	17,39	2	8,70
No fungus	9	39,13	10	43,48

There were 58.7% of samples showing positive results for pathogens growing in culture. Of the total culture samples, the pathogens with the highest percentage were *Escherichia coli* and *Candida albicans*, 13.04% each. In the preterm PROM group ≤ 6 hours, the majority was dominated by *Candida albicans* (17.39%) while the preterm PROM group > 6 hours was dominated by *Escherichia coli* (21.74%).

Table 3. Association between bacteria patterns and preterm premature rupture of membranes

Bacteria patterns	PPROM Preterm		OR	CI 95%	P
	≤ 6 hours n(%)	> 6 hours n(%)			
No growth	9 (39,1)	10 (43,5)	0,84	0,26-2,71	0,765
Growth	14 (60,9)	13 (56,5)			

**chi-square*

There is no significant relationship between bacteria growth pattern variables based on culture test results and the onset of preterm premature rupture of membranes in pregnant women with gestational age > 20 - 36 weeks 6 days with PPROM.

Table 4. Distribution of antibiotic susceptibility to gram-positive pathogens

Antibiotics	*E. faecalis* (n=4)		*E. raffinosus* (n=1)		*S. aureus* (n=2)		*S. agalactiae* (n=2)		*A. urogenitalis* (n=1)	
	n	%	n	%	n	%	n	%	n	%
Amoxicillin/clavulanate	NA	NA	NA	NA	2	100	NA	NA	1	100
Ampicillin	4	100	1	100	0	0	2	100	1	100
Azithromycin	NA	NA	NA	NA	NA	NA	1	50	0	0
Cefotaxime	NA	NA	NA	NA	NA	NA	1	50	NA	NA
Cefoxitin	0	0	NA	NA	NA	NA	NA	NA	NA	NA
Ceftriaxone	NA	NA	NA	NA	NA	NA	2	100	1	100
Clindamycin	0	0	NA	NA	2	100	2	100	0	0
Erythromycin	0	0	NA	NA	2	100	2	100	0	0
Fosfomycin	NA	NA	NA	NA	0	0	NA	NA	NA	NA
Meropenem	NA	NA	NA	NA	NA	NA	NA	NA	1	100
Nitrofurantoin	4	100	NA	NA	2	100	NA	NA	NA	NA
Oxacillin	NA	NA	NA	NA	2	100	NA	NA	NA	NA
Penicillin G	NA	NA	NA	NA	0	0	1	50	NA	NA
Vancomycin	4	100	1	100	2	100	1	50	1	100

NA: *not assessed*/not tested

Based on the data above, Enterococcus faecalis shows the highest sensitivity (100%) to ampicillin, linezolid, nitrofurantoin, and vancomycin. Enterococcus raffinosus showed the highest sensitivity (100%) to the antibiotics ampicillin and vancomycin. Staphylococcus aureus shows maximum sensitivity (100%) to the antibiotics amoxicillin/clavulanic acid, clindamycin, erythromycin, nitrofurantoin oxacillin, and vancomycin. Streptococcus agalactiae bacteria showed maximum sensitivity (100%) to the antibiotics ampicillin, ceftriaxone, clindamycin, and erythromycin. Meanwhile, Actinomyces urogenitalis bacteria showed the highest sensitivity (100%) to the antibiotics amoxicillin/clavulanic acid, ampicillin, ceftriaxone, meropenem, and vancomycin.

Table 5. Association between bacteria patterns and preterm premature rupture of membranes

Antibiotics	PPROM ≤ 6 hours										PPROM > 6 hours									
	E. faecalis (n=1)		*E. raffinosus* (n=0)		*S. aureus* (n=1)		*S. agalactiae* (n=2)		*A. urogenitalis* (n=1)		*E. faecalis* (n=3)		*E. raffinosus* (n=1)		*S. aureus* (n=1)		*S. agalactiae* (n=0)		*A. urogenitalis* (n=0)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Amoxicillin/clavulanate	NA	NA	NA	NA	1	100	NA	NA	1	100	NA	NA	NA	NA	1	100	NA	NA	NA	NA
Ampicillin	1	100	NA	NA	0	0	2	100	1	100	3	100	1	100	0	0	NA	NA	NA	NA
Azithromycin	NA	NA	NA	NA	NA	NA	1	50	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cefotaxime	NA	NA	NA	NA	NA	NA	1	50	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cefoxitin	0	0	NA	NA	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA
Ceftriaxone	NA	NA	NA	NA	NA	NA	2	100	1	100	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Clindamycin	0	0	NA	NA	1	100	2	100	0	0	0	0	NA	NA	1	100	NA	NA	NA	NA
Erythromycin	0	0	NA	NA	1	100	2	100	0	0	0	0	NA	NA	1	100	NA	NA	NA	NA
Fosfomycin	NA	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA
Meropenem	NA	NA	NA	NA	NA	NA	NA	NA	1	100	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nitrofurantoin	1	100	NA	NA	1	100	NA	NA	NA	NA	3	100	NA	NA	1	100	NA	NA	NA	NA
Oxacillin	NA	NA	NA	NA	1	100	NA	NA	NA	NA	NA	NA	NA	NA	1	100	NA	NA	NA	NA
Penicillin G	NA	NA	NA	NA	0	0	1	50	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA
Vancomycin	1	100	NA	NA	1	100	1	50	1	100	3	100	1	100	1	100	NA	NA	NA	NA

NA: *not assessed*/not tested

Table 6. Distribution of antibiotic susceptibility to gram-negative pathogens and fungi

Antibiotics	*E. coli* (n=6)		*C. koseri* (n=2)		*K. pneumoniae* (n=1)		*H. influenzae* (n=1)		*S. paucimobilis* (n=1)		*C. albicans* (n=2)	
	n	%	n	%	n	%	n	%	n	%	n	%
Amoxicillin/ clavulanate	4	66,7	1	50	1	100	1	100	0	0	NA	NA
Ampicillin	0	0	0	0	0	0	0	0	0	0	NA	NA
Amphotericin B	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2	100
Ampicillin/ sulbactam	0	0	2	100	NA	NA	1	100	NA	NA	NA	NA
Azithromycin	NA	NA	NA	NA	NA	NA	0	0	NA	NA	NA	NA
Aztreonam	4	66,7	2	100	1	100	NA	NA	0	0	NA	NA
Cefazolin	0	0	NA	NA	NA	NA	NA	NA	0	0	NA	NA
Cefepime	4	66,7	2	100	1	100	NA	NA	0	0	NA	NA
Cefotaxime	2	33,3	1	50	1	100	NA	NA	0	0	NA	NA
Ceftazidime	2	33,3	2	100	1	100	1	100	0	0	NA	NA
Ceftriaxone	NA	NA	1	50	NA	NA	1	100	NA	NA	NA	NA
Ertapenem	NA	NA	1	50	NA	NA	NA	NA	NA	NA	NA	NA
Fosfomycin	5	83,3	NA	NA	1	100	NA	NA	0	0	NA	NA
Imipenem	4	66,67	1	50	1	100	NA	NA	1	100	NA	NA
Meropenem	6	100	2	100	1	100	0	0	1	100	NA	NA
Nitrofurantoin	NA	NA	1	50	NA	NA	NA	NA	NA	NA	NA	NA
Piperacillin	2	33,3	0	0	1	100	NA	NA	0	0	NA	NA
Piperacillin/ Tazobactam	6	100	2	100	1	100	NA	NA	0	0	NA	NA

NA: *not assessed*/not tested

Distribution of antibiotic sensitivity to gram-negative pathogens and fungi based on PPROM duration groups where it can be observed regarding the type of bacteria and the percentage of their sensitivity to the antibiotics tested.

4. Discussion

Preterm premature rupture of membranes is the rupture of the amniotic membrane (amniotic sac) before labor begins, which occurs before 37 weeks of gestation. From a total of 46 samples in this study, researchers tested for differences in bacteria patterns and antibiotic sensitivity tests in groups with PPROM ≤ 6 hours and > 6 hours in the hope of providing valuable information regarding bacteria patterns and antibiotic sensitivity at Dr. RSUP. Kariadi Semarang so that it can determine more effective management policies in the future.

The sample population for this study was dominated by pregnant patients with maternal age 20-34 years (65.2%). These results are in accordance with research from Ayu et al (2015) which shows that the sample population for premature rupture of membranes is dominated by the 20-35 year age group (79.55%).[13] These results are more or less in accordance with research by Herzlich et al (2022) which showed that the average maternal age of patients with preterm premature rupture of membranes was 28.4 years.[14] In this study, there was no significant relationship between age and duration of PPROM. The author has not found previous research that specifically discusses the relationship between maternal age and the duration of PPROM. However, research from Husuni, et al (2022) shows a significant relationship between age and the incidence of PPROM. This is in accordance with the theory that at ages < 20 years and > 35 years, reproductive function is not at its most optimal condition, which causes the risk of PROM to be higher at that age compared to ages 20-35 years. However, age was proven not to be related to the incidence of PPROM in this study.[15]

Based on BMI data, patients with an overweight BMI category showed the greatest frequency (78.3%). This is in accordance with research from Sfregola et al. (2023) which shows that the mean BMI in patients with PPROM is 29.57 ± 4.44 kg/m^2.[16] BMI does not show a significant relationship with the duration of PPROM, because BMI as a demographic status has nothing to do with the process of premature rupture of membranes.

Most patients in this study were high school graduates, namely 60.9%. This is in accordance with research from Ayu et al (2015) where high school graduates are the largest category with a frequency of 43.18%. This research also shows that there is no significant relationship between education and the duration of PPROM. This is possibly because the educational factor is only a demographic status that has nothing to do with the process of premature rupture of membranes.[13]

Based on parity data, most of the sample in this study were nulliparous mothers who had never given birth before (56.5%). These results are different from research by Ayu et al (2015) which showed that most of the sample were multiparous patients (63.63%). Research from Husuni et al (2022) also shows that multiparas dominate the research sample (53%).[15] This difference is likely caused by variations in the patient population at each hospital. There was an insignificant relationship between parity status and duration of preterm PROM. Research regarding the relationship between parity status and the duration of preterm PROM is still very limited. However, research by Husuni et al (2022) shows a significant relationship between parity and the incidence of PPROM.[15] This can happen because the thin consistency of the cervix in multiparas can increase the risk of tearing of the amniotic membranes.[15,17]

The bacteria pattern of the culture results in this study found that most samples showed growth results (58.7%). These results are in accordance with research from Ambalpady et al (2022) which showed that most samples showed positive results for bacterial growth (85.09%).[18] However, these results are different from previous research from Sravya (2023) which showed that most PPROM samples showed culture results without bacterial growth (64.8%).[19]

This research shows that most pathogens found in vaginal swab culture tests are *E. coli* (22.22%) and *C. albicans* (22.22%). The research results from Sravya et al (2023) showed linear results where they found E. coli (52.6%) as the dominant pathogen found from the vaginal

swab culture results of patients with preterm PROM 19. The research results of Saghafi et al (2018) also showed *E. coli* as the dominant pathogen found in PPROM patients (24.2%). This research also found the presence of *C. albicans* (11.8%) although with a less dominant frequency.[20]

The bacterial flora in the maternal rectovaginal tract is more influenced by the occurrence of PPROM than by the duration of PPROM itself. A study by Liu et al (2022) regarding the characterization of the vaginal microbiota in third trimester PROM, the microbiome composition between the PPROM group and the healthy control group showed that the PPROM group had higher variations in the microbiome, such as Gardnerella, Megasphaera, Prevotella, Ureaplasma, Dialister, Aerococcus, and Arcanobacterium, compared with a healthy control group. However, duration of PPROM was not a significant factor in determining vaginal microbiome diversity.[21] Similarly, in a study by Yin et al (2022) regarding the analysis of the microbiome in the maternal, intrauterine and fetal compartments, the diversity of microorganisms increased significantly after 12 hours from membrane rupture, while the diversity of the amniotic fluid microbiome changed after 24 hours.[22] This study examined the effect of the duration of PPROM before and after 6 hours on the pathogen profile of vaginal swab culture results.

Antibiotic sensitivity testing showed that the antibiotic vancomycin showed high effectiveness against gram-positive bacteria that grew in culture tests. Vancomycin was shown to be effective against all strains except *Streptococcus agalactiae*. These results are in line with research from Ambalpady (2022) which shows that vancomycin is effective against bacteria-positive bacteria such as *S. aureus* and *Enterococcus sp* 18 Based on safety for use in pregnant women, vancomycin is known as a category B antibiotic which is considered proven to be safe and effective in treating cases of infection.[23]

Antibiotic tests on gram-negative bacteria showed that meropenem was the most effective antibiotic used on gram-negative bacteria even though the antibiotic showed resistance in tests against *Haemophilus influenzae*. This ineffective result may also be due to the limited number of samples with these bacteria, namely only 1 sample, where different results may be obtained in a larger number of samples. Research by Sravya et al (2023) shows that meropenem has proven to be effective for gram-negative bacteria such as *E. coli* which is dominantly found in vaginal swab culture results of PPROM patients.[19] Based on safety in pregnant women, meropenem is included in category B which is considered safe enough to use. Meanwhile, another antibiotic option that was found to be quite effective against gram-negatives is ceftazidime, which is in the cephalosphorin group and is considered safe for use in pregnant women (category B).[23]Antifungals such as amphotericin B have been shown to be effective against C. albicans in antibiotic susceptibility testing. Amphotericin B is included in category B based on the level of safety in pregnant women where this antifungal is considered the safest oral antifungal drug that can be used in pregnant women.[24,25]

This research objectively shows a picture of the distribution of bacteria patterns and antibiotic sensitivity based on the duration of PPROM. In this study, it was possible to observe the pathogens most frequently found in PPROM patients at RSUP dr. Kariadi, Semarang and antibiotics that show high effectiveness against these pathogens, both gram-positive, gram-negative and fungi. However, due to the small number of preterm PROM patients reaching RSUP dr. Kariadi, where many PPROM patients were completely treated in hospitals of a lower type, so the sample size in this study was relatively limited, which was susceptible to research bias due to the small sample size. In addition, due to the limited number of samples, antibiotic susceptibility test findings in certain species with limited frequency have the potential to be biased and different results may be obtained if a larger sample is used. It is hoped that future research can use a larger sample size to obtain more representative results for the population of pregnant women with PPROM.

5. Conclusion

Escherichia coli and *Candida albicans* are the most common types of pathogens found. The use of the antibiotic's vancomycin, merpenem, and the antifungal amphotericin B has proven to be effective in preterm PROM patients at RSUP dr. Kariadi. PROM patients ≤ 6 hours and > 6 hours did not show significant differences in bacteria patterns and antibiotic sensitivity results.

Ethical Approval

Ethical clearance was obtained from the Health Research Ethics Commission (KEPK) of Dr. Kariadi General Hospital, Semarang.

Conflicts of Interest

There is no conflict of interest in this research

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Author Contributions

Conceptualization, RBHM and BAP; methodology, BAP; software, RBHM; validation, RBHM and BAP; formal analysis, RBHM; investigation, RBHM; resources, RBHM; data curation, RBHM; writing-original draft preparation, RBHM; writing-review and editing, BAP;

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