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Original Article

Antibiotic Sensitivity Against *Klebsiella* spp. in the Post Debridement Culture an Open Fracture in Emergency Department of dr. Soebandi Hospital Jember

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ABSTRACT

Surgical site infection (SSI) in open fracture is often caused by bacterial contamination in the management of open fracture. Because of that, one of the most important thing in handling open fracture is debridement. Prophylactic antibiotics given are Cephalosporin and Aminoglycosides. Post-debridement culture is important in predicting the incidence of infection. One of the bacteria that is often found in post-debridement culture is Klebsiella spp. which can produce ESBL to fight β-lactam class of antibiotics. The purpose of this study was to determine antibiotic sensitivity against Klebsiella spp. in the post-debridement culture of cases of open fractures in the emergency department of dr. Soebandi hospital Jember. This study uses a laboratory exploratory research design. The sample of this study was the isolate of Klebsiella spp. which amounts to 5 from post debridement culture of open fracture patients in the emergency department of dr. Soebandi hospital Jember from March to May 2019.The method used is diffusion (Kirby Baurer) by matching using the CLSI standard table to determine sensitive, intermediate, or resistant. The results of this study showed that most antibiotics had resistance to Klebsiella spp., including β-lactam antibiotics, such as Amoxicillin, Ceftriaxone, Cefixime, Penicilin, Meropenem, and Cefadroxil. Vancomycin antibiotics are still sensitive to Klebsiella spp. in all patients. Gentamicin, Ciprofloxacin, Tetracycline, and Chloramphenicol antibiotics were sensitive in 1 patient. Erythromycin intermediates antibiotics against Klebsiella spp.. The conclusion of this study is that all β-lactam group antibiotics are resistant to Klebsiella spp while the most sensitive antibiotic is Vancomycin.

Keywords: *antibiotic sensitivity; ESBL; Klebsiella spp.; open fracture; post debridement*

ABSTRAK

Infeksi luka operasi pada patah tulang terbuka seringkali disebabkan oleh kontaminasi bakteri pada manajemen patah tulang terbuka. Oleh karena itu, salah satu hal yang penting pada penanganan patah tulang terbuka adalah debridemen. Kultur setelah debridemen penting dalam memprediksi kejadian infeksi. Salah satu bakteri yang sering ditemukan pada kultur setelah debridemen adalah Klebsiella spp. yang dapat menghasilkan Extended-spectrum β-lactamase (ESBL) untuk melawan antibiotik golongan β-lactam. Tujuan penelitian ini untuk mengetahui sensitivitas antibiotik terhadap Klebsiella spp. pada kultur post debridement kasus patah tulang terbuka di Emergency department dr. Soebandi hospital Jember. Penelitian ini menggunakan desain penelitian eksploratif laboratorik. Sampel penelitian ini adalah isolat bakteri Klebsiella spp. hasil kultur post debridement 5 pasien patah tulang terbuka di

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Emergency department dr. Soebandi hospital Jember periode Maret-Mei 2019. Metode yang digunakan adalah difusi (Kirby Baurer) dengan hasil pengukuran yang dikonversikan dengan tabel standar Clinical Laboratory Standards Institue (CLSI) untuk menentukan sensitif, intermediet, atau resisten. Hasil: Hasil penelitian ini menunjukan sebagian besar antibiotik mengalami resistensi terhadap Klebsiella spp., termasuk antibiotik golongan β-lactam, seperti Amoxicillin, Ceftriaxone, Cefixime, Penicilin, Meropenem, dan Cefadroxil. Antibiotik Vancomycin masih sensitif terhadap Klebsiella spp. pada seluruh pasien. Antibiotik Gentamicin, Ciprofloxacin, Tetracycline, dan Chloramphenicol sensitif pada 1 pasien. Antibiotik Erythromycin intermediet terhadap Klebsiella spp. Kesimpulan dari penelitian ini adalah semua antibiotik golongan β-lactam resisten terhadap Klebsiella spp. sedangkan antibiotik yang paling sensitif adalah Vancomycin.

Kata kunci: *ESBL; Klebsiella spp.; patah tulang terbuka; sensitivitas antibiotik; setelah debrimen*

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INTRODUCTION

Surgical site infection (SSI) in the open fracture is often caused by bacterial contamination in open fracture management. Because of that, debridement is one of the most important things in handling open fractures. An open fracture is a break in the continuity of the bone with injury to the skin above the site of fractures, with traffic accidents the most cause.[1–3] In open fractures, contact with the outside environment is susceptible to infection. In the treatment of open fractures, one of the important things to do is debridement.[4–7]

In a study at Third Hospital of Hebei Medical University, most SSIs (81.8 %,18/22) were found during subsequent hospitalizations. The total incidence of SSIs was 6.0 % (22/364). The superficial SSIs accounted for 2.4 % (9/364) and deep SSIs for 3.6 % (13/364).[8], whereas in The Second Hospital of Tangshan, the overall incidence of SSI was 18.6%, with 17.0% and 1.6% for superficial and deep infection, respectively. There were 2027 males and 665 females of the study sample.[9]

Post-debridement culture is more important in predicting infection incidence than pre-debridement culture. In post-debridement cultures of open fractures, infections are often caused by Gram-negative bacteria such as *Klebsiella* spp., *E. coli*, *Pseudomonas* spp., *Acinetobacter* spp., and *Enterobacter* spp..[10,11] Research by Sitati et al. (2017) mentioned that bacteria found in post-debridement culture of open fractures are *Klebsiella* spp., *S. aureus*, *Pseudomonas* spp., CON (negative coagulase) Staphylococci, and *E. coli*. This is in line with the preliminary study conducted from March to May 2019 at the Emergency department dr. Soebandi hospital Jember, in 30 patients with open fractures, it was found that in the culture of post-debridement, the most common bacteria were *Klebsiella* spp.[12]

Klebsiella spp. is a Gram-negative, rod-shaped bacterium and Lactose-positive colonies cultivated on MacConkey agar.[13] *Klebsiella* spp. is the main bacterium of the family Enterobacteriaceae, which can produce Extended-spectrum β-lactamase (ESBL) to fight the β-lactam class of antibiotics, such as the Penicillin, Cephalosporin, Carbapenem, and Monobactam groups. This enzyme hydrolyzes the β-lactam ring from antibiotics so that antibiotic resistance can occur.[14]

Prophylactic antibiotics such as the Aminoglycosides and Cephalosporin first generation are often given in cases of open fractures to prevent infection. This is what allows antibiotic resistance.[15] Antibiotic resistance could occur in some ways, such as destroying antibiotics with the enzymes produced, improving antibiotic capture point receptors, improving the physicochemical targets of antibiotic targets in bacterial cells, and antibiotics could not penetrate bacterial cell walls due to changes in bacterial cell wall properties. If someone is infected with

resistant bacteria, the effort to deal with infection with antibiotics is more complicated.[16]

Research conducted at Voi County Hospital, Kenya, by Sitati et al. in 2017, stated that Gram-negative bacteria *Klebsiella* spp. and *Pseudomonas* spp. pre and post-debridement experienced high resistance to Tetracycline and Amoxicillin-Clavulanic Acid by 27% and 23% and experienced resistance of 87.5%, 91%, and 47.6% in Gentamicin, Amikacin, and Cefuroxime.[12]

It was giving Ceftriaxone therapy as a prophylactic antibiotic and Cefixime when outpatient to patients with open fractures in the emergency room of Emergency department dr. Soebandi hospital Jember is not based on culture results and antibiotic sensitivity testing. This is what underlies the author's research on the sensitivity of 12 types of antibiotics, namely Amoxicillin, Tetracycline, Ceftriaxone, Gentamicin, Cefixime, Ciprofloxacin, Penicillin, Meropenem, Erythromycin, Vancomycin, Cefadroxil, and Chloramphenicol against *Klebsiella* spp. in the post-debridement culture of cases of open fractures in emergency department dr. Soebandi hospital Jember.

MATERIALS AND METHODS

Materials

The population of this study was 12 bacterial isolates from the post-debridement culture of open fracture patients in the emergency room of emergency department dr. Soebandi hospital Jember from March to May 2019 consisted of *Klebsiella* spp. (5 patients), *Pseudomonas* spp. (3 patients), *Shigella* spp. (2 patients), *Salmonella* spp. (1 patient), and *Proteus* spp. (1 patient). The sample of this study was *Klebsiella* spp. amounting to 5. The 12 types of antibiotics, namely Amoxicillin, Tetracycline, Ceftriaxone, Gentamicin, Cefixime, Ciprofloxacin, Penicillin, Meropenem, Erythromycin, Vancomycin, Cefadroxil, and Chloramphenicol. The research used McFarland standards, Mueller-Hinton Agar, plates, sterile cotton swabs, aluminum foil, tweezers, syringes, caliper, and ruler.

Methods

This study uses a laboratory explorative research design that is research that does not aim to look for relationships between variables, is only descriptive and is carried out at the Laboratory of Microbiology, Faculty of Medicine, University of Jember. The method used is diffusion (Kirby Baurer) by matching the inhibition zone diameters using the standard Clinical Laboratory Standards Institution (CLSI) table to determine sensitive, intermediate, or resistant. The steps of the research procedure was to prepare 0.5 McFarland standards made from 1% $BaCl_2$ and 1% H_2SO_4 and shake before use to adjust the turbidity of the bacterial suspension and Mueller-Hinton Agar from 15.2 grams of Mueller-Hinton and 400 ml aquadest.

Antibiotic sensitivity testing in this study used the method disc diffusion (Kirby-Baurer test) with Mueller-Hinton Agar. The steps taken were to make inoculums from *Klebsiella* spp. from each plate using a loop into 2 ml of NaCl 0,9%. The inoculum turbidity was adjusted to ensure an even or nearly even growth yield using McFarland standard. After turbidity obtained the same results as McFarland standard, the plate was inoculated using a sterile cotton swab dipped in the inoculum in laminar flow biobase.

Before being swabbed on Mueller-Hinton Agar, excess inoculum was removed by pressing and rotating the cotton swab firmly against the side of the tube. The swab was evenly distributed over the entire surface of Mueller-Hinton Agar by rotating the plate at an angle of 60˚ and allowed to dry for several minutes at room temperature with the cup closed. Then given 4 discs of antibiotics in each medium.

Discs are aseptically placed on the surface of Mueller-Hinton Agar using sterile tweezers to avoid contamination with other bacteria. The media that had been given an antibiotic disc was incubated for 24 hours at 37^0C. Repetition was carried out three times on different media.

Measurements were made the next day after 24 hours of media incubation at 37^0C. Measuring the diameter of the bacterial growth inhibition zone using a caliper or ruler is done on the back of the Mueller-Hinton Agar media so that you don't have to open the lid. The measurement results are adjusted to the Clinically and Laboratory Standards Institute (CLSI) in the classification of sensitive, intermediate, or resistant.

Ethical Approval

This research received ethical approval from the health research ethics comitte of Faculty of Medicine, University of Jember with the letter number 1.408/H25.1.11/KE/2020.

RESULTS AND DISCUSSION

Based on preliminary studies carried out from March to May 2019 at the IGD RSD, dr. Soebandi Jember, in 30 patients with open fractures, there were data that there were 12 patients in the culture of positive post-debridement growing bacteria, 42% *Klebsiella* spp., 25% *Pseudomonas* spp., 17% *Shigella* spp., 8% *Salmonella* spp., and 8% *Proteus* spp.. *Klebsiella* spp. is the most common bacteria in post-debridement culture, 5 isolates. Patients positive for *Klebsiella* spp. in the post-debridement culture there were 5 people with 4 male and 1 female. In contrast, the age distribution of patients was 1 person in range 17-25 years, 2 people in range 36–45 years, 1 person in range 56–65 years, and 1 person in range ≥ 66 years. All patients were diagnosed with varying degrees of open fracture according to the Gustilo-Anderson classification. Most patients experience open fractures due to traffic accidents. The clinical characteristics data of 5 patients with open fractures, such as diagnosis and Mode of Injury (MOI) (shown in Table 1).

Table 1. Diagnosis, Grade, and MOI of the Open Fractures Patients

Patients	Diagnosis	Grade	Mode of Injury (MOI)
P1	Traumatic amputation digiti 2, open fracture head metacarpal 2, and open fracture digiti 3 phalanx distal manus sinistra	IIIB	Exposed to a wood-cutting knife
P2	Open fracture fibula dextra and fracture iliac wing dextra	IIIA	Traffic accidents between 2 motorcycle riders
P3	Open fracture tibia-fibula 1/3 medial sinistra	IIIB	Traffic accidents between 2 motorcycle riders
P4	Open fracture digiti 1,2,3 phalanx proximal pedis dextra	IIIA	Traffic accidents between 2 motorcycle riders
P5	Open fracture kominutif tibia-fibula sinistra	II	Traffic accidents between 2 motorcycle riders

The results of medical record data on the type of antibiotic prophylaxis, antibiotics during hospitalization, and antibiotics consumed at home used by patients with open fractures as a sample of this study can be seen in Table 2. The antibiotics tested were adjusted to the CLSI standard for *Klebsiella* spp. as shown in Table 3.

Table 2. Antibiotics Are Given to Patients with Open Fractures at dr. Soebandi Hospital

Patients	Antibiotic		
	Prophylaxis	**Inpatient**	**Outpatient**
P1	*Ceftriaxone*	*Ceftriaxone*	*Cefixime*
P2	*Ceftriaxone*	*Ceftriaxone*	*Cefixime*
P3	*Ceftriaxone*	*Ceftriaxone*	*Cefixime*
P4	*Ceftriaxone*	*Ceftriaxone*	*Cefixime*
P5	*Ceftriaxone*	*Cefazoline and Gentamicin*	*Cefixime*

Table 2. The Result of the Antibiotic Sensitivity Test for *Klebsiella* spp.

Sample	AML	CRO	CFM	P	MEM	CFR	CN	CIP	TE	E	C	VA
P1	R	R	R	R	R	R	R	I	R	I	I	S
P2	R	R	R	R	R	R	S	I	I	R	S	S
P3	R	R	R	R	R	R	R	I	R	I	I	S
P4	R	R	R	R	R	R	R	S	I	I	I	S
P5	R	R	R	R	R	R	R	I	S	I	I	S

R= Resistent, I= Intermediate, S= Sensitive, P1= Patient 1, P2= Patient 2, P3= Patient 3, P4= Patient 4, P5= Patient 5, AML= *Amoxicillin*, CRO= *Ceftriaxone*, CFM= *Cefixime*, P= *Penicilin*, MEM= *Meropenem*, CFR= *Cefadroxil*, CN= *Gentamicin*, CIP= *Ciprofloxacin*, TE= *Tetracycline*, E= *Erythromycin*, C= *Chloramphenicol*, VA= *Vancomycin*.

This study found positive patients *Klebsiella* spp. in the post-debridement culture. There were 5 people, 4 male, and 1 female, with an age range of 22-70 years. The results of this study are consistent with research by Agarwal et al[2], which states that of the 70 open fracture patients studied, 63 patients (90%) were men with ages ranging from 3-75 years.[2] Research by Gupta et al[10] states that most open fracture patients have a 13 times higher incidence of males than females. This is because men are more often outdoors activities.[10] Traffic accidents are the most common cause of open fractures, followed by work-related injuries and falls from heights. High-energy trauma is the most common Mode of Injury (MOI) causing open fractures. Diagnosis of patients with open fractures dominated by phalanx, tibia, and fibula according to research by Sop and Sop[4], which states that phalanx fractures are the most common fractures, followed by tibia and fibula fractures.[4] Degree III open fractures, according to the Gustilo-Anderson classification, have a significantly higher infection rate than grades I and II. This is related to the severity of the wound and the degree III treatment's length of time.[17–19]

Management of open fracture cases requires the administration of antibiotic prophylaxis to prevent surgical site infection (SSI). Prophylactic antibiotics used in treating open fractures in RSD dr. Soebandi Jember uses the Ceftriaxone antibiotic, while the antibiotic given while outpatient is Cefixime. Ceftriaxone and Cefixime are included in the antibiotic. A cephalosporin is an antibiotic option in line with guidelines for treating open fractures in a journal by Zalavras[20]. The journal also describes the administration of Cephalosporin and Aminoglycosides antibiotics to prevent infection. Cephalosporin is given to prevent Gram-positive bacteria in first and second-degree open fractures. In contrast, third-degree open fractures require antibiotics to protect against Gram-positive and negative, and Aminoglycosides (Gentamicin) are given.[20] According to Sop and Sop[4], when antibiotics are given 66 minutes after injury, the infection rate is 0% and increases to 17% if it exceeds this time.[4] The British Orthopedic Association/British Association of Plastic Reconstruction and Aesthetic Surgeons (BOA/BAPRAS) supports the opinion of experts that antibiotics are given

24 to 48 hours for the degree I and a maximum of 72 hours in degrees II and III.[21]

In this study, a sensitivity test for 12 antibiotics was carried out on the *Klebsiella* spp. These bacteria can cause many of disease, cause problem to people with immunocompromised and the most common cause of hospital acquired pneumonia. In this study *Klebsiella* spp. that found in culture most likely caused of open fracture, even the management has been carried out according to the procedure.[22,23] Open fracture treatment depends on location of fracture but generally need irrigation, debridement, and antibiotic. Initial debridement in should be performed within 24 hours. The goals of open fracture management include decreasing risk of infection and promoting fracture union.[24,25]

Klebsiella spp. cultured after debridement in patients with open fractures developed resistance to β-lactam antibiotics. These antibiotics include amoxicillin, Ceftriaxone, Cefixime, Penicillin, Meropenem, and Cefadroxil. However, antibiotics such as Gentamicin, Ciprofloxacin, Tetracycline, Chloramphenicol, and Vancomycin, these bacteria are sensitive. Associated with the resistance of these bacteria to β-lactam class antibiotics, it proves that these bacteria are Extended-spectrum β-lactamase (ESBL) producing bacteria.

The results of this study different from studies conducted at Voi County Hospital, Kenya by Sitati et al[12] which states that patients with open fractures after culture in pre and post debridement, obtained high resistance data against Tetracycline, Erythromycin, and Amoxicillin-Clavulanic Acid in Gram positive and negative bacteria. Gram negative bacteria such as *Klebsiella* spp. and *Pseudomonas* spp. found in pre and post debridement experienced high resistance to Tetracycline and Amoxicillin-Clavulanic Acid by 27% and 23% and experienced resistance of 87.5%, 91%, and 47.6% in Gentamicin, Amikacin and Cefuroxime. This is likely due to differences in study locations and differences in the selection of antibiotics used in the treatment of open fracture patients.[12,27] The results of research that have been done have shown that antibiotics are still sensitive to *Klebsiella* spp. namely Gentamicin in 1 patient, Ciprofloxacin in 1 patient, Tetracycline in 1 patient, Chloramphenicol in 1 patient, and Vancomycin in all patients. ESBL-producing bacteria can be given Vancomycin antibiotics which can kill bacteria by breaking peptide bonds between amino acids in the peptidoglycan wall. Although using Vancomycin for open fractures is safe, it is still controversial, except for patients who are allergic to Penicillin. This is because Vancomycin added to Cefazoline has no benefit in patients with open fractures.

However, a recent 2016 publication by Tennent et al shows the benefits of using Vancomycin powder in local wounds of rats to prevent biofilm formation.[28] Gentamicin antibiotics were still sensitive according to the study of Ashwin and Thomas[29] , which stated that bacterial culture in third-degree open fractures was 83.3% *Klebsiella* spp. sensitive to Gentamicin.[29]

Chloramphenicol antibiotics are sensitive to *Klebsiella* spp. This is in accordance with research by Nitzan et al[30] which states that members of Enterobactericeae, such as the bacteria *Klebsiella* spp., *E. coli*, and *Enterobacter* spp. achieve statistical significance of a lower level of resistance to Chloramphenicol of 18.4%.[16] Ciprofloxacin antibiotics are sensitive to *Klebsiella* spp. by the 2018 Mangala study, which states that Ciprofloxacin has a 69% sensitivity to the Enterobacteriaceae family.[31]

Research on Carbapenem-Resistant Klebsiella Pneumoniae (CRKP) states that in data analysis from 1998–2010, resistance to Tetracycline increased only slightly. Next-generation Tetracycline may be helpful in the treatment of CRKP because of increased tissue penetration, antibiotic activity, and the decreased tendency for antibiotic resistance.[32] This is in line with research that has been done because the Tetracycline

antibiotic was found to be sensitive in 1 patient. Erythromycin antibiotics were concluded intermediates against the bacteria *Klebsiella* spp. because intermediates were obtained in 4 patients and resistant in 1 patient. Research by Khan et al[33] states that the bacteria *Klebsiella* spp. found to be more resistant to macrolide antibiotics, equal to 41.67% against Erythromycin.[33] resistant Antibiotics and intermediates cause the treatment of open fractures to be suboptimal, resulting in surgical site infection (SSI). The management of open fractures is focused on effective debridement measures, appropriate antibiotic therapy, and initial wound closure to prevent infection.[21]

The older age (71.5%) due to experiencing immune deficiency (decreased immune system) resulting in a longer recovery time. Degree III open fractures according to the Gustilo-Anderson classification have a significantly higher infection rate than grades I and II. This is related to the severity of the wound and the length of time of the third degree treatment.[13] The occurrence of SSI in these patients is likely due to the above SSI risk factors, such as age 70 years (> 60 years), male, experiencing high energy injuries due to accidents, and the degree of open fracture IIIB.

CONCLUSIONS

The conclusion of this study after an antibiotic sensitivity test was conducted on 5 samples of *Klebsiella* spp. in post-debridement culture in Emergency Department Soebandi General Hospital Jember is resistant to *Klebsiella* spp. the β-lactam class of antibiotics used in this study are Amoxicillin, Ceftriaxone, Cefixime, Penicillin, Meropenem, and Cefadroxil. *Klebsiella* spp. was still sensitive to other antibiotics such as Chloramphenicol Gentamicin, Ciprofloxacin, Tetracycline, and Vancomycin. Erythromycin antibiotics are stated intermediates to the bacterium *Klebsiella* spp. for the dr. Soebandi hospital Jember. The institution needs to have periodic culture tests and antibiotic sensitivity tests for inpatients so that an antibiogram can be made and used as a basis for the definitive treatment of diseases, especially in the field of Orthopedic.

The antibiotic sensitivity test towards *Klebsiella* spp. which contaminated the post-debridement procedure in patients with open fracture, showed an evidence that a comprehensive evaluation of the empirical antibiotic prophylactic strategies pre- and post-operative procedures so far need to be considered. This statement is based on the total resistance of Ceftriaxone and Cefixime in all *Klebsiella* spp samples. Based on this research, we also humbly recommend other antibiotics that can be alternative options as prophylactic agents to prevent perioperative contamination and postoperative surgical site infection in patients with open fractures, such as Gentamicin, Ciprofloxacin, Tetracycline, Chloramphenicol, and Vancomycin.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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