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A Case Report: Surgical Site Infection of Open Fracture Grade IIIC Caused by Methicillin-Resistant Staphylococcus aureus (MRSA)

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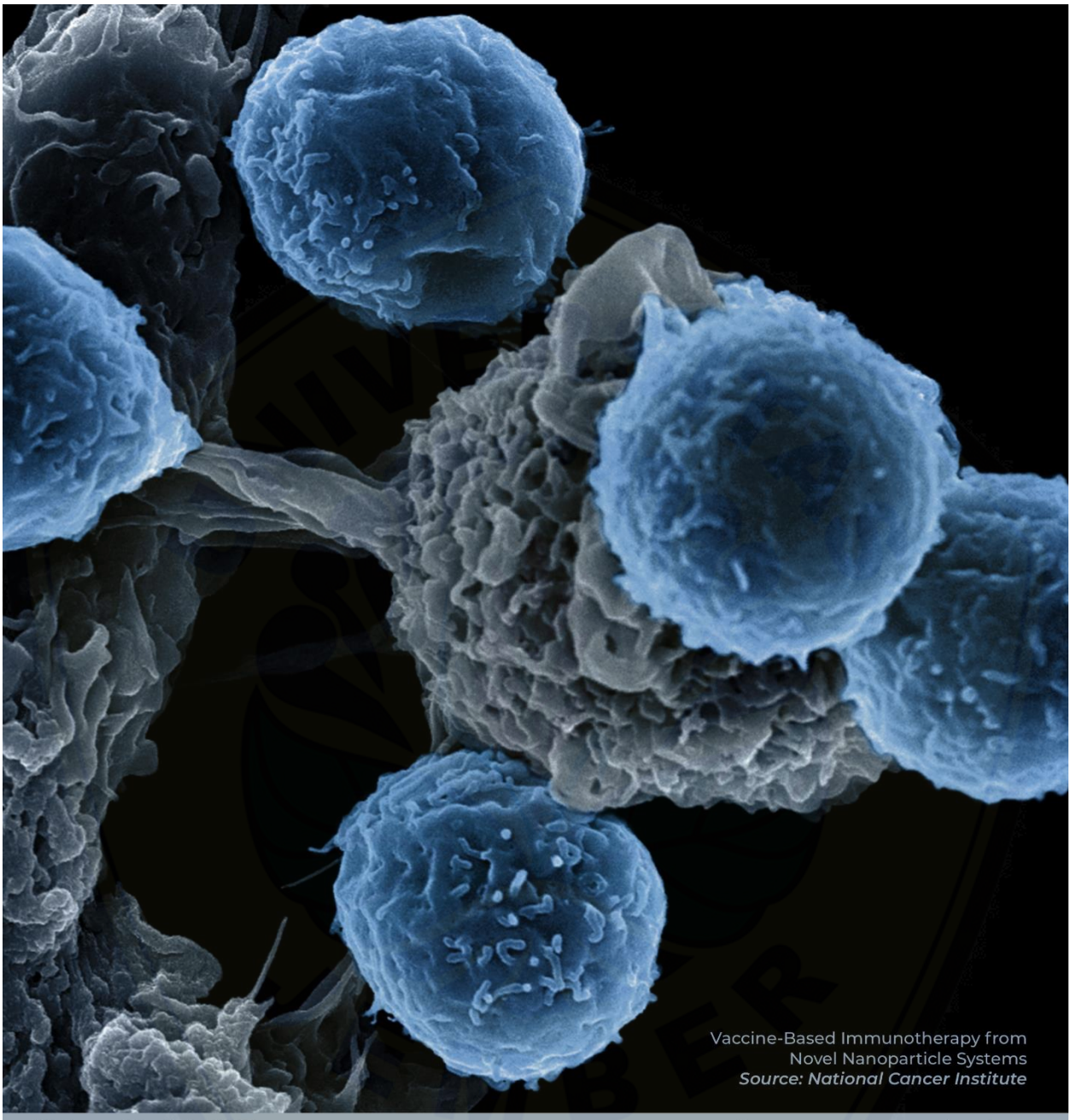

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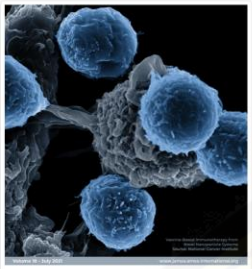

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A Case Report: Surgical Site Infection of Open Fracture Grade IIIC Caused by Methicillin-Resistant Staphylococcus aureus (MRSA)

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Introduction Based on World Health Organization (WHO) data in 2016, Surgical Site Infections (SSIs) occur in 11% of patients undergoing the procedure operations in developing countries. Overall, Staphylococcus aureus was the commonest bacteria isolated from the cultures in the postoperative period. Now, it is considered endemic to most hospitals as Hospital Associated MRSA.

Case History and Examination A 60-year-old male presented to Rumah Sakit Daerah (RSD) Dr. Soebandi Jember with a severe open fracture of his right lower extremity (cruris dextra) after being hit by a truck. The patient came with massive bleeding because of the rupture of the tibial and femoral arteries. He had been already given initial prophylactic antibiotic treatment such as cefazolin and amoxicillin before the operative procedure. After more than 3 months, he suffered a pyogenic infection with a biofilm plaque formation on his surgical sites.

Microbiology Examination and Diagnosis This Staphylococcus aureus resisted to 12 of 18 antibiotics that were tested including beta-lactams and macrolides groups of antibiotics.

Treatment and Course This case has already been reported to the hospital and the patient was given topical Gentamicin and oral Clindamycin

Discussion The initial mistreatment of fracture becomes the risk factor of surgical site infection, and also this patient's condition included significant risk factors for SSI because of his age, location of injury cleanliness, and high-energy injury.

Conclusion and Recommendations This case report of SSI in a postoperative of severe open fracture can be used to evaluate the empirical treatment that is used in RSD Dr. Soebandi Jember.

Introduction

As Open fractures are complex injuries involving the bones and surrounding tissue[1]. According to the 2017 American Academy of Orthopedic Surgeons (AAOS), open fractures are broken bones with open wounds and skin damage caused by bone fragments that penetrate the skin at the time of injury[2]. Open fracture has already classified by Gustilo and Anderson based on wound size, level of contamination, and osseous injury as follows: Type I is an open fracture with a wound less than 1 cm long and clean, Type II is an open fracture with a laceration more than 1 cm long without extensive soft tissue damage, and Type III is an open fracture that are segmented with extensive damage of soft tissue and can be followed by vascular injury[3]. Type III of Open Fracture is also divided into 3 subclasses, with the most severe is type C because it is associated with arterial injury and massive contamination[4]. Some open fracture cases need an operative fixation. The operative fixation of skeletal fractures can be highly complex due to the unpredictable nature of bone damage. One of the most challenging complications in this management is Infection after fracture fixation (IAFF)[5]. By breaking the skin, open fractures eliminate one of the major barriers to infection. Bacterial contamination has been shown to occur in up to 70% of open fracture wounds[1].

Instead of that, loss of skin integrity and exposure of the subcutaneous tissue provides a warm, conducive environment for the colonization and growth of microorganisms unless it is treated with prophylactic antibiotics and surgical debridement. The management of open fracture cases is different from closed fracture cases because there are indications of complications of bone and tissue infections around post-surgical sites. The goals of open fractures management include the prevention of infection, achievement of bone union, and restoration of function. Once the infection is established, wound healing is delayed, treatment cost rises, and wound management practices become more difficult[6]. Based on World Health Organization (WHO) data in 2016, Surgical Site Infections (SSIs) occur in 11% of patients undergoing the procedure operations in developing countries[7].

SSIs associated with external or internal fixation of fractures are regarded as serious complications. Septicemia, which can lead to septic shock, can be a serious emergency case for this complication. Based on the previous research by Oliveira in the Instituto de Ortopedia e Traumatologia, the primary infectious agent isolated from the SSI is Staphylococcus aureus. Because of that, the prophylaxis antibiotics that can be prescribed to the patient are usually beta-lactam, including the cephalosporin category. In accordance to that, patients with open fractures who underwent surgery for fixation of their fractures received Cefazolin empirically[8]. To make it clear, diagnostic microbiology plays a crucial role in the control of infection to prevent severe complications such as emergency septic shock[9].

Overall, Staphylococcus aureus is the commonest bacteria isolated from the cultures in the postoperative period. The higher rate of isolation of Staphylococcus aureus in the postoperative period may be due to the production of several virulence factors and also the property to form biofilms adhering to the wound. Sometimes, antibiotic resistance can be caused by biofilm formation[9].

Bacterial biofilms are communities of microorganisms that are attached to an underlying foreign body or tissue substrate and held together by a self-produced extracellular matrix. Bacteria that can form biofilms are Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, and many more. Inside the host, biofilms allow pathogens to inhibit innate immune defenses and are thus associated with long-term persistence[10].

Staphylococcus aureus is a Gram-positive, non-motile, pus-producing coccus. Microscopically, S.aureus has the appearance of 0.5- to 1.5-µm balls that are clumped together like grapes. Methicillin was introduced as an antibiotic against Staphylococcus aureus in 1959. In 1961, Staphylococcus aureus had begun developing resistance to methicillin and quickly spread worldwide. Now, methicillin-resistant Staphylococcus aureus (MRSA) may be resistant to penicillin and cephalosporin antibiotics, and more than 50% are resistant to antibiotics such as macrolides, lincosamides, fluoroquinolones, and aminoglycosides; and 30% are resistant to trimethoprim-sulfamethoxazole. Now it is considered as endemic to most hospitals as Hospital Associated MRSA. National Nosocomial Infection Surveillance (NNIS) System data demonstrate a steady increase in the incidence of nosocomial infections caused by MRSA among ICU patients over time. MRSA now accounts for>60% of Staphylococcus aureus isolates in United States hospital ICUs[11]. The proportion of surgical site infections due to S. aureus increased from 16.6% to 30.9% during the 1992-2002 period, and the percentage of MRSA also increased from 9.2% to 49.3%[12].

Resistance to penicillin, specifically in methicillin, is encoded and regulated by a sequence of genes found in a region of the staphylococcal cassette chromosome mec (SCCmec). This mecA gene encodes a low-affinity penicillin-binding protein (PBP2a) that is responsible for the resistance. They can alter their cell walls especially their peptidoglycan so that they can resist all the penicillin and cephalosporin groups.

There is currently the development of antibiotic resistance in Staphylococcus aureus that is different from MRSA. Vancomycin-intermediate Staphylococcus aureus (VISA) and Vancomycin-resistant Staphylococcus aureus (VRSA) can generally be isolated from a patient with complex infections who have prolonged treatment of vancomycin. VRSA also can be developed by acquiring the VanA gene that is derived from enterococci. VanA gene is responsible for resistance to vancomycin[13].

Case History And Examination

This A 60-year-old male presented to the Emergency Department at 4.08 p.m. on 23rd May 2019 with a severe open fracture of his right lower extremity, especially his right leg (cruris dextra). His mode of injury was a traffic accident. He was hit by a truck on the onset of time was around 8.00 a.m. As it's shown in Figure 1, the patient came with massive bleeding because of the rupture of the tibial and femoral arteries. His current blood pressure at that time is 90/60 mmHg. It was suspected as a hypovolemic shock since his Capillary Refill Time was delayed more than 2 seconds and his lower extremity lacked perfusion.

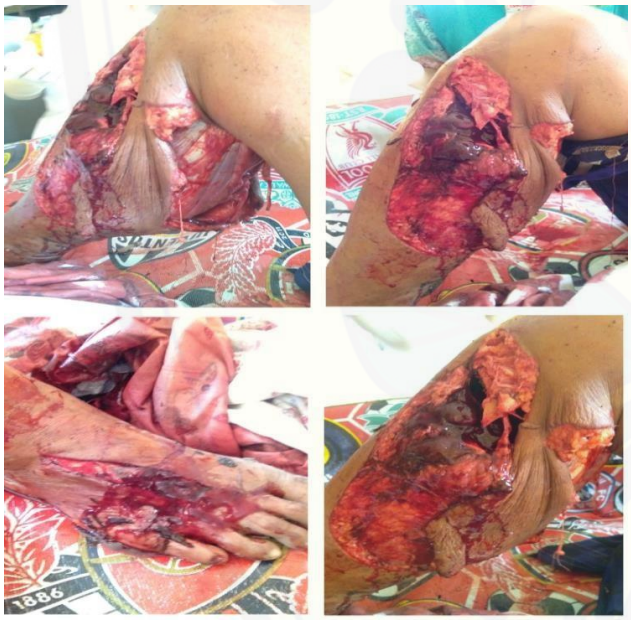

Figure 1 pre-operative condition

The operative procedure, initiated by anesthesia, with subarachnoid block method using the combination of Midazolam 1 mg, Fentanyl 25 mg, Ketamine 10 mg, and Marcain 10 mg. Because of the segmented fracture with soft tissue and vascular damage, open reduction and external fixation (OREF) method was needed. But, before the operative procedure, the patient needed to have laboratory tests to ensure the general condition of the patient was ready. The results of the blood examination are shown below in Table 1.

Table

Laboratory test	Value		Normal Range
	Pre-Operative	Post-Operative	
Hb	7.6g/dL	7.3g/dL	13.5-17.5g/dL
White blood cell	22.2k/mcL	12.4k/mcL	4-11k/mcL
Hematocrit	23.4%	21.2%	45% - 52%
Platelets	194k/mcL	128k/mcL	150-400k/mcL
AST	15 units/L	-	9-36 units/L
ALT	11 units/L	-	5-40 units/L
Serum Creatinine	1.3mg/dL	-	0.5-1.5mg/dL
BUN	15mg/dL	-	2-20mg/dL
Blood Glucose	101mg/dL	-	79-140mg/dL

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen

After the operative procedure, the patient needed to stay at the hospital for around 1 week to have a prophylaxis antibiotic and stabilization of his general condition. The

antibiotic that was applied to this patient was cefazolin 0.5-1 g/8 hour until 24 hours. Outpatient medication for preventing the Surgical Site Infection in this case was Amoxicillin 500 mg/8 hours. Unfortunately, this hospital doesn't have a strict guideline of antibiotics prophylaxis for preventing the SSIs.

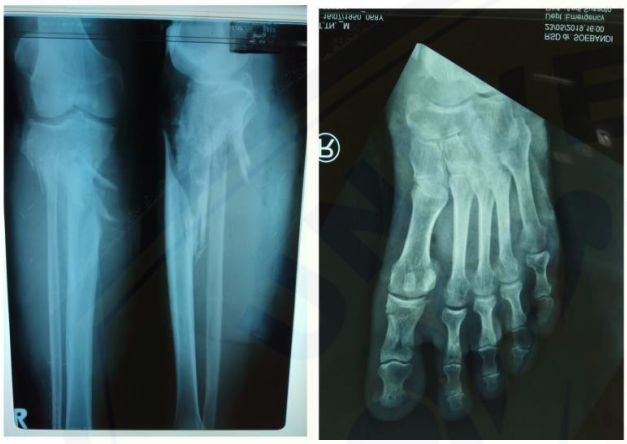

Figure 2. Radiography of lower leg fractures

After more than 3 months, the patient's surgical site develops pyogenic wounds. Uniquely, the wound produced a thin white membrane that covered several parts. It is suspected as a biofilm, since the definition of biofilm is an assemblage of microbial cells that is enclosed in an extracellular polymeric substance matrix. Biofilm formation and infection can possibly be formed, since he had a severe and life-threatening open fracture before. SSIs can be caused by bacteria resistance or bad hygiene environment. That resistance can be made by initial mistreatment of prophylaxis antibiotics. Our initial hypothesis was that there was resistance to amoxicillin and cefazolin given as initial treatment for this patient since he admitted not having a history of hypertension, diabetes, and other severe chronic diseases.

Microbiology Examination and Diagnosis

Because of having pyogenic white plaques wounds, this patient was suspected to have a biofilm-producing multidrug resistant bacteria. The white plaques are shown in Figure 3.

Microbiology Examination and Diagnosis

Because of having pyogenic white plaques wounds, this patient was suspected to have a biofilm-producing multidrug-resistant bacteria. The white plaques are shown in Figure 3.

Figure 3 White pyogenic plaques on surgical site (after 3 months of surgery and fixed with OREF method) suspected as bacterial biofilm infection.

Pus was taken away with a sterile transport media and sealed inside an icebox to maintain the mutual condition of the bacteria. Bacteria inoculation using Blood Agar Plate (BAP) was done immediately after the sample arrived at the Microbiology Department of Medical

Faculty of University of Jember. This inoculation must be done immediately after the wound swab. The results of that wound culture were identified biochemically and microscopically. The bacterial colony was cocci and was Gram-positive. Based on that staining, it was suspected as staphylococci or streptococci. The catalase and coagulase test results were positive. Catalase test was done to make sure that the pathogen is staphylococci, while coagulase test was done for ensuring that the pathogen is Staphylococcus aureus. The bacterial culture results were replanted on Mannitol Salt Agar (MSA) media. The results showed that bacteria could grow on MSA media and were able to ferment mannitol so that the environment around the colony turned yellowish.

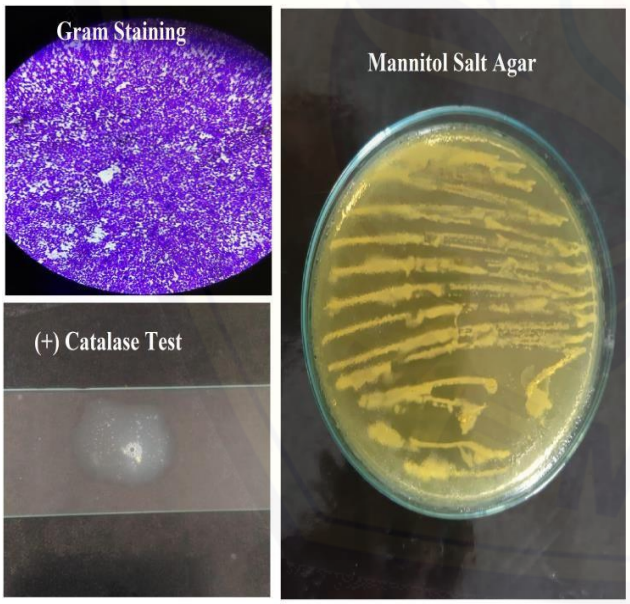

Figure 4 Bacterial Identification with Gram staining, Catalase test, and inoculation to Mannitol Salt Agar. The result was Staphylococcus aureus because it showed Gram-poisitve cocci with catalase positive and ferment mannitol.

To test the microbial susceptibility to antibiotics, we used the Kirby Bauer disc diffusion method using Mueller Hinton Agar. Based on the research that has already been done by Oliveira in 2016, the most primary causative agent in SSI cases is Community-Acquired Methicillin-resistant Staphylococcus aureus (CA-MRSA)[8]. The antibiotic discs that were used to test out this sample were Penicillin 10 μg, Meropenem 10 μg, Ampicillin-Sulbactam 20 μg, Gentamicin 10 μg, Amoxicillin 25 μg, Amoxiclav 25 μg, Ciprofloxacin 5 μg, Levofloxacin 5 μg, Ceftriaxone 30 μg, Erythromycin 15 μg, Clindamycin 10 μg, Cefixime 5 μg, Cotrimoxazole 25 μg, Cefazolin 30 μg, Amikacin 30 μg, Cefepime 30 μg, Cefotaxim 30 μg, and Vancomycin 30 μg. All of these antibiotic discs were used to detect whether this Staphylococcus aureus is classified as MRSA or VRSA. VRSA cannot be diagnosed only by the Disc Diffusion method, it needs further test to ensure the minimum inhibitory concentration of Vancomycin. Though, based on CDC Algorithm for diagnostic VRSA, this can be concluded as a suspected VISA/VRSA since the VA zone <15 mm. VRSA can be diagnosed by the disc dilution method only if VA inhibitory zone is 0 mm with the minimum inhibitory concentration above 16 μg/mL. Methicillin Susceptible staphylococci can be considered susceptible to Beta-lactam combination agents (amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam), Oral cephems (cefuroxime, cefaclor, cephalexin, cefpodoxime), parenteral cephems

including cephalosporin I, II, III, and IV (cefamandole, cefazoline, cefepime, cefmetazole, cefonicid, cefoperazone, cefotaxime, cefotetan, ceftizoxime, ceftriaxone, cefuroxime, ceftaroline, moxalactam), Carbapenems (doripenem, ertapenem, imipenem, and meropenem). Staphylococci that are resistant to those antibiotics can be suspected as Methicillin-resistant Staphylococcus aureus[14]. The antibiotics sensitivity can be quantified by measuring the diameter of inhibition of antibiotic disc and matching it to the standard from Clinical Laboratory Standard Institute (CLSI).

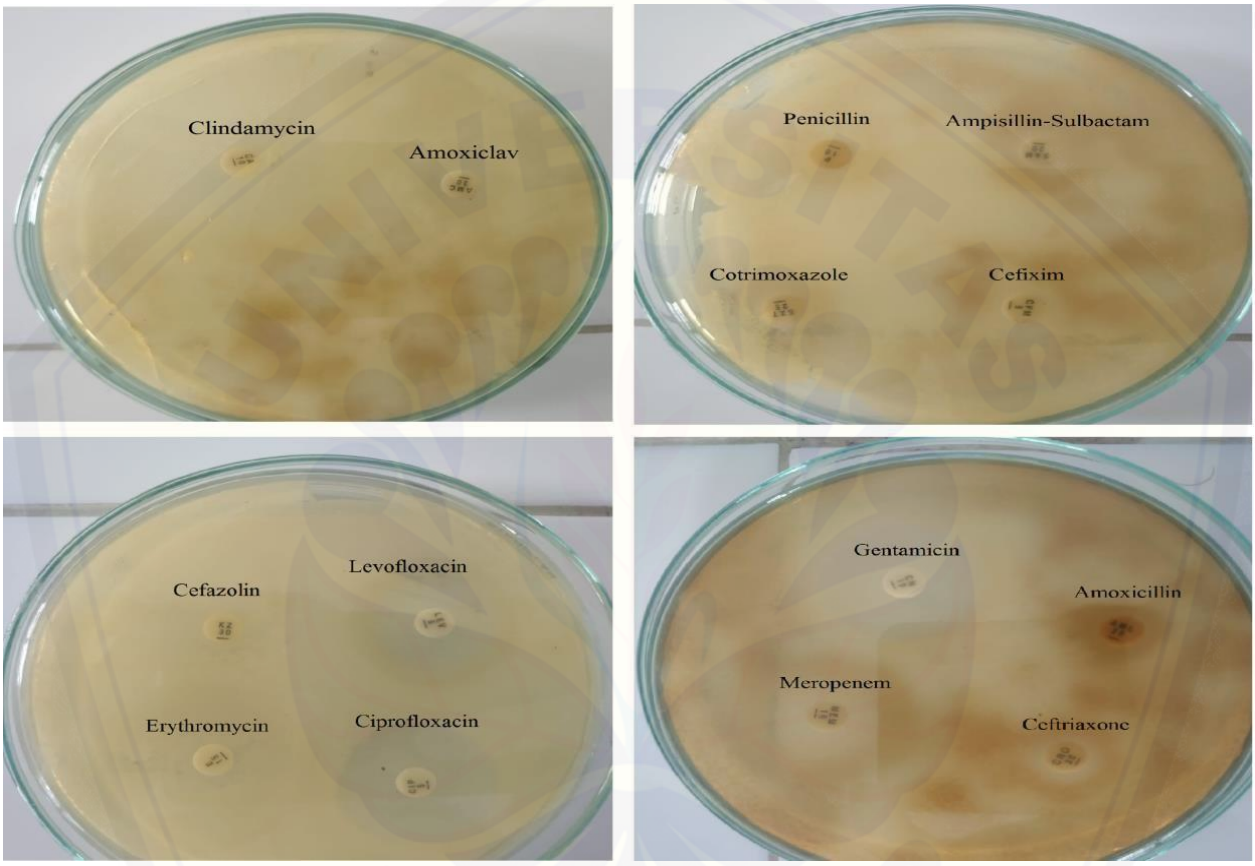

Figure 5 Antibiotic susceptibility test using Disc Diffusion method on Mueller Hinton Agar. It showed Resistance on most Beta-lactam including Penicillins and Cephalosporin class.

Treatment And Course

This case has already been reported to the hospital and the patient already has endeavored a proper treatment and control based on the microbiology examination result. For the treatment, the patient was given Gentamicin topically and Clindamycin orally. After the diagnosis of the surgical site infection caused by MRSA was established, patients were advised to follow several wound control and treatment schedules at the orthopedic specialist at the hospital for the first 3 months intensively. The patient and his family also have been educated well

about this condition and what they need to do after, especially about personal hygiene and wound care that should be done by medical personnel. The patient has also been told that he must obey the control program schedule to the hospital for evaluation and physiotherapy, so the doctor can control the healing progress of the patient's wound. Within 3 months, the patient's wound was getting better and the granulation of the wound area also improved.

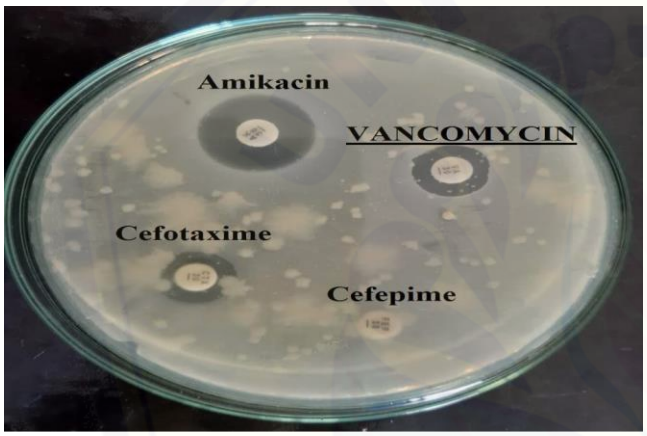

Figure 6 Diagnostic of Vancomycin Resistant Staphylococcus aureus. It is shown that this organism is suspected to resist the Vancomycin since its inhibitor zone under 15 mm

Challenges Faced

In developing countries like Indonesia, access to hospitals is quite difficult for some people with low financial status. Unfortunately, complex infections like this often happen to them. In addition, hospitals and health workers have not been able to reach and guarantee the health of all citizens in this country. In fact, to educate all the citizens about health programs, they are still having trouble because there are too many citizens in Indonesia.

The selection of initial optimum treatment of severe open fracture is also one of the challenges of this case. There is a consensus that the initial treatment of these fractures should ideally be held in less than 6 hours. The initial mistreatment of open fracture really becomes the high risk of SSIs.

Discussion

Symptoms of SSIs included purulent drainage, wound healing disturbance, erythema, and local pain[15]. Besides of that symptoms, there are three main clinical presentations to diagnose surgical site infection based on previous studies by Bonnvialle in 2016[16]:

1. A purulent discharge from the incision and/or surgical site with a fever, although strongly suggestive, is the least common presentation;
2. Healing disorders and/or unwanted and unusual local symptoms (local or regional pain or joint stiffness) are less obvious signs of infection;
3. Absence of radiological evidence of bone healing after a few months, with or without incipient fixation failure, may also indicate infection

Based on the anamnesis, this patient has all these symptoms even though it is already more than 3 months since he went out from the hospital to take an outpatient treatment. It appeared that the fractures most impacted by contamination were the severe type III injuries[14].

Table 2. Antibiotic Susceptibility Test Results of Staphylococcus aureus based on Clinical Laboratory Standard Institute (CLSI)

Antibiotic List	Content (µg)	CLSI M100 30th Ed. Standard Diameter of Inhibitory Zone (mm)				Diameter of Inhibitory Zone Sample (mm)	Conclusion (R/I/SDD/S)
		Resistant	Intermediate	Single Dose Dependent	Susceptible		
Penicillin	10	≤28	-	-	≥29	6	R
Meropenem**	10	≤15	16-18	-	≥19	12	R
Gentamicin	10	≤12	13-14	-	≥15	25	S
Ciprofloxacin	5	≤15	16-20	-	≥21	26	S
Levofloxacin	5	≤15	16-18	-	≥19	22	S
Ceftriaxone**	30	≤13	14-20		≥21	10	R
Amoxicillin**	25	≤19	-	-	≥20	0	R
Ampisillin-Sulbactam**	20	≤11	12-14		≥15	0	R
Erythromycin	15	≤13	14-22	-	≥23	8	R
Amoxiclav**	30	≤19	-		≥20	8	R
Clindamycin	2	≤14	15-20	-	≥21	30	S
Cefixime**	5	≤15	16-18		≥19	0	R
Cotrimoxazole	23.75	≤10	11-15	-	≥16	0	R
Cefazolin**	30	≤14	15-17		≥18	0	R
Amikacin	30	≤14	15-16		≥17	18	S
Cefepime**	30	≤14	15-17		≥18	0	R

Cefotaxime**	30	≤14	15-22		≥23	11	R
Vancomycin*	30	-	-	-	-	12	S

*VRSA cannot be diagnosed only by Disc Diffusion method, it needs further testing to ensure the minimum inhibitory concentration of Vancomycin. Though, based on CDC Algorithm for diagnostic VRSA, this can be concluded as suspected VISA/VRSA since VA zone <15 mm. VRSA can be diagnosed by disc dilution method only if VA inhibitory zone is 0 mm.

**The diameter of the inhibitory zone of antibiotics classified as penicillin derivatives tends to have the same resistance pattern so that the latest CLSI guideline does not include the value of diameter of the inhibitory zone as the value followed the penicillin inhibitory zone. So, the authors added the diameter of the inhibitory zone to the previous CLSI edition.

Treatment of compound fractures has been the subject of controversy. In hospitals treating patients suffering from trauma, there is consensus that the initial treatment of these fractures should ideally be held in less than 6 hours. The initial mistreatment of fracture really becomes the risk factor of surgical site infection[17]. Instead of that, the significant risk factors or predictors for SSI occurrence were open injuries, older age, incision cleanliness, high-energy injury, greater BMI, chronic heart disease, history of allergy, and area of injury that is mostly on tibia fracture[18]. This patient's condition included mostly on that criteria because of his age, location of injury cleanliness, and high-energy injury since his mode of injury is hit by a truck in a traffic accident. It is impossible to avoid the occurrence of SSI, as almost all of the identified risk factors were not alterable. Therefore, the injury characteristics, patient lifestyle habits, comorbidities, and preoperative laboratory results should be comprehensively and carefully evaluated to aid in stratifying the patients according to SSI risk and enable the implementation of appropriate preventive measures[18].

The white pyogenic plaques on the patient's wounds can be suspected as biofilm-producing bacteria[19]. But uniquely, this patient does not have most of the risk factors for biofilm formation based on the anamnesis and physical examination. He is always treated by medical personnel. He has no history of hypertension and diabetes. He also doesn't use antibiotics carelessly and always obeys the doctor's prescription. Not only that, he lives in a not-bad environment, tropical and temperature. There was only one major risk factor of biofilm formation that he had, that is initial mistreatment of antibiotic prophylaxis[20].

The microbiology test result showed that this patient suffered a surgical site infection caused by Methicillin-resistant Staphylococcus aureus (MRSA)[21-22]. We defined it as Staphylococcus aureus since it was positive in the catalase test and coagulation test. Staphylococci produce catalase, which converts hydrogen peroxide into water and oxygen. The positive catalase test differentiates the staphylococci from the streptococci, which are negative. Staphylococcus aureus also produces an extracellular coagulase, an enzyme-like protein that clots oxalated or citrated plasma. Coagulase binds to prothrombin, and together they become enzymatically active and initiate fibrin polymerization. Coagulase may deposit fibrin on the surface of staphylococci. To be more specific, our Staphylococcus aureus samples were cultured on a specific medium, which is Mannitol Salt Agar (MSA)[23-24].

Antibiotics susceptibility test was done by Kirby Bauer dilution method using 18 types of antibiotics disc[25]. Based on Clinical Laboratory Standard Institute (CLSI), this Staphylococcus aureus is resistant to Penicillin, Meropenem, Ceftriaxone, Amoxicillin, Ampicillin-Sulbactam, Erythromycin, Amoxiclav, Cefixime, Cotrimoxazole, Cefazonline, Cefepime, and Cefotaxime. It means that this Staphylococcus aureus can resist antibiotics of the group of beta-lactams,

cephalosporins, and also macrolides. Moreover, it can resist the Amoxicillin-Clavulanic acid. Clavulanic acid is an additional ingredient to inhibit beta-lactamases enzyme[26]. By this condition, this antibiotic is still not effective in this case. For this case, we can conclude that all the antibiotic treatment, including the prophylactic treatment, was done ineffective since it can totally resist the cefazolin and the erythromycin, a macrolide group[27].

Conclusion and Recommendations

This case report of SSI in a postoperative severe open fracture can be used to evaluate the empirical treatment that is used nowadays, since the causative agent of this infection is a really serious matter: MRSA. The take-away lesson from this case is that we must have the right and specific guidelines so we can provide the right initial treatment, especially to avoid cases of surgical site infection. This report is an initial step to do some studies to conclude the evidence of nosocomial infection. Hospital's Antibiogram is needed for having a high efficacy of nosocomial infection treatment. Future research should aim to identify and quantify the incidence risk of infection after treatment by the hospital, moreover, the next-level infection such as surgical site infection caused by vancomycin-resistant Staphylococcus aureus (VRSA). It also should aim to conclude the best practices for the management of infection and for prophylactic antibiotic use to ensure a strict treatment algorithm is established for the management of soft tissue and fracture morphology while avoiding unnecessary overuse.

Conflict of Interest

No conflicts of interest have been declared

Patient Consent and Ethical Clearance

An informed consent was obtained from the patients for research and publication. The ethical clearance or approval, No.1.310/H25.1.11/KE/2020, was given by the Research Ethic Commission Faculty of Medicine University of Jember, Indonesia

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