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Original Article

A retrospective surveillance of the prophylactic antibiotics for debridement surgery in burn patients

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Abstract: Burn injury is trauma with a high risk of infection. A method that can be used to prevent and decrease the incidence of infection and accelerate wound healing is debridement. The use of prophylactic antibiotics was considered in debridement to minimize surgical site infection. This study's objective was to characterize the usage of prophylactic antibiotics for debridement in burn patients, including the selection, dose, and route of administration. The second objective was to quantitatively calculate the use of prophylactic antibiotics using ATC/DDD. This was a retrospective study in burn patients admitted to the Dr. Soetomo Hospital's burn unit between 2017 and 2020. Ninety burn patients meet the inclusion criteria enrolled in this study. There were eight prophylactic antibiotics for debridement in this study. Only four from eight antibiotics met the guidelines for prophylactic antibiotics before surgery. All prophylactic antibiotics were given intravenously. The most common prophylactic antibiotics were cefazolin (39%) and followed by ceftazidime (31%) and ceftriaxone (11%). Ceftazidime, cefoperazone, amikacin, and meropenem were used as therapeutic antibiotics to treat burn infection and continued as prophylactic before debridement surgery. Cefazolin and ceftriaxone were the most antibiotics that comply their dose with the guideline. The total of DDD/100 operations was 6.23 and cefazolin was the highest consumed, 3.10 DDD/100 operations. The mortality rate in our study was 33%. For those who survived, there was a significant correlation between % TBSA and length of stay also debridement frequency. Our study concluded there was a difference between daily practice in the hospital and in the guidelines. Improvements were needed to use prophylactic antibiotics more precisely regarding quantity and choice of the type of antibiotics.

Keywords: Prophylactic antibiotics, debridement, burns, ATC/DDD

Introduction

A burn is a severe injury with high morbidity and mortality, especially in burn size over 40% in adults [1]. Burn causes skin disruption, which allows pathogenic bacteria to invade the body and leads to a high risk of infection [2]. Burn patients were more susceptible to infections compared to other injuries. A study by Belba et al, reported that the prevalence of infection in burns was 12% and the colonization was 44% [3]. One of the standard therapy of burn patients in the acute phase is early wound excision or debridement [4]. A method to reduce colonization of pathogenic bacteria and decrease infection risk in burn patients is debridement [5].

Debridement is a surgical procedure to remove necrotic tissue. Necrotic tissue due to burns inhibits wound healing and provides a good place for nosocomial bacterial growth [6]. The purpose of early debridement was to accelerate wound healing, reduce systemic infection and length of stay in the hospital, and improve survival [7]. Most studies reported that early excision within 24-48 hours after burns was significantly associated with reduced blood loss, systemic infection, length of stay, mortality, and increased skin graft [8, 9]. However, a reduction in mortality may only occur in burn patients without inhalation trauma [10].

Debridement was applied in partial-thickness and full-thickness of burns that was not com-

pletely healing within 14-21 days [11]. Debridement was classified as clean-contaminated surgery with a high risk of surgical site infection. Therefore, to reduce surgical site infection incidence after debridement surgery and its complication, prophylactic antibiotics administration was considered [5]. The pathogens related to a specific surgical procedure should be considered when selecting a prophylactic antibiotic.

Antibiotics with a broader spectrum, such as fourth-generation cephalosporins, carbapenems (meropenem, imipenem), and some aminoglycosides (kanamycin, amikacin) should be not be used for prophylactic antibiotics [12]. In Indonesia, it has been reported that compliance of antibiotics with the guidelines was poor. Only 6.1% of used in orthopedic surgery met The National Guideline for Antibiotic Use in Indonesia. Ceftriaxone was the most common antibiotic prophylaxis, 87.8% [13]. Prophylactic antibiotics administration for debridement surgery reduced intraoperative bacteremia was still debate [14]. To date, there were no established guidelines to support the use of prophylactic antibiotics for debridement surgery in burn patients [15].

There is still limited information regarding selecting prophylactic antibiotics for debridement and the quantity of DDD units. High DDD units will indicate the uncontrolled level of antibiotic consumption. So far, no previous study has evaluated the use of prophylactic antibiotics for debridement in burn patients. Based on this background, the purpose of this study was to obtain the appropriateness of prophylactic antibiotics for debridement based on the selection, dose, route of administration and to obtain the defined daily dose (DDD) for every 100 operations of prophylactic antibiotics.

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Materials and methods

Study design

This study was an observational retrospective using medical records of burn patients admitted to the burn center of Dr. Soetomo Hospital between January 2018 and September 2020. The ethical committee formally approved this study of Dr. Soetomo Hospital with ethical number 0121/LOE/301.4.2/IX/2020. This study was conducted from September to December

2020. Due to a retrospective design, the informed consent was waived. This study analyzed the appropriateness of prophylactic antibiotics for debridement surgery including type, dose, and route of administration, and unit of antibiotics as a defined daily dose (DDD).

Inclusion and exclusion criteria

This study's inclusion criteria were: 1) burned patients aged more than 18 years old, 2) partial or full-thickness burn, and 3) debridement surgery was performed at least once during hospitalization. The exclusion criteria were incomplete medical records, including unclearly written of the type, dose, and route of administration of the prophylactic antibiotics.

Data analysis

Baseline demographics including sex, age, % Total Body Surface Area (TBSA), depth of burns, length of stay, and mortality were recorded. The numerical data such as percentage of TBSA, age, length of stay, the dose of prophylactic antibiotics were expressed as mean \pm standard deviation. The categorical data such as sex, mortality, and inhalation trauma were presented as a percentage. American Society of Health-System Pharmacist (ASHP) therapeutic guideline was used to evaluate the selection, dose, and route of administration of prophylactic antibiotics for perioperative surgery [16].

The use of prophylactic antibiotics was quantitatively analyzed as the defined daily dose (DDD) per 100 procedures of debridement using the anatomical therapeutic chemical (ATC). In this study, we used DDD and DDD-100 operation days to represent prophylactic antibiotics. The DDD is a drug utilization figure that is compared to the WHO's DDD standard. The latter is a measurement unit for the assumed daily average maintenance dose of a drug used for its primary indication in adults. DDD per 100 operation days was only analyzed in burn patients who survived until discharged from the hospital. Each burn patient has undergone more than one debridement surgery. The selection and the dose were presented as a descriptive report. According to the Anatomical Therapeutic Chemical (ATC) classification for antibacterials for systemic use, the antibiotics were divided into five groups (J01) in this study [17].

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Table 1. Demographic data

Variables	n=90
Sex, n (%)	
Female	27 (30)
Male	63 (70)
Age (years)	
Range	19-81
Mean ± SD	44.3 ± 14.8
TBSA (%)	
Range	1-94
Mean	32.7 ± 23.2
TBSA > 20%	56 (62.2)
Depth of Burn	
Grade I/II	52 (58)
Grade III	38 (42)
Length of stay (days)	
Range	3-55
Mean ± SD	16.1 ± 10.0
Cause of Burns	
Fire	63 (70)
ElHV	19 (21)
Scald	8 (9)
Mortality	
Survive	60 (67)
Death	30 (33)
Inhalation Trauma	
Yes	38 (42.2)
No	52 (57.8)

The following equation was used for calculation of DDD per 100 operation days.

$$\text{DDD 100/operation days} = \frac{\text{antibiotic (gram)} \times 100}{\text{DDD WHO (gram)} \times \text{LoS}}$$

DDD WHO = Defined Daily Dose WHO; LoS = Length of stay.

The DDD per patients was calculated as follow:

$$\text{DDD per patients} = \frac{\text{Total DDD}}{\text{Number of patients}}$$

To determine the accuracy of the dose of prophylactic antibiotics, the following equation is used:

$$\frac{\text{the rights amount of antibiotic dose}}{\text{the total amount of antibiotic}} \times 100\%$$

We used Spearman correlation to correlate the percentage of TBSA with length of stay and

debridement frequency, and we used bivariate analysis (chi-square test) to associate variables (age, TBSA, and inhalation trauma) with developing mortality in burn patients. The data were stated to correlate with the Spearman correlation and have an association through the Chi-square test if the p-value was less than 0.05. The statistical strength of correlation is stated to be very weak if the correlation coefficient (r) between 0.0- < 0.2, weak 0.2- < 0.4, moderate 0.4- < 0.6, strong 0.6- < 0.8, and very strong 0.8-1.0. All statistical analyzes were performed using the SPSS version 16 software program.

Results

Demographic profile

A total of ninety medical records of burn patients were analyzed in this study. Of these, 63 (70%) were men with a mean of 44.3 years. The most frequent cause of burns was fire with a percentage of 70. The length of stay had a mean of 16.1 days (3-55). The most frequent outcome was hospital discharge, occurring in 60 (67%) of the burned patients. We found 42.2% of burn patients had trauma inhalation. Detailed information was shown in Table 1. Spearman correlation in burn patients who survived between the percentage of TBSA and length of stay also the percentage of TBSA and debridement frequency were shown in Table 2. We found a positive correlation between the percentage of TBSA with length of stay and debridement frequency.

Profile of prophylactic antibiotics

The most frequent prophylactic antibiotics were cefazolin (39%), ceftazidime (31%), and ceftriaxone (11%). All prophylactic antibiotics were given with a mean of more than one gram. Detailed information of profile and dose of prophylactic antibiotics for debridement were shown in Table 3.

Number of DDD of prophylactic antibiotics

According to the guideline, all prophylactic antibiotics were given intravenously. Cefazoline, ceftriaxone, cefuroxime, and cefotaxime were 100% comply with the guideline among burned patients. Furthermore, cefazoline and ceftriaxone were the most prophylactic antibiotics that

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Table 2. Spearman correlation among variables (n=58)

No	Variables	Mean ± SD	p-value	r
1	Total Body Surface Area (TBSA) %	20.7 ± 14.9		
2	Length of Stay (LoS)	17.9 ± 9.8	0.018	0.311
3	Debridement Frequency	2.3 ± 1.0	0.014	0.323

Table 3. Profile and dose of prophylactic antibiotics for debridement

Antibiotics	Total*	Percentage (%)	Dose range (g)	Mean ± SD (g)
Cefazolin	70	39	1-2	1.9 ± 0.1
Ceftazidime	56	31	1-2	1.2 ± 0.4
Cefuroxime	17	9.5	0.75-2	1.7 ± 0.4
Ceftriaxone	20	11	1-2	1.7 ± 0.4
Amikacin	4	2	0.75-1.5	1.0 ± 0.3
Cefotaxime	1	0.5	2	2.0
Cefoperazone-Sulbactam	3	1.5	1-2	1.3 ± 0.5
Meropenem	8	4.5	1-2	1.1 ± 0.3

*: the total was counted from 90 burn patients who undergone debridement surgery.

Table 4. Frequency of antibiotic prophylactic based on the guideline

Antibiotics	Compliance with the guideline	
	No. of patients (%)	Dose (%)
Cefazolin	51 (100)	70 (97)
Ceftriaxone	18 (100)	56 (75)
Ceftazidime	40 (0)	17 (0)
Cefuroxime	15 (100)	20 (29)
Amikacin	15 (0)	4 (0)
Cefotaxime	1 (100)	1 (0)
Cefoperazone	3 (0)	3 (0)
Meropenem	4 (0)	8 (0)

Note: ninety burned patients received more than one prophylactic antibiotics.

comply with the guideline, 97% and 75%, respectively (Table 4). A total of DDD/100 operations of prophylactic antibiotics was 6.23, with the highest DDD was cefazolin (3.10 DDD/100 operations). Table 5 showed the number of DDD of each antibiotic.

Association of mortality

To analyze the association percentage of TBSA, age, and inhalation trauma to mortality, bivariate analysis (Chi-square) was performed as shown in Table 6.

Discussion

Based on demographic data, males are higher than females with a ratio of F:M was 1:3. All burn patients in this study included second and third-degree burns, thus requiring debridement. Forty-two percent of burn patients in our study had inhalation trauma on admission. Our study was higher than those of Liadaki et al, reported that the inhalation injury incidence was 28.9%. Burn patients with inhalation injury were significantly longer in hospitalization than those without inhalation injury [18]. This study found a significant correlation between Total Body Surface Area (TBSA) and length of stay (LoS) and TBSA and debridement frequency.

The inflammation process was extensively higher in TBSA, more than 20% characterized by the release of inflammatory mediators such as IL-6, TNF- α , and fagocytic cells. If the releasing of inflammatory mediators simultaneously continues, it will suppress immunity and leads to severe infection. Burn patients with severe infection cause the medication was more complex and prolonged the hospital stay. The higher the percentage of TBSA, the bigger the burned body area. Therefore, to stimulate new tissue and promote wound healing, debridement surgery was more likely to be performed. Our study was similar to the study by Romero et al, stated there was a significant correlation between the percentage of TBSA and LoS [19].

Infection in the wound can occur during treatment in the hospital caused by the hospital environment, medical equipment, and surgery. A study by Junior et al, stated that on the first day after burns, as many as 96% of patients did not find any bacterial growth and only found it on the fifth day after burns [20]. Several studies have been evaluated the effectiveness of prophylactic antibiotics for debridement in burn patients. However, the results were still controversial. Some burn surgeons recommended using routinely prophylactic antibiotics, while others did not. A single dose of pre-operative

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Table 5. Number of DDD/100 operations of prophylactic antibiotics (n=58)

Antibiotics	ATC Code	DDD-WHO (gram)	Total Dose	DDD	DDD/100 operations
Cefazolin	J01DB04	3	97	32.4	3.10
Ceftriaxone	J01DD04	2	25	12.5	1.20
Ceftazidime	J01DD02	4	38	9.5	0.92
Cefuroxime	J01DD02P	3	21.5	7.2	0.70
Amikacin	J01GB06	1	1.5	1.5	0.14
Cefotaxime	J01DD01	4	3	0.75	0.07
Cefoperazone	J01DD12	4	3	0.75	0.07
Meropenem	J01DH02	3	1	0.33	0.03
		Total	190	64.93	6.23

*DDD: defined daily dose. *the number of DDD was calculated only in survived patients until discharge.

Table 6. Chi-square analysis to mortality

Variables		Death		p-value	OR	CI 95%
		Yes, n (%)	No, n (%)			
Age (Years)	> 60	8 (53)	7 (47)	0.072	2.753	0.890-8.520
	< 60	22 (29)	53 (71)			
TBSA (%)	> 20	29 (52)	27 (48)	0.000*	35.44	4.530-277.355
	< 20	1 (3)	33 (97)			
Inhalation trauma	Yes	20 (53)	18 (47)	0.000*	5.309	2.033-13.865
	No	9 (17)	43 (83)			

*statistically significant (p-value < 0.05).

antibiotic decreases the possibility of surgical site infection, especially for auto-grafting procedures. However, the risk and benefits of pre-operative antibiotics for newer minimally invasive debridement and grafting techniques are lacking [21].

The antibiotic should be selected based on the antibacterial spectrum and the indication. In clean-contaminated procedures, bacteria causing surgical site infections are similar to those caused by skin flora in clean surgery, plus gram-negative rods and enterococci. Cefazoline, a first-generation cephalosporin, is used to prevent such infections under the Indonesia Ministry of Health guideline. Gentamicin is the recommended prophylactic antibiotic for patients who are allergic to beta-lactams [22]. In our study, all prophylactic antibiotics were administered intravenously as a single dose. Administration of a single dose in a short time relatively achieves a high concentration above minimum inhibitory concentration (MIC) to inhibit infection during or after surgery compared

to infusion in an extended period. The advantages of the single-dose prophylactic antibiotics were cheap and relatively small errors.

A study by Dalley et al, reported after the administration of single dose 1 gram of cefalotin or 4.5 gram of piperacilin/tazobactam intravenously for debridement surgery in burn patients, the mean duration of piperacilin concentration above MIC (64 mg/L) for *Pseudomonas aeruginosa* was only 1.15 hours. In contrast, in a cefalotin group, the mean duration of cefalotin concentration above MIC (0.2 mg/L) for *Staphylococcus aureus* was 6.49 hours. The duration of debridement ranged from 2.25 to 8.5 hours. None of the patients in piperacilin/tazobactam group was adequately protected for the duration of debridement and only four of nine patients in cefalotin group were protected [23]. These findings suggested re-dose of beta-lactams by continuous infusion to minimize infection risk after debridement in burn patients. The administration of prophylactic antibiotics should be repeated if the duration of surgery more than two half-lives after the first dose to maintain their concentration above MIC. We could not evaluate the second dose of prophylactic antibiotics during debridement because there was no information.

Overall, in this study, the antibiotic use was 6.23 DDD per 100 operation days meaning that on average, there were 0.62 WHO's DDD per patient per day or 6.23 WHO's DDD for 100 patients per day. This indicates that 6.23% of the patients received a DDD of a prophylactic antibiotic per day. The commonly used prophylactic antibiotic in our study was cefazolin. Based on number of DDD/100 operations, cefazoline was the highest consumed with 3.14

DDD per 100 operations. Cefazolin was the most commonly used prophylactic antibiotic in our study with 3.14 DDD per 100 operations. Based on number of DDD/100 operations, cefazoline was the highest consumed with 3.14

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DDD/100 operations. It indicated that every operation or debridement procedure, the average use of cefazolin 3.14 times from the WHO standard DDD of cefazolin, 3 grams. Cefazolin is first generation of cephalosporin, actively against gram positive bacteria such as *S. aureus*, *Staphylococcus epidermidis*, and *Escherichia coli*. These bacteria are normal flora in human skin, but cause infection in opened skin. The dose of cefazolin in our study was 1.2 gram. Based on ASHP, the dose of cefazolin for perioperative prophylactic was 2 grams.

In our study, the DDD per patient was 1.12, and similar to a study by Herawati et al. the overall DDD per patient for hospital A was 1.5 and a 1.7 for hospital B in Indonesia. For hospital B, the overall DDD-100 bed days (DDD-100BD) was 30, with the highest surgery percentage was cesarean delivery. Ceftriaxone was the most commonly used prophylactic antibiotic among the 24 antibiotics administered in both hospitals [24]. In another study By Hadi et al, the antibiotic use was 39 DDD/100 patient-days in two hospitals in Indonesia. Out of 2058 antibiotic prescriptions, 15% of them categorized as prophylactic antibiotics with beta-lactam accounted for more than 50% of the total DDD/100 patients days for obstetric and gynecology procedures [25].

We found the DDD value was smaller than the results of several studies because the number of antibiotics was only measured in burn patients' debridement surgery, while all surgical procedures were used in other studies. The total patient's length of stay was 1,038 days, and it was shorter than those in a study by Herawati et al, 1868 days [24]. Based on DDD, the number of prophylactic antibiotics given in this study was smaller than that determined by WHO, as shown in Table 5. It indicates that the level of prophylactic antibiotics for debridement procedures in terms of quantity is quite good.

Two grams of cefazolin at anesthesia induction, followed by a repeat dose after initiation of cardiopulmonary bypass provides sufficient drug concentrations to target the majority of pathogens associated with surgical site infections [26]. A study by Ramos et al, stated in burn patients without administration of prophylactic antibiotics, ten from thirty-five surgical procedures (28%) was confirmed as bacteraemias.

Burn patients with TBSA more than 40% was significantly as a risk factor to bacteremia with RR 3.78 (0.93-15.33) [27]. However, one study reported that prophylactic antibiotic should not be routinely recommended in debridement surgery [28]. Bacteria colonizing the burn wound or before debridement surgery may not be susceptible to cefazolin, but the administration of broad-spectrum antibiotics to cover all possible bacteria or microorganisms may develop resistant organisms and overgrowth fungi. Therefore, prophylactic antibiotics' risks and benefits should be weighed carefully to minimize the adverse effects of antibiotics [29].

As much as 9.5% of ceftriaxone was used as prophylactic, 75% of its dose comply with the guideline. Several studies recommended using ceftriaxone as prophylactic antibiotics perioperative, especially in surgery that suspected gram-negative bacteria contamination [30]. However, it was more expensive, and some studies reported that it was no more effective than first or second-generation cephalosporins. A study by Alemkere reported that ceftriaxone was the most commonly used as prophylactic antibiotic (85%) in the surgical ward of Nekemte hospital, Ethiopia. However, surgical antibiotic adherence was significantly lower than the guideline recommendation [31]. The effectiveness of cefazolin or ceftriaxone to prevent surgical site infection in clean surgeries was remained unclear. One study reported there was no differences in the rate of surgical site infection in patients receiving two grams of cefazolin or ceftriaxone as perioperative antibiotic in orthopaedic surgeries [32].

Cefotaxime was administered with a dose of 2 grams in our study. However, the dose did not meet with ASHP guideline stating the dose of cefotaxime for perioperative prophylactic was one gram. Cefotaxime was metabolized in the liver into an active metabolite, disacetylcefotaxime, and it has similar antimicrobial effects as the parent drug, cefotaxime. Disacetylcefotaxime has a half-life elimination of 1.3-1.9 hours, longer than cefotaxime, 1.0-1.5 hours [33]. In burn patients, hypermetabolism increases hepatic clearance of extensively metabolized drugs in the liver and leads to reduced plasma concentration of cefotaxime and its metabolite. Thus, an increase of cefotaxime dose

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was required to maintain the antimicrobial therapeutic concentration.

We found four antibiotics to be used for prophylactic debridement, including ceftazidime, amikacin, cefoperazone-sulbactam, and meropenem that were not recommended as prophylactic antibiotics for surgery in several guidelines, including ASHP. These antibiotics were used as therapeutic antibiotics for nosocomial pneumonia for burn patients in our study. Meropenem and amikacin are highly potent broad-spectrum antibiotics. They were used as alternatives if the bacteria are resistant to cephalosporins and gentamicin. Ceftriaxone, amikacin, and meropenem are not recommended for specific gram-positive skin flora. Consequently, ceftriaxone should be limited and only applied in the presence of bacteria based on antibiotic susceptibility. Prophylactic antibiotics that were not appropriate from the type, dose, and administration route caused an increase in antibiotics resistance. Resistance can be defined as no bacterial growth inhibition by systemic administration of antibiotics at their minimum inhibitory level or standard dose [34].

In the last few decades, there has been an increase in the prevalence of multidrug-resistant organisms (MDROs) worldwide [35]. Currently, clinicians face an increasing number of *P. aeruginosa* and *A. baumannii* infections resistant to nearly all beta-lactam, aminoglycosides, and quinolone antibiotics. A study by Aisyah et al, stated that the profile of bacteria found in burn patients who were treated at Dr. Soetomo from February to May 2018 was MDRO bacteria including *P. aeruginosa* (11%), *Klebsiella pneumoniae* (6%), *A. Baumannii* (12%), as well as extended beta-lactamase spectrum (6%). Other results were the sensitivity level for amikacin was 55%, cefoperazone-sulbactam (33%), meropenem (33%), and ceftazidime (4%) [36].

Other results in this study were TBSA above 20%, age over 60 years, and inhalation trauma significantly affecting mortality in burn patients (p -value <0.05). Our study was similar to the study by Chung et al, stated that age and percentage of TBSA were significant risk factors for mortality [37]. In our study, out of 90 patients, 30 of them (33.3%) died during their hospitalization. Of the 30 patients who died, 15 of them (50%) were accompanied by acute kid-

ney injury. This study's mortality rate was greater than the study by Wardhana et al, the mortality rate of burns patients treated at Ciptomangunkusumo hospital in 2013-2015 ranged from 14.43% to 27.77%. The leading cause of death was septic shock, multiple organ failure (MOF), and acute respiratory distress syndrome (ARDS) [38].

There were some limitations in our study, including the retrospective design and a limited number of samples. Time to administer prophylactic antibiotics and whether a second dose was given during debridement were unavailable during data collection. Furthermore, we did not observe the efficacy of prophylactic antibiotics to minimize surgical site infection after debridement. Further research was required to determine if prophylactic antibiotics confer benefits in a burn patient population's debridement surgery.

Conclusion

A significant improvement in the use of prophylactic antibiotics for debridement in burn patients is required. Every hospital must publish an antibiotic use guideline or clinical pathway for every type of surgery. To prevent the occurrence of microbial resistance, we recommend narrow-spectrum antibiotics. As a result, the findings of our study are essential for future policy decisions in this field. Raising awareness among medical staff, adapting the Indonesian government's antibiotic use policy, and continuous monitoring and adjustment to improve will result in an enhanced Indonesian health care system in terms of rational prophylactic antibiotic use. Pharmacists and plastic surgeons should elaborate on each other to consider the administration of prophylactic antibiotics for debridement in burn patients.

Disclosure of conflict of interest

None.

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