



Amoxicilin-Klavulanate and Cefadroxyl Resistance Toward Staphylococcus Aureus Isolate from Children's Nose Mucosa

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ABSTRACT

Developing countries play an important role in the emergence of bacterial resistance to antibiotics because they are home to the majority of the world's population. Increased bacterial resistance to antibiotics has been widely reported, one of which is *Staphylococcus Aureus* against various β -lactam antibiotics. The high level of resistance to amoxicillin causes the use of amoxicillin-clavulanate to start increasing in the community even without culture data or epidemiological data. Antibiotics that are often used in the treatment of fever complaints in children in Indonesia are cefadroxil, followed by cefixime and amoxicillin. This research objective was to analyze the antibiotic resistance of amoxicillin-clavulanate and cefadroxil against *Staphylococcus Aureus* bacteria in children. This research used *Staphylococcus Aureus* samples from the nasal mucosa of healthy children. Cultures were tested with an antibiotic disk of amoxicillin-clavulanate, cefadroxil and cefoxitin using the Kirby-Bauer diffusion disk method to assess the zone of inhibition of each antibiotic. The diameter of the growth inhibition zone of *Staphylococcus aureus* was different between amoxicillin-clavulanate and cefadroxil. Amoxicillin-clavulanate has experienced resistance in 5 of the 6 samples tested while cefadroxil is sensitive to the 6 tested samples so it can be concluded that amoxicillin-clavulanate has been resistant and cefadroxil is still sensitive to *Staphylococcus Aureus*.

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Resistensi Amoxicilin-Klavulanate dan Cefadroxyl terhadap Isolasi Staphylococcus Aureus dari Mukosa Hidung Anak

ABSTRAK

Negara berkembang memegang peranan penting dalam kemunculan resistensi bakteri terhadap antibiotik karena merupakan tempat tinggal bagi mayoritas penduduk dunia. Peningkatan resistensi bakteri terhadap antibiotik telah banyak dilaporkan, salah satunya *Staphylococcus aureus* terhadap berbagai antibiotik golongan β -laktam. Tingginya tingkat resistensi terhadap amoksisilin menyebabkan penggunaan amoksisilin-klavulanat mulai meningkat di masyarakat walaupun tanpa data kultur atau data epidemiologi. Antibiotik yang sering digunakan dalam terapi keluhan demam pada anak di Indonesia adalah sefadroksil, diikuti oleh sefiksim dan amoxicillin. Penelitian ini bertujuan untuk menganalisis resistensi antibiotik amoksisilin-klavulanat dan sefadroksil terhadap bakteri *Staphylococcus aureus* pada anak. Penelitian ini menggunakan sampel *Staphylococcus aureus* hasil kultur dari mukosa hidung anak sehat. Kultur di uji dengan disk antibiotik amoksisilin-klavulanat, sefadroksil dan

Kata kunci:

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cefoxitin dengan metode disk difusi Kirby-bauer untuk menilai zona hambat masing-masing antibiotik. Diameter zona hambat pertumbuhan *Staphylococcus aureus* berbeda antara amoksisilin-klavulanat dengan sefadroksil. Amoksisilin-klavulanat telah mengalami resistensi pada 5 dari 6 sampel yang diuji sedangkan sefadroksil sensitif terhadap 6 sampel yang diuji sehingga dapat disimpulkan bahwa amoksisilin-klavulanat telah resisten dan sefadroksil masih sensitif terhadap *Staphylococcus aureus*.

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INTRODUCTION

Developing countries play an important role in the emergence of bacterial resistance to antibiotics because they are home to the majority of the world's population (WHO, 2001). There are several factors that cause developing countries to become a place for resistance to emerge, including poverty, misdiagnosis, empirical and prophylactic use of antibiotics, use in agriculture, antibiotic-free sales by pharmacies and poor drug supply systems (Thakuria & Lahon, 2013) (Okeke, 2010) (Togoobaatar et al., 2010).

Research in developing countries found that there are 30% of antibiotic sales in pharmacies without using a doctor's prescription (Baseline health research of Republic Indonesia, 2013). Amoxicillin is an antibiotic that is very often used by the community for self-medication (Widayati et al., 2011). The β -lactam group is a class of antibiotics that often receives reports of resistance. This is due to: 1) β -lactam antibiotics are antibiotics that are often prescribed to the public as empiric therapy and prophylaxis by doctors; 2) β -lactam antibiotics are often purchased freely by the public in pharmacies; 3) β -lactam antibiotics are often used with inappropriate doses, inaccurate indications, inappropriate methods of administration with time intervals, and inappropriate duration of use (Lahsounne et al., 2013) (Heidi Frynkewicz, Hannah Feezle, 2012) ((IMS), nd) (Thompson Coon, 2010).

The high level of resistance to amoxicillin causes the use of amoxicillin-clavulanate to start increasing in the community even without culture or epidemiological data (Thompson Coon, 2010) (Alburyhi et al., 2013). Antibiotics that are often used in the treatment of fever complaints in children in Indonesia are cefadroxil, followed by cefixime and amoxicillin (Lorensia et al., 2012).

Antibiotic resistance causes approximately 2,049,442 morbidity and 23,000 mortality rates globally (Lahsounne et al., 2013). Initially resistance occurred at the hospital level, but slowly it also began to develop in the community. Society plays an important role in the spread of bacterial resistance to antibiotics. One of the bacteria reported to have a high level of resistance to antibiotics is *Staphylococcus aureus* (Regulation of the Minister of Health of the Republic of Indonesia (Permenkes) Number 2406, 2011).

Staphylococcus Aureus resistance to the β -lactam group has been widely reported, such as, penicillin in 1940, methicillin in 1962, vancomycin in 2002, linezolid in 2011 and ceftarolin in 2011 (Lahsounne et al., 2013). Research in Asia has found that resistance to ciprofloxacin reaches 37%. The study also found resistance to Methicillin Resistant *Staphylococcus Aureus* (MRSA) with a percentage in the

Philippines of 5%, China 20%, Taiwan 60%, Singapore 60% and Hong Kong 70% (Refdanita, Maksum R, Nurgani A, 2010).

Several cases of resistance have been found in Indonesia, namely research at the Fatmawati hospital in Jakarta in 2001-2002 which found resistance of *Staphylococcus Aureus* to Penicillin G, ampicillin, sulbenicillin and amoxicillin in the intensive care room of the hospital (Refdanita, Maksum R, Nurgani A, 2004). Research in Lampung also found cases of *Staphylococcus Aureus* resistance to ampicillin and amoxicillin which continued to increase from 2008-2012 (Muttaqein and Soleha, 2013). Research in Pekanbaru also states that there is high resistance of *Staphylococcus Aureus* in patients with Urinary Tract Infection (UTI) to various antibiotics such as amoxicillin, erythromycin, cephalixin, ciprofloxacin, aztreonam, ceftriaxone, gentamycin, kanamycin, penicillin G and tetracycline by 100% (End et al., 2012).

RESEARCH METHODS

Research participants

The sample of this study was *Staphylococcus Aureus* which was taken from the nasal mucosa of the children. The criteria for children who were sampled were 8-10 years old who were not sick, never hospitalized, and had no developmental disorders. This research was conducted in March 2019 at the Microbiology Laboratory of the Faculty of Medicine and Health Sciences, Abdurrahman University.

Research procedure

Before taking the sample, the parents of the participants were asked to sign a consent form to become respondents in the research. Samples were taken from the participants' nasal mucosa with a cotton swab following the procedure established by WHO in 2003. Swab samples were rubbed into MSA medium and left to stand for 24 hours.

Furthermore, the colony identification test was carried out by looking at the colony color in MSA medium, gram staining, coagulase test, and catalase test. Of the six samples taken, all gave positive results for *Staphylococcus Aureus* bacteria.

The sensitivity test was carried out using the diffusion disk method with MHA media. The samples were tested with the antibiotic amoxicillin-clavulanate disk, cefadroxyl and cefoxitin using the Kirby-bauer diffusion disk method to assess the inhibition zone of each antibiotic.

Instrument

No	Materials
1	Mannitol Salt Agar (MSA)
2	Muller Hinton Agar (MHA)
3	Antibiotic amoxicillin-clavulanate acid disc
4	cefadroxil Antibiotic Disc
5	Cefoxitin Antibiotic Disc
6	Nasal Smear Samples
7	EDTA
8	Sterile NaCl solution
9	Blood Media
10	Tissue
11	Aquades
12	Lugol's solution
13	BaCl ₂
14	Crystal Violet Solution
15	H ₂ SO ₄
16	Emersion Oil
17	Alkohol 96%
18	H ₂ O ₂

No	Tools
1	Ose Round
2	Object Glasses
3	Straight Ose
4	Incubator
5	Scissors
6	Oven
7	Cotton Buds
8	Blank Disc
9	Autoclave
10	Elenmeyer
11	Hot Plate
12	Petri Dishes
13	Centrifuge
14	Bunsen
15	Matches
16	Microscope

Table 1
 The result of measurement on inhibition zone diameter

Disk	Diameter group 1 (mm) <i>Amoxiclav</i>	Diameter group 2 (mm) <i>Sefadroksil</i>	Diameter group 3 (mm) <i>Cefoxitin</i>	Diameter group 4 (mm) <i>Aquades</i>
1	19,33 [r]	27,33 [s]	25,66 [s]	0
2	19,33 [r]	26,66 [s]	27,66 [s]	0
3	18,33 [r]	28,66 [s]	27,33 [s]	0
4	18,33 [r]	31,66 [s]	31,66 [s]	0
5	20,00 [s]	26,66 [s]	28,00 [s]	0
6	19,00 [r]	26,00 [s]	29,00 [s]	0

Table 2
 Descriptive Analysis of inhibition zone diameter

Variables	Mean inhibition zone diameter (mm)	SD	Interpretation
Group 1	19,06	±0,64	Resistance[r]
Group 2	27,82	±2,08	Sensitive [s]
Group 3	28,21	±2,00	Sensitive [s]
Group 4	0,00	±0,00	-

The results of the sensitivity test showed that amoxicillin-clavulanate acid had experienced resistance in 5

Data analysis

Data analysis in this research used univariate (descriptive) analysis and bivariate analysis. Bivariate analysis was performed using the ANOVA test because the data were normally distributed and homogeneous. Post Hoc analysis using the Tukey method was carried out to determine which groups had differences.

RESULTS AND DISCUSSION

After conducting experiments with treatment in the form of administration of -lactam antibiotics (amoxicillin-clavulanate acid (group 1), cefadroxyl (group 2)) and cefoxitin (group 3) as the gold standard in *S. aureus* colonies from samples taken from 6 children. Then the sample characteristics are obtained according to those listed in Figures 1 and 2. Tested, cefadroxil was sensitive to 6 samples tested and cefoxitin was sensitive to 6 samples tested based on the 2014 CLSI inhibition zone diameter criteria. Table 2 describes the results of the descriptive analysis of the inhibition zone.

Bivariate analysis was performed using ANOVA test and obtained p value <0.05, so it can be stated that there is a significant difference. Post Hoc analysis using the Tukey method showed that the groups that had differences against *S. aureus* were amoxicillin-clavulanate acid and cefadroxyl, amoxicillin-clavulanate acid and cefoxitin. Cefadroxil and cefoxitin were equally sensitive to *S. aureus*.

Antibiotic resistance is a growing global public health challenge due to overuse in various parts of the world. Antibiotic resistance to an organism spreads rapidly and threatens society with new strains that are more difficult to treat and at a high cost. Antibiotic resistance often causes therapy failure which even ends in death (Llor & Bjerrum, 2014). The increase in antibiotic resistance was dominated by first-line antibiotics, namely the β-lactam group and last-line antibiotics (Centers for Disease Dynamics, 2015).

samples and was sensitive in 1 sample based on the 2014 CLSI inhibition zone diameter criteria.

This is supported by previous research which states that amoxicillin-clavulanic acid which was initially very effective against beta-lactamase-producing bacteria has experienced resistance by 73.3% of the 109 *S. aureus* isolates tested (Batabyal, 2012). Another study on 10 samples of *S. aureus* isolates tested found a resistance level of amoxicillin / clavulanic acid of 50% (Gaetti-Jardim EC, Marqueti AC, Faverani LP, 2010). Similar studies have shown that amoxicillin-clavulanic acid has experienced moderate resistance to *S. aureus*. This was evidenced by the 139 *S. aureus* isolates tested, it was found that about 23% experienced resistance (Duran N, Ozer B, Duran GG, Onlen Y, 2012). Research that has been conducted in Indonesia has also shown the occurrence of amoxicillin / clavulanic acid resistance of 67.16% (Nurmala, Virgiandhy IGN, Andriani, 2015).

The resistance that occurs to amoxicillin / clavulanic acid can be caused by various factors. A study stated that the increase in -lactam antibiotic resistance was caused by MRSA strains (Padian, 2008). Research on MRSA shows that MRSA has a prevalence of 28% in Indonesia and states that MRSA is starting to increase in a community called Community MRSA (CA-MRSA) (Huang, 2014).

The results of the sensitivity test showed that cefadroxil was sensitive to 6 samples tested based on the 2014 CLSI inhibition zone diameter criteria. This is different from previous studies which showed that cefadroxil had 67.2% resistance against 58 *S. aureus* isolates (Zafar Ahmed, Shaukat Saeed Khan, 2013). Other studies also showed that cefadroxil experienced resistance of 65.38% of 124 *S. aureus* isolates (R Kumar, 2013). In other studies conducted in Indonesia, it shows that cefadroxil has experienced resistance by 91.5% (Nurmala, Virgiandhy IGN, Andriani, 2015).

The difference between the results and previous studies could be due to various factors including differences in sampling sites, differences in isolated strains and different brands of antibiotic disks used. Previous research was conducted on patients who were being treated in hospital, while this research was conducted in a community environment (Nurmala, Virgiandhy IGN, Andriani, 2015) (Zafar Ahmed, Shaukat Saeed Khan, 2013). Previous research revealed that MRSA is widely available in hospitals known as healthcare-associated MRSA (HA-MRSA) (Usman Hadi, Kuntaman Kuntaman, Mariyatul Qiptiyah, 2013). Research on antibiotic resistance shows that most -lactam antibiotics have experienced resistance to MRSA (K Rajadurai pandi, K R Mani, K Panneerselvam, M Mani, M Bhaskar, 2006). CA-MRSA has a different antibiotic susceptibility pattern from HA-MRSA (David & Daum, 2010). A study shows that different brands of antibiotic disks used can cause differences in sensitivity test results (Arya et al., 2006).

The results of the sensitivity test showed that cefoxitin was sensitive to 6 samples tested based on the 2014 CLSI inhibition zone diameter criteria. 7% and a specificity of 100%. Cefoxitin replaced oxacillin as the gold standard previously used (Jana M. Swenson, David Lonsway, Sigrid McAllister, Angela Thompson, Laura Jevitt, Wenming Zhu, 2007). The same study but with a larger sample to re-compare the ability of cefoxitin and oxacillin obtained a sensitivity of 97.3% and a specificity of 100% (Jana M. Swenson, David Lonsway, Sigrid McAllister, Angela Thompson, Laura Jevitt, Wenming Zhu, 2007).

The increase in antibiotic resistance is caused by several factors such as poverty, misdiagnosticism, empirical and prophylactic use of antibiotics, use in the agricultural sector, antibiotic-free sales by pharmacies and poor drug supply

systems (Thakuria & Lahon, 2013) (Okeke, 2010) (Togoobaatar et al., 2010). The -lactam class of antibiotics is a class of antibiotics that often receives reports of resistance. One of the bacteria reported to have a high level of resistance to -lactam antibiotics is *S. aureus*. The *S. aureus* strain that has a high level of resistance is MRSA (Lahsounne et al., 2013) (Heidi Frynkewicz, Hannah Feezle, 2012) ((IMS), nd) (Thompson Coon, 2010) (General Guidelines for the Use of Antibiotics, 2011).

CA-MRSA is a new MRSA strain that appears in a different community environment from HA-MRSA. CA-MRSA infects different patient groups, causes different clinical symptoms, gives rise to different patterns of antimicrobial susceptibility and spreads rapidly in the community (David & Daum, 2010). CA-MRSA is the cause of 75% of *S. aureus* infections in children in the community in various countries (Sheldon L. Kaplan, Kristina G. Hulten, Blanca E. Gonzalez, Wendy A. Hammerman, Linda Lamberth, James Versalovic and Edward O. Mason, 2005).

CONCLUSIONS AND SUGGESTIONS

Research Diameter of the growth inhibition zone of *Staphylococcus Aureus* was different between amoxicillin-clavulanic acid and cefadroxyl. Amoxicillin-clavulanic acid has experienced resistance in five of the six samples tested. Cefadroxyl is sensitive in six samples tested. Future studies are expected to use a larger number of participants and on a broader scale.

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Declaration of Conflicting Interests

The authors declared that no potential conflicts of interests with respect to the authorship and publication of this article.

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