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The Examination of *mecA* gene in *Methicillin-Resistant Staphylococcus aureus* (MRSA) and inappropriate antibiotic uses of healthcare workers and communities in Banyumas

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ABSTRACT

Background: *Methicillin-Resistant Staphylococcus aureus* (MRSA) has become a major pathogene and its incidence continues to increase in various countries. The resistance to methicillin is caused by the *mecA* gene that encodes the expression of *Penicillin Binding Protein* 2a (PBP2a) so it has a low affinity for beta-lactam antibiotics. One of the factors that can increase the incidence of MRSA is inappropriate antibiotics use.
Objective: This study is to identify presence of the *mecA* gene in MRSA and to compare histories of inappropriate antibiotic uses of healthcare workers and communities in Banyumas.
Methods: This was a cross-sectional study conducting 120 samples from nasal swabs. Isolates of MRSA tested by bacteriological examinations and PCR of the *mecA* genes. Histories of antibiotic uses were assessed by using questionnaires and then analysed descriptively by using Fisher Exact test (SPPS, version 20).
Result: One sample of *S. aureus* from the microbiology examination (0.83%) was an MRSA although there was no a *mecA* gene identified by using the PCR method. 66.1% of the healthcare workers and 88,3% of the communities used antibiotics inappropriately. The results showed that there was a statistically significant difference in the histories of irrational uses of antibiotics ($p<0.05$).
Conclusion: A number of the communities who used inappropriate antibiotics was higher than the health workers. Furthermore, one MRSA strain with a negative *mecA* gene was found in the health worker group.

Latar Belakang: *Methicillin-Resistant Staphylococcus aureus (MRSA) telah menjadi patogen utama dan angka insidensinya terus meningkat di berbagai negara. Resistensi terhadap methiciline disebabkan karena S.aureus memiliki gen mecA yang menyandi ekspresi dari Penicillin Binding Protein 2a (PBP2a) sehingga memiliki afinitas yang rendah terhadap antibiotik beta-laktam. Salah satu faktor yang dapat meningkatkan insidensi MRSA adalah penggunaan antibiotik tidak rasional*
Tujuan Penelitian: *Tujuan penelitian ini adalah untuk mengetahui keberadaan gen mecA pada MRSA dan membandingkan riwayat penggunaan antibiotik pada tenaga kesehatan dan masyarakat di Banyumas.*

Metode: *Penelitian ini adalah penelitian cross-sectional dengan jumlah sampel 120 yang didapatkan dari nasal swab responden. Isolat MRSA diperiksa menggunakan pemeriksaan bakteriologi dan PCR gen mecA. Riwayat penggunaan antibiotik didapat dengan menggunakan kuisioner, kemudian dianalisis secara deskriptif dan dengan menggunakan uji fisher Exact (SPSS versi 20).*

Hasil: *Satu sampel (0,83%) diidentifikasi sebagai MRSA meskipun dengan pemeriksaan PCR tidak ditemukan adanya gen mecA. Sebanyak 66,1% tenaga kesehatan dan 88,3% masyarakat tidak menggunakan antibiotik secara bijak. Hasil menunjukkan terdapat perbedaan riwayat penggunaan antibiotik tidak bijak yang signifikan secara statistik (Nilai p<0,05).*

Kesimpulan: *Jumlah masyarakat yang menggunakan antibiotik tidak bijak lebih banyak dibandingkan tenaga kesehatan. Satu strain MRSA ditemukan pada kelompok tenaga kesehatan dengan gen mecA negatif.*

INTRODUCTION

Staphylococcus aureus (*S. aureus*) is a Gram-positive, coccus-shaped bacteria which is normal flora of human's nares anterior and skin.[1] In 1961, *S. aureus* resistant to methicillin, which is now known as *Methicillin-Resistant Staphylococcus aureus* (MRSA), was found. The resistance happened because *S. aureus* has a mecA gene which codes Penicillin Binding Protein 2a (PBP2a) having low affinities for beta-lactam antibiotics.[2,3]

Methicillin-Resistant Staphylococcus aureus (MRSA) infection is still increasing in some parts of the world. *Methicillin-Resistant Staphylococcus aureus* (MRSA) is found as a main pathogen in developing countries and is one of causes for Healthcare-Associated Infections (HAIs).[4,5] Asia is one of the continents with the highest MRSA level, either from the community (CA-MRSA) or from hospital (HA-MRSA). An estimation for MRSA is 28% in Hongkong and Indonesia.[6] A previous study in Banyumas region showed that 25% nurses in government's hospital and 15% nurses in private hospitals were carriers of HA-MRSA. One of factors that increase HA-MRSA incidence is a direct contact with the MRSA carrier as a nurse, an important person in a hospital, has the longest contact with patients.[7] Meanwhile in CA-MRSA, one of risk factors is inappropriate antibiotic uses.[8,9]

Based on the discussion above, the author finds a need to exam *mecA* genes on MRSA and histories of inappropriate antibiotic uses in healthcare workers in hospitals and communities in Banyumas. This study is needed as a depiction of antibiotic resistance carrier incidences based on antibiotic exposure intensity. Therefore, the author can contribute for scientific information about the need to use the antibiotics appropriately to healthcare workers and communities.

METHODS

Research design

This study was a cross-sectional study aimed to demonstrate *mecA* gene examination on MRSA and histories of antibiotic uses of healthcare workers and communities in Banyumas.

Study subjects

The samples of this study were collected from 120 samples, which consisted of 60 healthcare workers in a hospital, namely Rumah Sakit TK III Wijayakusuma Purwokerto and 60 communities in RW 5, Kranji, Purwokerto Timur, Banyumas. Its inclusion criteria were healthcare workers (especially nurses who have worked at Rumah Sakit TK III Wijayakusuma Purwokerto) and communities at RW 5, Kranji, Purwokerto Timur, Banyumas who were 30-55 years old and were ready to be respondents. The age range was selected in relation to the age homogeneity of the two sample groups. Meanwhile, the exclusion criteria were those who had upper respiratory tract infection and had severe mental disorders and were not cooperative.

Measurements

Data on inappropriate antibiotic uses were collected by using a modified questionnaire from Pulungan (2011).[9] A validity test of the questionnaire using the Product Moment Pearson showed that values of all statement items were > 0.361. This indicated that all

the statement items were valid. Meanwhile, a Cronbach's alpha value on the reliability test showed > 60 (reliable). This questionnaire had 6 questions about antibiotic uses in the last one month, types of antibiotics, time of antibiotic uses , sources and collection of the antibiotics. The criteria of appropriate antibiotic used in this study were based on Permenkes (2015): narrow- spectrum antibiotic uses, tight indication and adequate dosages, interval and length of time given.[10]

Laboratory analysis

Identification of *S.aureus*

Samples were collected by using nasal swabs by inserting sterile cotton swabs into respondents' right nares anterior around 2 cm depth and rotating the swabs 3 times. The cotton swabs were then dipped into amies (OXOID) as transport media before sent to a laboratory to be planted grown in MSA media; next, they were incubated for 24 hours in 37°C under anaerobic condition.[11] Colony growth results after 24 hours which were round, convex, smooth-surfaced, and whitish with tender concentration were then selected.[12] A Gram staining examination was performed to determine the colony cell morphology of *S. aureus* which had a Gram positive cocci in grape-like clusters; therefore, confirmed coccus shaped with Gram (+). Catalase and coagulase test was conducted to determine the existence of *S. aureus*.

Identification MRSA

Assessment of antibiotic sensitivity was conducted by using cefoxitin 30 µg by a disc diffusion (Kirby Bauer) method. Based on Clinical Laboratory Standard Institute (CLSI) 2019, MRSA bacteria were identified if there was restricted growth zone <21 mm in diameter, indicating that *S. aureus* was resistant to the tested antibiotic.[13]

Identification of the *mecA* gene in MRSA by PCR

DNA from pure culture resulted from incubation in MSA media was extracted by using a protocol of Quick DNA Fungal/Bacteria Miniprep Kit (Zymo Research Coorp), as used in previous studies.[14] Then, the *mecA* genes were amplified by using a forward primer: 5'-TGGCTATCGTGTCACAATGC-3' and a reverse primer: 5'-CTGGAACTTGTTGAGCAGAG-3'.[15] DNA isolation mixture composition for 1 time solution was performed as follows:

Master Mix	: 6,5 µl
Primer forward *mecA*	: 1 µl (0.01 pmoles/ul)
Primer reverse *mecA*	: 1 µl (0.01 pmoles/ul)
Wate	: 3,5 µl
DNA Sample	: 1 µl (7.50 ng/mL)

Denaturation initials were conducted in 94°C for 10 seconds; denaturation was for 1 minute in 94°C; annealing was for 30 seconds in 58°C; elongation for 1 minute in 72°C was maintained for 30 cycles; and the last elongation was done in 5 minutes under 72°C; then the reaction was maintained in 4°C. The amplification product was visualized by electrophoresis using a 2% agarose gel. The positive control was MRSA and the negative control was H_2O in this study. The MRSA was identified if *mecA* genes could be found in 304 bp.

Statistical analysis

Data analysis of *mecA* genes as well as histories of inappropriate antibiotic uses of the healthcare workers and the communities was examined by a software called SPSS ver.20 for windows. The fisher Exact test was used as a data analysis. Next, data resulted from the questionnaires were edited, coded, entered, and cleaned. Demographic data of the respondents such as gender, age, education and profession were demonstrated in a table.

Ethical clearance

The Medical Research Ethics Commission, Faculty of Medicine, Universitas Jendral Soedirman stated that a research protocol of this study had complied with the ethical rules based on the 2008 Helsinki Declaration and could be implemented. Ethical Approval

Ref:1491/KEPK/III/2019.

RESULTS

In this study, the samples were 120 respondents consisting of 60 healthcare workers and 60 communities. Demographic data could be seen in Table 1. The gender was dominated by women (77.5%). The age mostly were 41-50 years (54.2%). Most of the education level of health workers in hospitals was undergraduate, while in the communities their education mostly were Senior High School. Professions in the population varied, but they mostly are housewives.

Table 1. Respondent Demography (N= 120)

Characteristics		N		
		Healthcare Workers	Community	%
Gender	Man	21	6	22.5
	Woman	39	54	77.5
Age (years)	30-40	29	7	30
	41-50	27	38	54.2
	51-55	4	15	15.8
Education	No study	0	1	0.8
	Elementary	0	11	9.2
	Secondary	0	17	14.2
	High	6	24	25
	Bachelor	54	7	50.8
Profession	Employee	60	4	53.3
	Entrepreneur	0	9	7.5
	Worker	0	5	4.2
	Housewife	0	42	35
	Farmer	0	0	0

Identification of *S.aureus*

Of 120 samples examined, 53 samples (24 healthcare worker samples and 29 communities) showed colony growth results in the MSA media as follows: they were big-round form; they were smooth-surfaced; they were flat-edged; and they changed mannitol salt agar (Minipore corp.) media colour into golden yellow. Next, the samples underwent gram test, catalase test, and coagulation test; results for these tests could be seen in Table 2. It could be concluded that there were 7 samples identified as *S. aureus* (5 healthcare workers, 2 communities).

Table 2. Results of gram, catalase and coagulase examination

Examination	Result	Healthcare Workers	Community	%
Gram	Positive	24	29	100
	Negative	0	0	0
Catalase	Positives	24	29	100
	Negative	0	0	0
Coagulase	Positives	5	2	13.2
	Negative	19	27	86.8

Antibiotic Resistance Test

7 samples successfully identified as *S. aureus* underwent antibiotic resistance test by using cefoxitin 30 µg. Samples with restricted growth zone ≤21 mm were identified as MRSA, shown in sample 1.20 with only 10 mm restricted growth zone. The sample observation results could be seen in Table 3.

Table 3 showed that, one strain of MRSA was found in the healthcare workers at the hospital. Meanwhile, *S.aureus* found in the communities was sensitive to the antibiotic test.

Table 3. Antibiotic Resistance Test

Sample	Code	Growth inhibition diameter	Result
Healthcare Worker	1.9	30 mm	MSSA*
	1.15	31 mm	MSSA
	1.20	10 mm	MRSA**
	1.50	24 mm	MSSA
	1.51	30 mm	MSSA
Community	2.13	24 mm	MSSA
	2.44	34 mm	MSSA

*MSSA : Methicillin susceptible *Staphylococcus aureus*; **MRSA: Methicillin Resistant *Staphylococcus aureus*

Identification of the *mecA* gene

MRSA samples were examined for *mecA* gene detection. The results showed that absorbance in A260/A280 wavelength was 1.500 (dsDNA concentration was 7.50 ng/ml). PCR examination results on MRSA sample did not find any band in 304 bp (Figure 1).

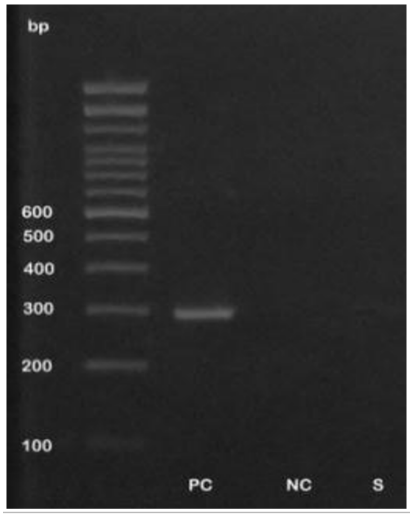

Figure 1. The *mecA* gene. PC: Positive Control (Clinical MRSA strain 3809); NC : Negative Control (H_2O); S: Sample (MRSA 1.20)

History of Antibiotic Usage

The questionnaires showed that 15 respondents of the healthcare workers and 7 respondents of the communities used antibiotics within the last 1 month. Antibiotics used in the last month in healthcare worker group were amoxicillin, cefadroxil, metronidazole, cefixime, and ciprofloxacin, while the communities used

amoxicillin and cefadroxil. The questionnaire results showed that the respondents mostly used antibiotics for inflammation and common cold, followed by fever, urinary tract infection and upper respiratory tract infection. The data show that 66.67% healthcare worker respondents and 88.3% general population respondents was found to use antibiotics inappropriately. Bivariate analysis was performed to analyse differences in histories of antibiotics uses between the two groups. Its results showed that there was a statistically significant difference ($p < 0.05$).

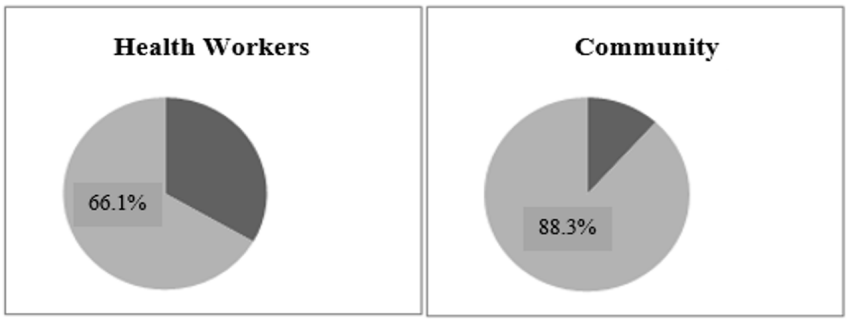

Figure 2. Inappropriate uses of antibiotic in healthcare workers (66.67%) and in the communities (88.3%).

Table 4. Analysis of differences of antibiotic use histories between the two groups

Antibiotic use histories	Healthcare workers	Communities	p value
Appropriate	20	7	
Inappropriate	40	53	
Total	60	60	0.000

The number of communities who used antibiotics inappropriately was higher than in the healthcare workers. The histories of appropriate or inappropriate uses of antibiotics in both groups was statistically significant.

DISCUSSION

In this study, only seven positive *S. aureus* colonization of the 120 nasal swab samples was found. *S. aureus* isolation was not easy to perform because it was often contaminated with other normal flora like *S. epidermidis* and *Staphylococcus haemolyticus* of coagulase-negative staphylococcus (CoNS).[16] Specimens of this study were obtained from the nasal cavity. The sample collection site played a role in the *S. aureus* colonization. This study showed that 36.7% MRSA samples were collected from respiratory system (tracheal aspiration, sputum); 24.8% were collected from blood; 18.7% were from skin and connective tissue; 9.3% were from nasal swab, 5.4% were from urine, 4.1% were from ears, and 1% were from sterile body fluid.[17] A nasal swab method for screening MRSA has a quicker turnaround time rather than other bacterial culture methods; the result will be available within 24 hour and give a high specificity method for 93.9% (95% CI 90.0%–96.3%).[18]

MRSA found in this study was from an ICU nurse. Patients who underwent treatment in the ICU had a higher role getting infected by the MRSA with OR 3.0519. In this study, the authors found one positive MRSA sample. Approximately 30% of humans were MRSA nasal carriers.20 MRSA nasal carrier is one of the most important risk factors for S. aureus infection, and it can happen if a host's body is in an immunocompromised condition. MRSA-positive patients which haven't been detected play a role as a reservoir and

potentially spread the bacteria to other people in the same ward and healthcare workers; they also contaminate medical equipment in hospital that then functions as a transmission media of MRSA.[21,22]

This study found one MRSA strain from bacteriological examination, while PCR examination did not find the *mecA* genes from that strain. There were some studies that couldn't detect *mecA* genes in the MRSA as well. A study showed that 12 samples of 123 samples identified as MRSA were found as negative *mecA*.[23] A study in Spain showed that some MRSA strains having no *mecA* genes and methicillin resistance were caused by *mecC* genes in *SCCmecXI chromosomes*.[24] A study in Nigeria showed that failures to detect *mecA* genes in MRSA probably happened because of β-lactamase hyperproduction which was probably a mechanism causing the resistance. There was a specific change in different amino acid happened in protein-binding proteins (PBPs 1, 2, and 3) cascade which could be a basis of resistance in MRSA.[25] Another study showed a plasmid carrying *mecB* genes as a cause of resistance.[26] In addition, another study showed that the *icaA*/D gene was found to be a cause of resistance in MRSA.[14]

In this study, the authors found that some of the healthcare workers in Wijayakusuma Hospital, Purwokerto and the communities of RW V Kranji, Banyumas still uses antibiotics inappropriately to treat common cold which is a contagious disease caused by influenza virus and is a self-limiting disease. Antibiotics should not be used in non-infectious diseases or in self-limiting diseases.[10] In this case, roles of medical personnel is needed to educate about antibiotic uses to decrease risks of antibiotic resistance. Continuous uses of antibiotics can cause antibiotic resistance through a mechanism called selective pressures. When the resistant bacteria reproduce rapidly, a person in a short time will be filled with resistant bacteria which make antibiotic treatment harder.[10,15] Table 4 showed that the number of communities who used antibiotics inappropriately was higher than the workers. Pathways of the patients to buy antibiotics without prescription were divided into two routes. The first was an illegal way. Some patients tended to receive antibiotics without a prescription from a doctor and buy it from drug stores. The second was use of antibiotics left at their home from a previous medication that they kept at home. Moreover, inappropriate uses of antibiotics especially in general population contribute to the emergence and spread of antibiotic resistance.[27] There are some limitations in this study, including other risk factors beside antibiotic use histories affecting antibiotic resistance which hasn't been researched in this study. Another limitation is the sample which was only from right nasal swab which makes the collected *S. aureus* colonization very limited; this is a note for the author to collect samples from other places for a further study to get more *S. aureus* colonization. Antibiotic resistance was also only tested in plaktonic bacteria only, while resistance potential in biofilm-producing bacteria and the probability of other genes beside *mecA* causing *S. aureus* resistance were not studied.

CONCLUSION

The MRSA percentage of healthcare workers in Wijayakusuma Hospital, Purwokerto was 0.83%, while the community in Banyumas did not get a positive sample of the MRSA. In this study the MRSA samples did not show positivity of the *mecA* genes on the PCR examination. The proportion of inappropriate antibiotic uses in community were higher than in healthcare workers in Banyumas.

CONFLICT OF INTEREST

The authors declared that there were no competing interests in this work.

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