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Detection of methicillin-resistant *Staphylococcus aureus* and multidrug resistance isolated from cats in animal clinic at Sidoarjo District, East Java, Indonesia

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Abstract. *Waruwu YKK, Khairullah AR, Effendi MH, Lukiswanto BS, Afnani DA, Kurniawan SC, Silaen OSM, Riwu KHP, Widodo A, Ramandinianto SC. 2023. Detection of methicillin-resistant* Staphylococcus aureus *and multidrug resistance isolated from cats in animal clinic at Sidoarjo District, East Java, Indonesia. Biodiversitas 24: 106-111.* Methicillin-resistant *Staphylococcus aureus* is the name given to the strain of bacteria that is multidrug-resistant (MDR) and resistant to β-lactam antibiotics. Compared to other livestock, companion animals have been highlighted more often as potential MRSA reservoirs. This study looked for MDR and cat-derived MRSA strains in Sidoarjo. One hundred cats with nasal swabs were accessed, along with the veterinary hospital and other clinics. Samples were collected using a sterile cotton swab and buffered peptone water as the transport medium, and then identified using a microbiological standard operating procedure. On five different antibiotic discs, the Kirby-Bauer diffusion method was used to determine the *S. aureus* antibiotic resistance profile. As a confirmatory test for MRSA, *S. aureus* isolates that were resistant to cefoxitin continued to grow on Oxacillin Resistance Screening Agar Base (ORSAB). Out of the seven MRSA isolates that were assumed to be MRSA, four of the seven MRSA isolates were confirmed to be MDR *S. aureus*. Humans and companion animals can both act as reservoirs for the recirculation of MRSA strains within the same household because cat nasal swabs resemble nosocomial MRSA and because both are more likely to get colonized than infected. It illustrated how cats might be a health risk to the public and acted as a cautionary tale about the inappropriate use of antibiotics.

Keywords: Cats, MDR, MRSA, public health

INTRODUCTION

The prevalence of pets like dogs and cats has significantly increased in modern culture (González-Ramírez et al. 2021). Home pets, like cats, may live in the same space as their owners and receive antibiotics similar to those recommended for humans (Singleton et al. 2020). Close contact between pets and their owners allows the transmission of zoonotic bacteria either directly through contact or indirectly through food and environmental contamination (Decline et al. 2020; Cinquepalmi et al. 2012). This could make pets like cats into potential zoonotic antimicrobial resistant bacterium reservoirs, including multidrug resistance (MDR) bacteria (Bhat 2021). Since pets frequently come into contact with their owners, there is a risk of spreading pathogenic bacteria, which is a problem for public health (Stull et al. 2015).

Staphylococcus aureus is a natural part of the skin and mucous membrane flora of mammals and birds, but it has also evolved into a prominent opportunistic pathogen in both human and veterinary medicine (Khairullah et al. 2022a; Bierowiec et al. 2016). *S. aureus*, a Gram-positive, non-spore-forming coccus, has round, smooth, and shiny colonies (Naznin et al. 2020; Ramandinianto et al. 2020a). When antimicrobial drugs first started to be used in the practice of contemporary human and veterinary medicine, *Staphylococci* underwent evolutionary processes in response to their presence in biological systems (Prestinaci et al. 2015). This evolution implied the development of mechanisms for antimicrobial treatment resistance, as well as the proliferation and dissemination of clinically relevant pathogenic staphylococci strains affecting human and animal populations (Economou and Gousia 2015). Changes to the binding and active sites, the production of trans membrane proteins known as efflux proteins, and the production of plasmids containing antibiotic resistance genes are all components of *S. aureus* anti-antibiotic defense mechanism (Reygaert 2018).

Staphylococcus aureus first became resistant to methicillin and other β-lactam medications in 1961, which marked the beginning of the formation of methicillin-resistant *Staphylococcus aureus* (MRSA) (Wang et al. 2022). If at least three medications cannot be overcome by *S. aureus*, it is referred to as MDR (Foster 2017; Yunita et al. 2020). MDR *S. aureus*, also known as MRSA, is the name given to germs that have developed a resistance to β-lactam antibiotics, which includes penicillin and its derivatives such as methicillin, oxacillin, and amoxicillin (Okwu et al. 2019; Khairullah et al. 2020). Methicillin resistance develops as a result of the *mec*A gene (Rolo et al. 2017; Rahmaniar et al. 2020). This results in the production of a brand-new protein termed PBP2a (Penicillin Protein Binding 2a), an enzyme necessary for the manufacture of bacterial cell walls (Wacnik et al. 2022). The protein (PBP2a), which has a very low affinity for β-lactam antibiotics, is resistant to methicillin and other β-lactam antibiotics (Saraiva et al. 2019). A mobile genetic component called staphylococcal cassette chromosome *mec* (SCC*mec*) *mec*A, which carries the *mec*A gene, is found on the *S. aureus* chromosome upstream orf X (Hiramatsu et al. 2013).

MRSA has been found in dogs, cats, rabbits, seals, cockroaches, guinea pigs, lambs, cattle, horses, and chinchillas, among other animals (Aires-de-Sousa et al. 2017). Although many staphylococci species frequently inhabit domestic animals, these germs do occasionally reside on them (Bertelloni et al. 2021). *S. aureus* can cause a variety of illnesses when it enters the body, from mild skin infections to severe invasive infections that can be fatal (Pollitt et al. 2018). The nasal mucosa, particularly in cats can be cited as a source of MRSA colonization and transmission since this bacterium has a symbiosis that benefits both itself and its host, which is commensalism, which implies it is not useful to the host but is harmless in most situations (Sakr et al. 2018). MRSA is becoming a public health concern because companion animals frequently have intimate physical contact with their owners through stroking, licking, and caressing, which exposes them to dangerous MRSA infections (Overgaauw et al. 2020).

Given the possibility of MRSA transmission between cats and people, it is necessary to conduct research related to the phenotypic detection of MRSA and the resistance profile of *S. aureus* isolated from cat nose swabs at a veterinary clinic in Sidoarjo District because no one has conducted this study in Indonesia. The results of this study are expected to provide knowledge about antibiotics that are resistant to MRSA in cats.

MATERIALS AND METHODS

Study area and sample collection

Between March to April 2022, 100 cat nasal swabs were collected from several clinics and a veterinary hospital in each of the three regions of Sidoarjo, East Java, Indonesia. Sample testing was done at the Faculty of Veterinary Medicine, Airlangga University's Laboratory of Veterinary Public Health.

Isolation and identification of *Staphylococcus aureus*

Buffer Peptone Water (BPW) was used as a medium transfer to extract nasal swab samples from cats, which were then stored at 4°C in the icebox. The material was then incubated in BPW for 24 hours. Using sterile cotton swabs from the BPW medium transport, the swab samples were isolated and streaked on Mannitol Salt Agar (MSA). Bacterial inoculum was incubated on MSA media for 24 hours at 37°C (Rahmaniar et al. 2020). *S. aureus* was isolated and identified using gram staining, positive catalase and coagulase test results, as well as yellow colonies with yellow zones on MSA medium (Ramandinianto et al. 2020a).

Antibiotic sensitivity test and MRSA confirmation test

Kirby-Bauer diffusion techniques were used to conduct an antibiotic sensitivity test on five different antibiotic disks, including Gentamicin 10 g, Cefoxitin 30 g, Ampicillin 10 g, Erythromycin 15 g, and Tetracycline 30 g, 3-5 *S. aureus* colonies from MSA medium were placed on Mueller Hinton Agar (MHA) medium, which was then streaked with a sterile cotton swab using a sterile loop in a tube containing physiological NaCl adjusted to McFarland 0.5 (1.5 x 10^8 CFU/mL) bacterial suspensions. The MHA media was then incubated at 35°C for 24 hours. The findings of antibiotic sensitivity tests were determined by measuring the diameter of the inhibition zone of clear region surrounding the antibiotic disk in milimeter (mm) scale in accordance with Clinical and Laboratory Standards Institute (CLSI).

Several *S. aureus* isolates from MHA that are cefoxitin-resistant were used in the MRSA confirmation test, and they were streaked on ORSAB with oxacillin resistance selective supplement (Khairullah et al. 2022a).

RESULTS AND DISCUSSION

Bacterial isolates

Total 100 nasal swab samples from cats were examined in all, and 82 (82%) of them tested positive for *S. aureus*. Figures 1.A and 1.B depict morphological culture and gram staining appearance based on MSA isolates. Numerous causes can contribute to the presence of *S. aureus* in the population, including the possibility of animal-to-human transmission of the illness (Tong et al. 2015). Due to the opportunistic nature of these organisms, *Staphylococcus aureus* has been identified as the most prevalent Staphylococcal strain in cats (Bierowiec et al. 2019).

Antibiotic resistance of *Staphylococcus aureus*

Antibiotic susceptibility testing revealed that total 54 isolates of *S. aureus* (65.83%) were found to be resistant, and total 15 of these isolates (18.29%), which are depicted in Figure 1.C, were classified as MDR because they were resistant to three different classes of antibiotics. This condition was shown in Table 1.

Staphylococcus aureus isolates that had become resistant to the drug cefoxitin were subjected to MRSA testing. Four of the *S. aureus* isolates shown in Table 2 that were initially believed to be MRSA later tested positive for ORSAB, according to the study's findings (Figure 1.D). In this examination, six *S. aureus* isolates were found; four were MRSA and two were MDR.

Discussion

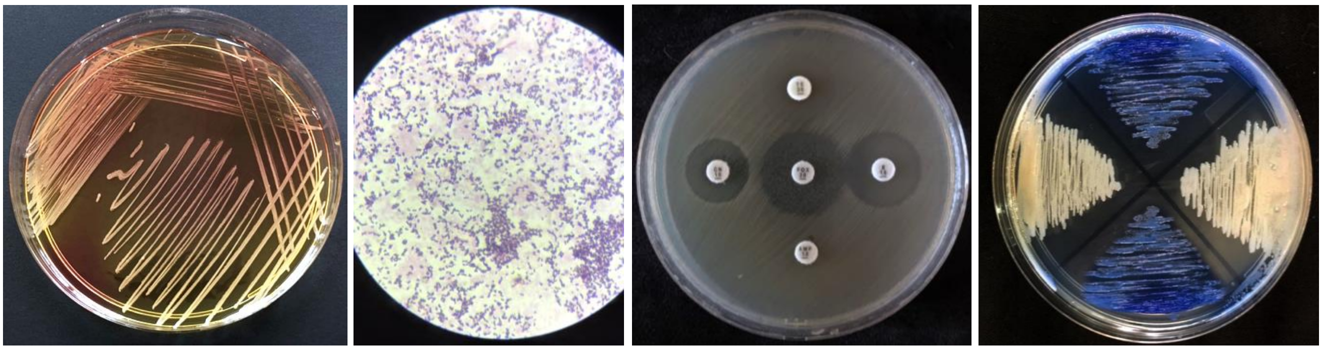
Several MDR *S. aureus* strains are known resistant to three to five different antibiotics, according to the results of resistance tests conducted on cat nose swab samples from the veterinary clinic in the Sidoarjo District. In this study, 16 MDR isolates of *S. aureus* were found as shown in table 1. Treatment for *S. aureus* that is resistant to many types of antibiotics is challenging, and it contributes to the spread of antibiotic resistance (Foster 2017). By using plasmid and transposon recombination mechanisms, *Staphylococcus aureus* can develop multidrug resistance (Vrancianu et al. 2020). The MDR strain of *S. aureus* found in cats and other pets is strongly associated with the use of antibiotics in earlier therapies (Ramandinianto et al. 2020b). Continuous use of antibiotics can stress out bacteria, which can activate resistance mechanisms in their DNA and lead to mutations and genetic changes in their cells (Coculescu 2009). Cats can additionally develop antibiotic resistance from their environment (Munita and Arias 2016).

It can be inferred that an isolate of methicillin-resistant *S. aureus* was found based on the percentage of antibiotic resistance test findings shown in Table 2. The findings are in consistence with Garoy et al. (2019), who found that relatively few of all *S. aureus* isolates currently in existence are MRSA, and also in agreement with the study published by Lade and Kim (2021) which found that practically all *S. aureus* with MRSA strains are resistant to β-lactam antibiotics, aminoglycosides, tetracyclines, and macrolides. 4.87 % (4/82) of the total *S. aureus* isolates were MRSA-positive. Similar to prior studies on the subject, Bender et al. (2012) reported that 9.09% of cats in veterinary clinics had MRSA colonization. MRSA has been found in several additional domesticated species, including cats, horses, chickens, and dogs according to Petinaki and Spiliopoulou (2015). MRSA has been identified in numerous European nations, Singapore, and North America according to a global geographic distribution of its prevalence (Kitti et al. 2018).

Table 1. Isolates of *Staphylococcus aureus* with different antibiotic resistance profiles

Group of antibiotics	Resistance profile	Resistant isolates (%) No. of *S. aureus* isolates (n=82)	Total number of isolates (%)
0	No antibiotic resistance	34.14% (28/82)	28 (34,14%)
1	AMP	3.65% (3/82)	3 (3.65%)
	CN	4.87% (4/82)	4 (4.87%)
	E	12.19% (10/82)	10 (12.19%)
	TE	2.43% (2/82)	2 (2.43%)
2	AMP-E	5.55% (5/82)	1 (5.55%)
	AMP-CN	2.43% (2/82)	2 (2.43%)
	AMP-TE	1.21% (1/82)	1 (1.21%)
	E-CN	1.21% (1/82)	1 (1.21%)
	E-TE	4.87% (4/82)	4 (4.87%)
	FOX-AMP	1.21% (1/82)	1 (1.21%)
	FOX-TE	2.43% (2/82)	2 (2.43%)
	TE-CN	6.09% (5/82)	5 (6.09%)
≥3	AMP-E-CN	1.21% (1/82)	1 (1.21%)
	AMP-E-TE	2.43% (2/82)	2 (2.43%)
	E-TE-CN	3.65% (3/82)	3 (3.65%)
	FOX-AMP-E	1.21% (1/82)	2 (2.43%)
	FOX-AMP-TE	1.21% (1/82)	1 (1.21%)
	FOX-E-TE	1.21% (1/82)	1 (1.21%)
	FOX-TE-CN	1.21% (1/82)	1 (1.21%)
	AMP-E-TE-CN	3.65% (3/82)	3 (3.65%)
	FOX-AMP-E-TE-CN	2,43% (2/82)	2 (2.43%)

Note: TE: Tetracycline, E: Erythromycin, AMP: Ampisilin, FOX: Cefoxitin, CN: Gentamicin, %: percentage. Info: Total 16 isolates Resistance with ≥3 Group of Antibiotics are classified as MDR.



A B C D

Figure 1. A.Colonies of *S. aureus* on MSA. B. *S. aureus* colonies stained with Gram under a microscope. C. Test for antibiotic sensitivity on an MRSA isolate grown on MHA. D. The color blue represents positive confirmation results from the ORSAB test for MRSA, while the color white indicates negative confirmation results

Table 2. Results of MRSA screening from cat nasal swabs and the proportion of antibiotic resistance test (%)

Sample code	Presumptive MRSA Cefoxitin resistant	MRSA confirmation by ORSA	Antibiotic-resistant pattern	Multidrug-resistant
B9	+	Negative	FOX-AMP-E-TE-CN	+
G8	+	Negative	FOX-AMP-E-TE-CN	+
H10	+	Positive	FOX-AMP	-
P3	+	Negative	FOX-E-TE	+
S3	+	Positive	FOX-AMP-E	+
V5	+	Positive	FOX-TE-CN	+
V8	+	Positive	FOX-TE	-

Human-animal relationship that is close to perfect being in direct touch with humans often by most cats increases the risk of MRSA transmission (Silva et al. 2022). There are four MRSA isolates that are positive, and one of them is a cat that is healthy. It suggests that healthy cats can have MRSA even when they don't exhibit any symptoms of the infection (Vitale et al. 2006). Bramble et al. (2011) report that MRSA has been found in asymptomatic carriers, including cats and other animals. Cats carried the MRSA strain on their paws and fur, which is potentially a significant factor as a potential vehicle of transmission (Mustapha et al. 2014). It is related to a previous study by Petinaki and Spiliopoulou (2015) in the USA, where USA100 (ST5), a strain of methicillin-resistant *S. aureus* (HA-MRSA) that is commonly found in hospitals, was shown to be the most common MRSA type in dogs. MRSA found in cats is the same as that found in humans, and it has a comparable regional distribution (Penna et al. 2021). Studies have shown that MRSA can spread through direct touch, aerosols, and inanimate objects (Jaradat et al. 2020).

According to molecular detection tests, the transfer of bacterial strains between companion animals and their owners has been linked to the incidence of identical MRSA strains in dogs and people living in the same home (Ferreira et al. 2011). Humans and companion animals can both act as reservoirs for the recirculation of MRSA strains within the same household because cat nasal swabs resemble nosocomial MRSA and because both are more likely to get colonized than infected (Pantosti 2012). It's believed that people can transmit MRSA to companion animals (Marami et al. 2022). Although studies have shown that indirect contact with companion animals is an important pathway to infection, direct companion animal exposure is still thought to be an efficient method of MRSA transmission to humans, based on study findings by Hanselman et al. (2006), veterinarians who handle cats and dogs were more frequently colonized and carried the same strain as the 12.8% of household contacts with MRSA positivity. This was validated in UK research, where 12.3% and 7.5%, respectively, of veterinarians and pet owners who had contact with animals were colonized with MRSA (Vincze et al. 2014). Even though pet owners don't appear to be at an increased risk for MRSA infections, their MRSA colonization rate (18%) is significantly higher than that of the general population (1-2%), according to a different study carried out in Canada and the US (Faires et al. 2010).

MRSA infections, including colonization, are found using culture (Nelson et al. 2019). Nasal swab samples should be carried out via media transfer, followed by *S. aureus* culture on specific medium (Lagler et al. 2022). The method used to identify and isolate the bacteria may have an impact on how quickly it is found in clinical specimens and biochemical assays to distinguish *S. aureus* from other Staphylococci, coagulase tests of this type are utilized (Karmakar et al. 2016). Antibiotic susceptibility tests, such as the disk diffusion test, can be used to identify MRSA; the majority of these tests employed cefoxitin because methicillin antibiotic disk is no longer readily available commercially (Anand et al. 2009). Antibiotic susceptibility testing has certain disadvantages compared to identifying *mec*A or PBP2a (Ozkaya et al. 2019). *S. aureus* isolates that are resistant to cefoxitin continued to undergo ORSAB as a phenotypic test; however, depending on conditions like temperature, it may also vary throughout growth (Maharjan et al. 2022). As the gold standard for identification, Polymerase Chain Reaction (PCR) is the genotypic test used to identify MRSA from its gene, *mec*A (Khairullah et al. 2022b).

MRSA transmission from animals to animals and from animals to humans must be controlled and prevented due to the lack of a suitable therapy for the condition (Cuny et al. 2015). Early detection with microbiological surveillance and prudent antibiotic use can also help avoid MRSA in both humans and animals (Collignon and McEwen 2019). When the environment was routinely cleaned and disinfected, re-infection was prevented, and colonization in cats and other animals frequently seems to be brief, some animals have spontaneously eliminated MRSA (Morris et al. 2012). To lessen MRSA cross-contamination, veterinary hospitals and animal clinics must strictly adhere to their established protocols (Kadariya et al. 2014). Prevention calls for maintaining excellent hygiene, which includes washing hands and sanitizing the environment (Odonkor et al. 2019). Barrier precautions should be used when treating animals with MRSA infections, including appropriately donning gloves and masks and isolating those animals (Sharma & Gautam 2018; Bauchner et al. 2020). Entry-level screening allows for the fast isolation of MRSA carriers (Ouidri 2018). All accepted animals may require regular inspection, which could be costly and only beneficial for referral procedures (Warwick et al. 2018).

From this study, it may be inferred that MRSA is a significant global issue, that is not just restricted to human health, and that there are numerous modes of MRSA transmission between humans and animals. Cats can serve as a reservoir for the spread and colonization of MRSA in humans, endangering public health, according to research on the antibiotic sensitivity test results from cat nasal swabs. The significance of MDR and MRSA isolates could be utilized as a guide to manage and prevent MRSA infection as well as to raise public awareness, especially among those at risk for human infection, such as veterinarians, paramedics, and pet owners. Additional research is required to determine the length of MRSA colonization and infection in companion animals, as well as strategies for preventing MRSA transmission between species.

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