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A Narrative Review of *Staphylococcus hominis* Resistance Pattern: Multidrug- and Possible Extensively Drug-Resistance

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ABSTRACT

Staphylococcus hominis is the third most frequent opportunistic pathogen in neonates and immunosuppressed patients that cause bacteremia, septicemia, endophthalmitis, and endocarditis. The emergence of methicillin-resistant *S. hominis* (MRSHo) has been reported and is a growing concern. This review was intended to determine the susceptibility of *S. hominis* to antibiotic agents with a pharmacokinetics/pharmacodynamic approach. In addition, this review determined the phenotypic criteria and antibiotic choice of *S. hominis* infection. Four databases, namely PubMed, PlosOne, ScienceDirect, and Google Scholar were employed in the search process. Antibiotic resistance was identified using the minimum inhibitory concentration (MIC) and the percentage of resistance. The breakpoint value was based on The European Committee on Antimicrobial Susceptibility Testing (EUCAST) Breakpoint tables for interpretation of MIC and zone diameters Version 11.0. There were 876 articles identified, and 35 duplicates were removed. These gave a total of 841 articles screened yet 820 articles were irrelevant. Eventually, 21 articles were reviewed in this report. This review found that *S. hominis* potentially had MDR activity and a possible XDR bacterium that is resistant to some antibacterial agents. The susceptibility of antibiotics to bacteria is not identical, and the regional reported drug resistance varies commonly due to differences in environment and antibiotic use. The resistance profile of *S. hominis* is a complex interaction that is affected by multifactorial such as: pharmacokinetics/pharmacodynamics index, mutant prevention concentration (MPC), mutant selection window (MSW), and the capability to produce biofilm.

Keywords: Biofilm; Minimum inhibitory concentration; Percentage of resistance; Pharmacokinetics/pharmacodynamics index; *S. hominis*

INTRODUCTION

Coagulase-negative staphylococci (CoNS) are mainly associated with human and animal biota and are opportunistic pathogens that persist and multiply on a variety of environmental surfaces (Seng, *et al*., 2017). Among CoNS species, *S. hominis* is the third most frequent specie as an opportunistic pathogen in the blood of neonates and immunosuppressed patients. In recent years, reports of *S. hominis* infection-induced bacteremia, septicemia, endophthalmitis, and endocarditis have increased rapidly (Frickmann *et al*., 2018; Mendoza-Olazarán *et al*., 2013; Natsis & Cohen, 2018; Pereira *et al*., 2018).

S. hominis develops resistance to various antibacterial agents causing difficulties in treatment strategies. The emergence of MRSHo has been reported and is a growing concern. MRSHo occurs because of the acquisition of the *mecA* gene, which encodes an altered penicillin-binding protein with a low affinity for beta-lactam antibiotics such as penicillin (Oliveira *et al*., 2016; Pereira *et al*., 2018). A recent study reported *S. hominis* can produce a biofilm as an important factor of resistance. However, *S. hominis* is categorized as a weak biofilm producer when compared to other CoNS species (Mendoza-Olazarán *et al*., 2013, 2015).

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The bacteria which produce biofilms can be up to 1000 times more resistant to antibiotic therapy than planktonic cells of the same microorganism. However, planktonic cells are still used in antibiotic susceptibility tests performed in routine clinical laboratory es. This fact impairs the assessment of the efficacy of the antibiotic tested. The bacteria are protected by the biofilm and the response will not be the same as that obtained in the tests (Oliveira *et al*., 2016). However, in areas where surveillance programs lack widespread access to large-scale sequencing and analyzed for their antibiotic susceptibility using minimum biofilm eradication (MBEC), phenotypic analysis using MIC and percentage of resistance provides important practical information on trends in antibacterial resistance (Michael *et al*., 2020; Mulla *et al*., 2016a). MIC data remains an important tool to allow for a better understanding of the bactericidal activity of antibiotics and how it relates to resistance using the MIC's breakpoint based on EUCAST (Committee *et al*., 2015; Falagas *et al*., 2012; Michael *et al*., 2020).

Until now, a recent study shows that five of ten CoNS isolates were multidrug-resistant (MDR) and two of ten CoNS isolates were extensively drug-resistant (XDR) to antibiotic agents. According to Basak *et al* (2016), the CoNS antibiotic resistance profile does not specifically provide the phenotypic criteria of *S. hominis* (Basak *et al*., 2016). The effectiveness of antibiotic therapy against *S. hominis* infection depends on the resistance profile, phenotypic criteria of *S. hominis*, and pharmacokinetics/pharmacodynamics profile (Basak *et al*., 2016; Kowalska-krochmal & Dudek-wicher, 2021). There have been limited studies on the *S. hominis* resistance profile. To that point, this review is intended to identify the susceptibility of *S. hominis* to antibiotic agents of different drug classes used to treat *S. hominis* infection based on the pharmacokinetics/pharmacodynamic approach. In addition, this review determined the phenotypic criteria (MDR and XDR) of *S. hominis*.

MATERIALS AND METHODS

This review adopted a systematic review method to eliminate potential bias and improve the quality of the narrative review (Ferrari, 2015; Greenhalgh *et al*., 2018; Satibi *et al*., 2022). This review was conducted in four steps; formulating the research question, searching the literature, selecting the relevant studies, and extracting data from selected articles. Data extracted were antibiotic resistance (MIC, percentage of resistance), phenotypic criteria, and mechanism of resistance to the antibiotic.

Formulating the research question

The questions include the susceptibility pattern of *S. hominis* to antibiotic agents, phenotypic criteria, antibiotic choice of *S. hominis* infection, pharmacokinetics and pharmaco-dynamics index related to antibiotic resistance, and the *S. hominis* mechanism of antibiotics resistance.

Searching the Literature

PubMed, PlosOne, ScienceDirect, and Google Scholar were used in searching for articles relevant to this topic. Keywords used for the search were "*S. hominis*" AND ("*antibiotic resistance*" OR *antimicrobial resistance*") AND (*MIC* OR "*inhibition zone*"). The search of articles was done for articles published in English and published from 1st January 2015 to 31st March 2021.

Selecting of Relevant Studies

The inclusion criteria of the studies were: (a) original articles (observational or experimental study) and published from 1st January 2015 to 31st March 2021; (b) studies related to *S. hominis*; (c) no country limitation; (d) reported any of the following outcomes: percentage of susceptibility, percentage of antibiotic resistance, MIC value. Case reports, case series with <10 cases, expert opinions, short communications, editorials, newspaper articles, and other forms of traditional media were excluded in the current review

The selected studies were reviewed by four persons (HM, DAS, RAJ, DKE). Two reviewers independently performed screening and identification of the articles. The screening process included duplications, language, abstracts, and outcomes of the studies retrieved during the searches to remove irrelevant reviews. A 20% sample of the articles will be double-screened by the other two reviewers independently and an 80% agreement level between the reviewers will be required before proceeding to screen the full-text papers. The assessment of the quality of the articles was conducted using Critical Appraisal Skills Program (CASP) assessment tools (Satibi *et al*., 2022).

Extracting the data

Antibiotic resistance was identified using MIC and the percentage of resistance. If the MIC is greater than breakpoint values, the bacteria are considered resistant to the antibiotic and vice versa. Breakpoint is a concentration (mg/L) of antibiotic, which defines whether the bacteria is sensitive or resistant to the antibiotic. In this study, the breakpoint values were based on EUCAST Breakpoint tables for interpretation of MICs and zone diameters Version 11.0 (Committee *et al*., 2015). The percentage of resistance is the percent of isolates that tested non-susceptible or resistant to certain antibiotics for each defined phenotype. Antibiotic resistance based on the percentage of resistance consists of three criteria: (1) recommended for therapy (if the percentage of resistance < 40%); (2) considered for therapy (if the percentage of resistance is between 40% - 70%); and (3) Not recommended for therapy (if the percentage of resistance >70%) (Fadlilah *et al*., 2016). The percentage of resistance was presented in the median and interquartile range (IQR).

The antibiotics classification was based on the WHO Anatomical Therapeutic Chemical (ATC) classification system. The antibiotic resistance profile was categorized based on The Centers for Disease Control and Prevention (CDC) phenotypic criteria. The criteria are MDR (multidrug-resistant), XDR (extensively drug-resistant), and PDR (pan-drug-resistant). According to the CDC, MDR is a phenotypic category for bacteria that has been resistant to at least one antibiotic from three antibiotic classes. XDR is a phenotypic category for bacteria that have been resistant to at least one antibiotic from all antibiotic classes except two or fewer antibiotic classes that are available for empirical treatment. PDR is defined as a category of bacteria that are resistant to all antibiotic classes available for empirical treatment (Basak *et al*., 2016; Magiorakos *et al*., 2012). This study also describes antibiotic resistance mechanisms and antibiotic resistance profiles with pharmacokinetics and pharmaco-dynamics approaches.

RESULTS AND DISCUSSION

The search for articles was done for articles published in English and published from 1st January 2015 to 31st March 2021 (Figure 1). In total, 876 articles were identified, and 35 duplications were removed. A total of 841 articles were screened and 820 articles were irrelevant. In this study, 21 articles were included, of which 11 articles were experimental studies and 10 articles were observational studies. More studies used clinical isolates (n=19) than non-clinical isolates (n=2) (Table I). Clinical isolates were collected from the patients' blood, urine, sputum, and other body fluid cultures at the hospital. Non-clinical isolates sourced from hospital and community environments. The findings of the 21 articles were summarized in (Table II – V).

S. hominis is the third most frequent species as an opportunistic pathogen that can cause septicemia, bacteremia, endocarditis, and endophthalmitis. This bacterium is found in the blood of neonates and immunosuppressed patients. *S. hominis* infections are difficult to treat because they are highly resistant to antibiotics, such as linezolid and vancomycin (Frickmann *et al*., 2018; Mendoza-Olazarán *et al*., 2013; Natsis & Cohen, 2018; Pereira *et al*., 2018).

Phenotypic Criteria and *S. hominis* resistance pattern

MIC provides an important tool for the surveillance of antibiotic resistance. MIC provides valuable and unique insights into resistance patterns, including adaptive resistance that can be paired with genomics data to provide more insight into acquired resistance (Michael *et al*., 2020). In this review, if the MIC is greater than breakpoint values based on EUCAST's MIC breakpoint, the antibiotic is not recommended for therapy because the bacteria is considered resistant to the antibiotic and vice versa (Kowalska-krochmal & Dudek-wicher, 2021).

Based on the MIC value, the antibiotic resistance of *S. hominis* toward eight antibiotic classes (Table II and III). The tables show that *S. hominis* was resistant to eight of ten antibiotic classes, namely tetracyclines (tetracycline), penicillin (amoxicillin and oxacillin), trimethoprim/sulfamethoxazole, macrolides, and lincosamides (azithromycin, erythromycin, clarithromycin, and clindamycin), aminoglycosides (amikacin and gentamicin), fluoroquinolone (ofloxacin, moxifloxacin, ciprofloxacin, and levofloxacin), and linezolid (Almeida *et al*., 2013; Alter *et al*., 2019; Biedenbach *et al*., 2015; Chamon *et al*., 2014; Maria *et al*., 2015; Mendoza-Olazarán *et al*., 2015; Menezes *et al*., 2019; Narita *et al*., 2016; Oliveira *et al*., 2016; Rehman *et al*., 2016; Sader *et al*., 2016, 2021b; Zidour *et al*., 2019). Thus, *S. hominis* is MDR and possible XDR bacteria.

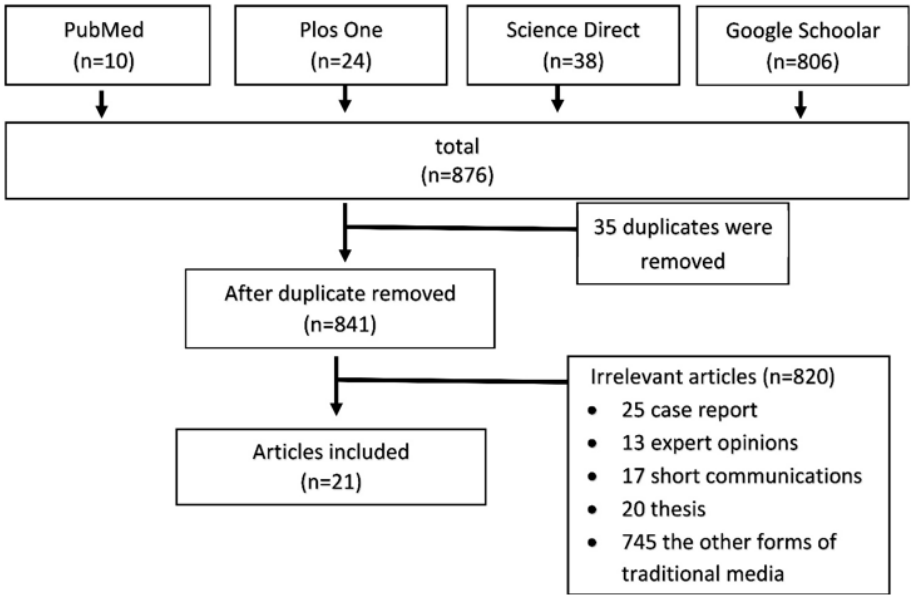

Figure 1. Diagram of The Article Selection Procedure. The search of articles was done for articles published in English and published from 1st January 2015 to 31st March 2021.

Table I. Study Characteristic

Study Characteristic	
Study Design	**n (paper)**
Experimental study	11
Observational study	10
Source of Isolates	**n (paper)**
Clinical isolates	19
Non-clinical isolates	2

Interestingly, the isolate *S. hominis* was resistant to chloramphenicol (Table II) and vice versa (Table III) shows that the *S. hominis* is sensitive to tobramycin (Table III) vice versa (Alter *et al*., 2019; Mendoza-Olazarán *et al*., 2015; Rehman *et al*., 2016). The susceptibility of antibiotics to bacteria is not identical, and the regional reported drug resistance varies commonly due to differences in environment and antibiotic use (Tao *et al*., 2017). The local antibiotic resistance pattern is essential to confirm the choice of antibiotics against *S. hominis* (Luyt *et al*., 2014; Rezaie *et al*., 2016). The susceptibility of *S. hominis* to some antibiotic classes in the percentage of resistance (Table IV and V) some antibiotics with MICs greater than breakpoint values, and have a low percentage of resistance (percentage of resistance $\leq$ 60%). For instance, tetracycline, chloramphenicol, trimethoprim/sulfamethoxazole, clindamycin, amikacin, gentamicin, oxacillin, and fluoroquinolones (ofloxacin, ciprofloxacin, levofloxacin, and moxifloxacin) (Alter *et al*., 2019; Asai *et al*., 2020; Chiquet *et al*., 2015; Mendoza-Olazarán *et al*., 2015; Menezes *et al*., 2019; Morgenstern *et al*., 2016; Sader *et al*., 2016, 2021a; Soroush *et al*., 2017). Performing antibiotic sensitivity evaluation is critical to combine MIC and other parameters such as the percentage of resistance. MIC data obtained at the sampling time may shift during storage including loss of resistance (Humphries *et al*., 2018). Furthermore, different results from MIC and the percentage of resistance will be clinically significant in relation to pharmacokinetic parameters (Kowalska-krochmal & Dudek-wicher, 2021).

Table II. The antibiotic resistance of *Staphylococcus hominis* based on MIC value

ATC Classification	Antibiotic	Resistance Category	References
	Tetracyclines		
J01AA07	Tetracycline	R	(Sader *et al*., 2016)
J01AA12	Tigecycline	S	(Sader *et al*., 2016)
	Amphenicol		
J01BA01	Chloramphenicol	R	(Mendoza-Olazarán *et al*., 2015)
	Penicillin		
J01CA04	Amoxicillin	R	(Narita *et al*., 2016)
J01CF04	Oxacillin	R	(Chamon *et al*., 2014; De Almeida *et al*., 2013; de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; E. M. Pereira *et al*., 2019; Sader *et al*., 2016; Soroush *et al*., 2017)
	Cephalosporins		
J01DC09	Cefmetazole	NA	(Narita *et al*., 2016)
J01DD17	Cefcapene	NA	(Narita *et al*., 2016)
J01DI02	Ceftaroline	S	(Sader *et al*., 2016)
	Trimethoprim and derivatives		
J01EA01	Trimethoprim	R	(Mendoza-Olazarán *et al*., 2015)
	Macrolides and Lincosamides		
J01FA01	Erythromycin	R	(de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; Sader *et al*., 2016; Zidour *et al*., 2019)
J01FA09	Clarithromycin	R	(Narita *et al*., 2016)
J01FA10	Azithromycin	R	(Narita *et al*., 2016)
J01FF01	Clindamycin	R	(Narita *et al*., 2016; Sader *et al*., 2016)
	Aminoglycosides		
J01GB01	Tobramycin	S	(Rehman *et al*., 2016)
J01GB03	Gentamicin	R	(de Oliveira *et al*., 2016)
J01GB06	Amikacin	R	(Mendoza-Olazarán *et al*., 2015)
	Fluoroquinolone		
J01MA01	Ofloxacin	NA	(Narita *et al*., 2016; Rehman *et al*., 2016)
J01MA02	Ciprofloxacin	R	(Mendoza-Olazarán *et al*., 2015; Narita *et al*., 2016; Rehman *et al*., 2016)
J01MA12	Levofloxacin	R	(Sader *et al*., 2016)
	Glycopeptides and lipoglycopeptides		
J01XA01	Vancomycin	S	(Chamon *et al*., 2014; Cidral *et al*., 2015; De Almeida *et al*., 2013; de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; E. M. Pereira *et al*., 2019; Sader *et al*., 2016; Soroush *et al*., 2017)
J01XA02	Teicoplanin	S	(Sader *et al*., 2016)
-	Norvancomycin	NA	(Yang *et al*., 2021)
	Other antibacterials		
J01XX09	Daptomycin	S	(Sader *et al*., 2016)

NA: Breakpoint is not available in EUCAST antibiotic MIC breakpoint
S: MIC less than EUCAST antibiotic MIC breakpoint; R: MIC more than EUCAST antibiotic MIC breakpoint; *) isolate linezolid-resistant CoNS

Table III. The antibiotic resistance profile of CoNS which includes isolate *Staphylococcus hominis* based on MIC value

ATC Classification	Antibiotic	Resistance Category	References
	Tetracyclines		
J01AA07	Tetracycline	R	(Sader *et al*., 2021a)
	Amphenicol		
J01BA01	Chloramphenicol	S	(Alter *et al*., 2019)
	Penicillin		
J01CF04	Oxacillin	R	(Biedenbach *et al*., 2015; Sader *et al*., 2021a)
	Sulfonamides and Trimethoprim		
J01EA01	Trimethoprim	R	(Alter *et al*., 2019)
J01EE01	Trimethoprim/ Sulfamethoxazole	R	(Biedenbach *et al*., 2015; Sader *et al*., 2021a)
	Macrolides and Lincosamides		
J01FA01	Erythromycin	R	(Biedenbach *et al*., 2015; Sader *et al*., 2021a)
J01FA10	Azithromycin	R	(Alter *et al*., 2019)
J01FF01	Clindamycin	R	(Alter *et al*., 2019; Biedenbach *et al*., 2015; Sader *et al*., 2021a)
	Aminoglycosides		
J01GB01	Tobramycin	R	(Alter *et al*., 2019)
J01GB03	Gentamicin	R	(Biedenbach *et al*., 2015)
	Fluoroquinolone		
J01MA01	Ofloxacin	R	(Alter *et al*., 2019)
J01MA02	Ciprofloxacin	R	(Alter *et al*., 2019)
J01MA12	Levofloxacin	R	(Alter *et al*., 2019; Biedenbach *et al*., 2015; Sader *et al*., 2021a)
J01MA14	Moxifloxacin	R	(Alter *et al*., 2019)
J01MA16	Gatifloxacin	NA	(Alter *et al*., 2019)
S01AE08	Besifloxacin	NA	(Alter *et al*., 2019)
	Glycopeptides and lipoglycopeptides		
J01XA01	Vancomycin	S	(Alter *et al*., 2019; Biedenbach *et al*., 2015; Sader *et al*., 2021a)
J01XA02	Teicoplanin	S	(Sader *et al*., 2021a)
J01XA04	Dalbavancin	S	(Sader *et al*., 2021a)
J01XA05	Oritavancin	NA	(Biedenbach *et al*., 2015)
	Other antibacterials		
J01XX08	Linezolid	R*)	(Biedenbach *et al*., 2015; Decousser *et al*., 2015; Sader *et al*., 2021a)
J01XX09	Daptomycin	S	(Biedenbach *et al*., 2015; Sader *et al*., 2021a)

NA: Breakpoint is not available in EUCAST antibiotic MIC breakpoint
S: MIC less than EUCAST antibiotic MIC breakpoint; R: MIC more than EUCAST antibiotic MIC breakpoint; *) isolate linezolid-resistant CoNS

Table IV. Percentage of resistance *Staphylococcus hominis* to some antibiotic classes

ATC Classification	Antibiotic Class	Percentage of Antibiotic Resistance Median (IQR)	Recommendation for Therapy	References
	Tetracyclines			
J01AA07	Tetracyclines	45.4 (28.3 – 62.5)	CT	(Sader *et al*., 2016, 2021a; Soroush *et al*., 2017)
J01AA12	Tigecycline	6.1 (0 – 12.2)	RT	
	Amphenicol			
J01BA01	Chloramphenicol	33.6 (22.4 – 44.8)	RT	(Mendoza-Olazarán *et al*., 2015; Soroush *et al*., 2017)
	Penicillins			
J01CF03	Methicillin	52.0	CT	(Asai *et al*., 2020; de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; Sader *et al*., 2016, 2021a; Soroush *et al*., 2017)
J01CF04	Oxacillin	85 (50.4 – 100.0)	NR	
	Sulfonamide and Trimethoprim			
J01EA01	Trimethoprim	80.6 (79.1 - 82.1)	NR	(Chang *et al*., 2017; de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; Sader *et al*., 2016, 2021a; Soroush *et al*., 2017)
J01EE01	Trimethoprim/ Sulfamethoxazole	6.7 (0.0-81.2)	RT	
	Macrolides, Lincosamides and Streptogramins			
J01FA01	Erythromycin	79.2 (30.7 – 100.0)	NR	(de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; Sader *et al*., 2016, 2021a; Soroush *et al*., 2017)
J01FF01	Clindamycin	23.3 (15.4 – 25)	RT	
	Aminoglycosides			
J01GB03	Gentamicin	100.0 (25.0 – 100.0)	NR	(de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; Soroush *et al*., 2017)
J01GB06	Amikacin	6.0 (3.0 – 9.0)	RT	
	Fluoroquinolone			
J01MA02	Ciprofloxacin	58.2 (25.0 – 62.7)	CT	(Mendoza-Olazarán *et al*., 2015; Sader *et al*., 2016; Soroush *et al*., 2017)
J01MA12	Levofloxacin	33.3	RT	
J01MA16	Gatifloxacin	12.5	RT	
	Glycopeptides and lipoglycopeptides			
J01XA01	Vancomycin	0.0 (0 – 4.5)	RT	(de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; Sader *et al*., 2016, 2021a)
J01XA02	Teicoplanin	4.5 (2.6 – 6.7)	RT	
J01XA04	Dalbavancin	0.0	RT	
	Other antibiotics			
J01XX08	Linezolid	0.0 (0.0 – 6.0)	RT	(de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; Sader *et al*., 2016, 2021a)

NR: Not recommended for therapy (percentage of resistance >70%); CT: considered (percentage of resistance 40% - 70%)' RT: recommended for therapy (percentage of resistance <40%)

Table V. CoNS Percentage of resistance which includes isolate *Staphylococcus hominis*

ATC Classification	Antibiotic Class	Percentage of Antibiotic Resistance Median (IQR)	Recommendation for Therapy	References
	Tetracyclines			
J01AA02	Doxycycline	20.0	RT	(Asai *et al*., 2020; Chiquet *et al*., 2015; Morgenstern *et al*., 2016; Sader *et al*., 2021a)
J01AA07	Tetracycline	16.2 (13.2 - 38.0)	RT	
J01AA08	Minocycline	7.0	RT	
J01AA12	Tigecycline	0.0	RT	
	Amphenicols			
J01BA01	Chloramphenicol	7.4 (1.2 - 11.1)	RT	(Mendoza-Olazarán *et al*., 2015)·(Alter *et al*., 2019)
	Penicillins			
J01CA	Penicillin	99.0 (81.4-100.0)	NR	(Asai *et al*., 2020; Biedenbach *et al*., 2015; Chiquet *et al*., 2015; Morgenstern *et al*., 2016; Sader *et al*., 2021a; Seng, Kitti, *et al*., 2017)
J01CA10	Mezlocillin	81.4	NR	
J01CA12	Piperacillin	81.4	NR	
J01CE01	Penicillin G	80.0	NR	
J01CF04	Oxacillin	51.9 (26.6 - 67.1)	CT	
J01CR01	Ampicillin-Sulbactam	26.6	RT	
J01CR03	Ticarcillin-Clavulanic Acid	26.6	RT	
	Cephalosporins			
J01DC01	Cefoxitin	91.9 (26.6-100.0)	NR	(Morgenstern *et al*., 2016; Seng, *et al*., 2017)
J01DC02	Cefuroxime	26.6	RT	
J01DD01	Cefotaxime	26.6	RT	
	Sulfonamide and Trimethoprim			
J01EA01	Trimethoprim	28.1	RT	(Chang *et al*., 2017; de Oliveira *et al*., 2016; Mendoza-Olazarán *et al*., 2015; Sader *et al*., 2016, 2021a; Soroush *et al*., 2017)
J01EE01	Trimethoprim/ Sulfamethoxazole	12.5 (3.1-43.5)	RT	
	Macrolides and Lincosamides			
J01FA01	Erythromycin	62.5 (2.0-88.9)	CT	(Alter *et al*., 2019; Asai *et al*., 2020; Biedenbach *et al*., 2015; Chiquet *et al*., 2015; Morgenstern *et al*., 2016; Sader *et al*., 2021a; Seng, Kitti, *et al*., 2017)
J01FA10	Azithromycin	63.3	CT	
J01FF01	Clindamycin	26.5 (14.0-73.3)	RT	
J01FG01	Pristinamycin	0.0	RT	
	Aminoglycosides			
J01GB01	Tobramycin	9.5 (6.2-30.0)	RT	(Alter *et al*., 2019; Asai *et al*., 2020; Biedenbach *et al*., 2015; Chiquet *et al*., 2015; Morgenstern *et al*., 2016; Seng, Kitti, *et al*., 2017)
J01GB03	Gentamicin	18.8 (0.0-41.3)	RT	
J01GB04	Kanamycin	30.0	RT	
J01GB06	Amikacin	6.2	RT	
J01GB07	Netilmicin	6.2	RT	
	Fluoroquinolones			
J01MA01	Ofloxacin	19.3 (10.1-28.5)	RT	(Alter *et al*., 2019; Asai *et al*., 2020; Biedenbach *et al*., 2015; Chiquet *et al*., 2015; Morgenstern *et al*., 2016; Sader *et al*., 2021a; Seng, Kitti, *et al*., 2017)
J01MA02	Ciprofloxacin	28.5 (10.7-41.4)	RT	
J01MA12	Levofloxacin	38.5 (10.6-52.7)	RT	
J01MA14	Moxifloxacin	16.5 (9.9-23.0)	RT	
J01MA16	Gatifloxacin	23.9	RT	

Table V. CoNS Percentage of resistance which includes isolate *Staphylococcus hominis*

ATC Classification	Antibiotic Class	Percentage of Antibiotic Resistance Median (IQR)	Recommendation for Therapy	References
	Glycopeptides and Lipoglycopeptides			
J01XA02	Teicoplanin	8.1 (4.0-15.0)	RT	(Alter *et al.*, 2019; Asai *et al.*, 2020; Biedenbach *et al.*, 2015; Chiquet *et al.*, 2015; Morgenstern *et al.*, 2016; Sader *et al.*, 2021a; Seng, Kitti, *et al.*, 2017)
J01XA01	Vancomycin	0.0 (0.0-0.1)	RT	
J01XA04	Dalbavancin	0.9	RT	
	Other Antibiotics			
J01XX08	Linezolid	0.3 (0.0-2.2)	RT	(Alter *et al.*, 2019; Asai *et al.*, 2020; Biedenbach *et al.*, 2015; Chiquet *et al.*, 2015; Morgenstern *et al.*, 2016; Sader *et al.*, 2021a; Seng, Kitti, *et al.*, 2017)
J01XX09	Daptomycin	0.0 (0.0-0.1)	RT	

NR: Not recommended for therapy (percentage of resistance >70%); CT: considered (percentage of resistance 40% - 70%); RT: recommended for therapy (percentage of resistance <40%)

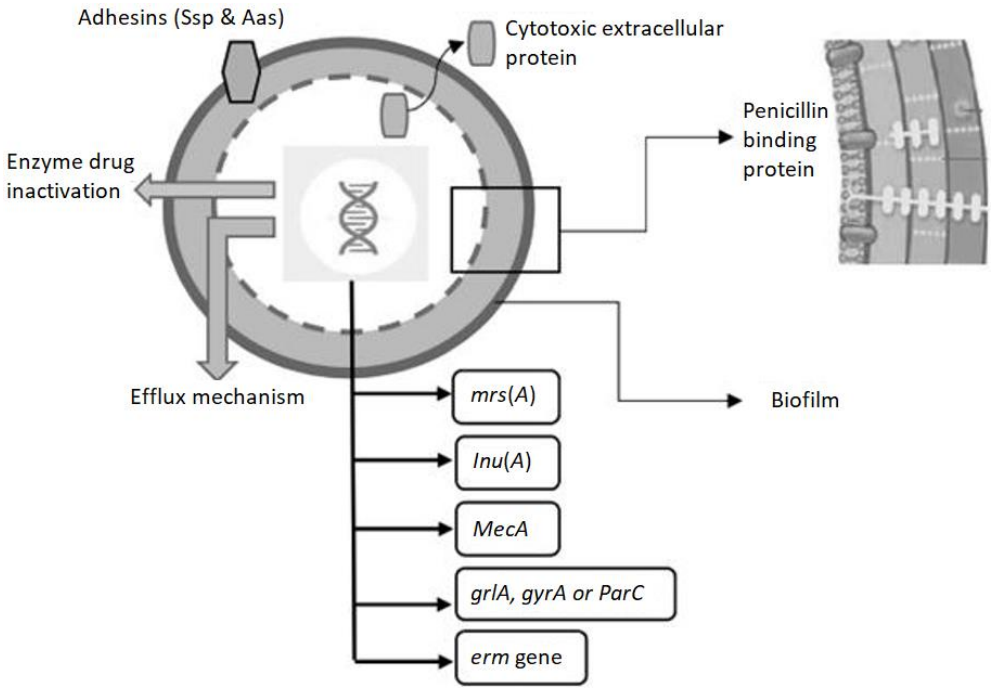

Figure 2. *Staphylococcus hominis* resistance mechanism. Adhesins are proteins on the surface cell wall that help the bacteria to attach to the cell host for instance Staphylococci surface protein (Ssp) and autolysin protein (Aas); *Staphylococcus hominis* produce cytotoxic extracellular protein to invade the host cell; several genes encode difference resistance mechanism: mrs(A) mediated antibiotic efflux; lnu(A) mediated enzymatic antibiotic inactivation; mecA encodes PBP2a, a transpeptidase with a low affinity for beta-lactam antibiotics such as penicillin; grlA, gyrA or ParC genes encode mechanism of resistance by biofilm formation; erm gene encodes the proteins that methylate adenine residue A2058 in peptidyl transferase region of 23S rRNA (domain V), the part of the large ribosomal subunit (50S) and prevents the binding of the antibiotic to the target site.

Pharmacokinetics/pharmacodynamics indices related to antibiotic efficacy and antibiotic resistance

Successful treatments using antibiotics are affected by the complex triangle interactions between the patients (the hosts), the antibiotic used, and the bacteria. These interactions include the host pathophysiologic and immune system, the type of antibiotic (type, dose, pharmacokinetics, pharmacodynamics, and toxicity), and the resistant mechanism of the bacteria. MIC is the major indicator that provides information about antibiotic efficacy and antibiotic resistance (Kowalska-krochmal & Dudek-wicher, 2021). However, the clinical outcome is not only affected by the MIC value, it is also dependent on the interaction between the host and bacteria (Rodríguez-Gascón *et al*., 2021). The parameter which quantitatively describes antibiotic efficacy and antibiotic resistance is the pharmacokinetic and pharmacodynamics index (PK/PD index) (Asín-Prieto *et al*., 2015; Mouton *et al*., 2012). The PK/PD analysis integrates and analyzes simultaneously both the PK and PD information to optimize antibiotic use (Rodríguez-Gascón *et al*., 2021).

Several PK/PD indices related to antibiotic efficacy are T>MIC (the time during the concentration of the drug was above the MIC), Cmax/MIC (the peak concentration and MIC ratio), and AUC/MIC (the ratio of the 24-h area under the concentration-time and MIC). According to the PK/PD index, antibiotics are divided into three types. The first type is time-dependent antibiotics with no or very short persistent effects that include all β-lactam antibiotics such as cephalosporins, carbapenems, monobactams, and penicillin. The PK/PD parameter for the time-dependent antibiotic is T>MIC. The T>MIC is the percentage of time in which the antibiotic's concentration remains above the MIC. If the T>MIC is closer to 100% it means the antibiotic has great efficacy (Kowalska-krochmal & Dudek-wicher, 2021). The second type is concentration-independent antibiotics with prolonged persistent effects. The antibiotic classes included in this type are tetracyclines (Tetracycline and Tigecycline), macrolides (Azithromycin and Clindamycin), oxazolidinones (Linezolid), Chloramphenicol, Trimethoprim, Sulfonamides, and Vancomycin (Asín-Prieto *et al*., 2015). The PK/PD parameter for this type of antibiotic is AUC/MIC. The AUC/MIC (∫AUC/MIC) characterizes time and concentration-dependent antibiotics. The AUC value depends on several factors such as the patient's age, weight, and organ dysfunction. On the other hand, the MIC value influences the antibiotic effect (Kowalska-krochmal & Dudek-wicher, 2021). The third type of antibiotic is concentration-dependent with prolonged persistent effects, for instance, fluoroquinolones, aminoglycosides, daptomycin, metronidazole, and polymyxins. The PK/PD parameter for this type of antibiotic is Cmax/MIC and AUC/MIC. Cmax/MIC is a parameter that describes the antibiotic effectiveness depending on the maximum concentration, not the time above the MIC. The antibiotic which has a lower MIC value is more likely to meet the antibiotic efficacy while reducing the risk of toxic concentrationn (Kowalska-krochmal & Dudek-wicher, 2021). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) established the PK/PD breakpoint, which is an essential value microorganism, considered susceptible, intermediate, or resistant to antibiotics. One antibiotic may have different PK/PD breakpoints in different bacteria (Asín-Prieto *et al*., 2015; Rodríguez-Gascón *et al*., 2021).

To date, there is no study about antibiotic PK/PD indices in *S. hominis* infection. Further studies are needed to explore the PK/PD indices profile in *S. hominis.* Despite the MIC and PK/PD index, other parameters can be used to describe resistance profiles comprehensively such as MPC and MSW. MPC describes the lowest antibiotic concentration that prevents mutant growth in a large bacterial population (more than 10^{10} CFU/mL bacteria). MSW is the range of antibiotic concentrations above the MIC and below the MPC. MPC parameters can be used to compare antibiotic susceptibility and to explore the relationships between PK/PD indices and resistance in several bacteria (Feng *et al*., 2019; Gianvecchio *et al*., 2019).

Antibiotic selection against *S. hominis* infection

According to Table II and Table III, based on the MIC value, *S. hominis* has been sensitive to tetracycline (tigecycline), cephalosporin (ceftaroline), aminoglycoside (tobramycin), glycopeptides and lipoglycopeptides (vancomycin, teicoplanin, and dalbavancin) and other antibacterial treatments (daptomycin) (Almeida *et al*., 2013; Alter *et al*., 2019; Biedenbach *et al*., 2015; Chamon *et al*., 2014; Maria *et al*., 2015; Mendoza-Olazarán *et al*., 2015; Menezes *et al*., 2019; Narita *et al*., 2016; Oliveira *et al*., 2016; Rehman *et al*., 2016; Sader *et al*., 2016, 2021b; Zidour *et al*., 2019). Table IV and Table V showed the antibiotic that can be

recommended for *S. hominis*, such as tetracycline (doxycycline, tetracycline, minocycline, and tigecycline), amphenicol (chloramphenicol), penicillin (methicillin, ampicillin-sulbactam, and ticarcillin-clavulanic acid), cephalosporin (cefuroxime and cefotaxime), trimethoprim/sulfamethoxazole, macrolide and lincosamide (clindamycin and pristinamycin), aminoglycosides (tobramycin, gentamycin, kanamycin, amikacin, and netilmicin), fluoroquinolones (ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin, and gatifloxacin), glycopeptides and lipoglycopeptides (vancomycin, teicoplanin, and dalbavancin), linezolid, and daptomycin (Alter *et al*., 2019; Asai *et al*., 2020; Chiquet *et al*., 2015; Mendoza-Olazarán *et al*., 2015; Menezes *et al*., 2019; Morgenstern *et al*., 2016; Sader *et al*., 2016, 2021a; Soroush *et al*., 2017).

The mechanisms of *S. hominis* to counter antibiotics are shown in Figure 2. *S. hominis* possesses an inducible mecA gene, encoding PBP2a, a transpeptidase with a low affinity for beta-lactam antibiotics. In addition, *S. hominis* possesses an inducible MRS gene mediated antibiotic efflux; lnu(A) mediated enzymatic antibiotic inactivation; grlA, gyrA or ParC genes encode mechanism of resistance by biofilm formation; erm gene encodes the proteins that methylate adenine residue A2058 in peptidyl transferase region of 23S rRNA (domain V), the part of the large ribosomal subunit (50S) and prevents the binding of the antibiotic to the target site. Adhesins are proteins on the surface cell wall that help the bacteria to attach to the cell host, for instance, the Staphylococci surface protein (Ssp) and the autolysin protein (Aas) (Bui & Preuss, 2021; Chiang *et al*., 2020; Drago, 2019; Fishovitz *et al*., 2014; Jenner *et al*., 2013; Kapoor *et al*., 2017; Lahiri & Alm, 2016; Öztürk *et al*., 2015; Prescott, 2013; Ślusarczyk *et al*., 2018).

Penicillins and cephalosporins are extended-spectrum antibiotics that have a broad spectrum towards gram-positive, gram-negative, and anaerobic bacteria. Penicillins and cephalosporins are beta-lactam agents which have the beta-lactam ring. The primary targets for the actions of beta-lactam agents are the Penicillin Binding Proteins (PBPs). The antibacterial activity of beta-lactam agents is due to the inhibition of PBPs which are essential proteins involved in peptidoglycan synthesis in bacteria (Bui & Preuss, 2021; Kapoor *et al*., 2017; Prescott, 2013; Ślusarczyk *et al*., 2018). There are several types of PBPs inside the Penicillin Binding Domain, and every type of bacteria has a specific type of PBP (Fishovitz *et al*., 2014; Öztürk *et al*., 2015). Ceftaroline is the one of cephalosporins that inhibits several types of PBPs. It not only inhibits PBP1 to PBP4 but also has a high affinity in PBP2a that is responsible for the resistance to penicillin and the older generation of cephalosporin (Lahiri & Alm, 2016; Lee *et al*., 2018). Another mechanism related to the mechanism of ceftaroline eradicating *S. hominis* is ceftaroline not only binding to the active site but also in the allosteric site of PBPa2 that covalently inhibits the active site of the PBPa2 (Chiang *et al*., 2020).

Macrolides, lincosamides, and streptogramin B antibiotics are recommended as second-line drugs in the treatment of staphylococci infection. Moreover, erythromycin and clindamycin are the preferred alternative for patients with a β-lactam allergy. Macrolides, lincosamides and streptogramin B antibiotics are functionally similar, whereas structurally distinct. They can inhibit protein synthesis by binding to the 50S subunit (23S rRNA) of the bacterial ribosome (Szczuka *et al*., 2016).

The other expanded broad-spectrum antibiotics that can be recommended to treat *S. hominis* are aminoglycosides, chloramphenicol, and tetracycline (Alter *et al*., 2019; Block & Blanchard, 2021; Perutelli *et al*., 2018). Similar to Macrolides, lincosamides, and streptogramin B antibiotics, the primary targets for the action are bound to the bacteria ribosomal (Abdollahi & Mostafalou, 2022; Block & Blanchard, 2021; Hutchings *et al*., 2019). Aminoglycosides bind to the bacterial ribosomal 30S subunit. Aminoglycosides bind to the A-site (aminoacyl) on the 16S rRNA, as a part of the ribosomal 30S subunit. This binding produces the genetic code that is received misread and the interpretation is disrupted, thus the bacteria is unable to complete protein synthesis (Block & Blanchard, 2021). Tobramycin is one of the aminoglycosides also effective in biofilm. Producing bacteria through a diffusion mechanism in a biofilm matrix leads to bacterial inhibition (Alzahrani *et al*., 2022; Bassenden *et al*., 2016; Zárate *et al*., 2018).

The mechanism of chloramphenicol is directly preventing the formation of bacterial protein by binding to the 50S ribosomal subunit. Chloramphenicol obstructs protein synthesis by interfering with the attachment of transfer RNA to the A site on the 50S ribosome (Abdollahi & Mostafalou, 2022; Diseases, 2017). Chloramphenicol interferes with bacterial

adhesion before the biofilm formation, and also penetrates the biofilm matrix. Therefore, chloramphenicol can eradicate infection by combating biofilm-associated infections and improving patient outcomes (Drago, 2019).

Tetracyclines such as tigecycline are glycylcycline potent antibacterials that have an expanded broad spectrum of antimicrobial activity, ranging from gram-positive to gram-negative, from aerobic to anaerobic bacteria, multidrug-resistant pathogens, intracellular pathogens, and to atypical organisms (Perutelli *et al*., 2018). Inhibition of bacterial protein synthesis by tigecycline was 3-fold more potent than inhibition by minocycline and 20-fold more potent than inhibition by tetracycline. Tigecycline affinity to the 30S and 70S ribosomes is 5-fold greater than minocycline. Tigecycline also has >100-fold greater affinity than tetracycline. Tigecycline dissociates more easily from the initial bimolecular interaction and rapidly binds to the 30S and 70S ribosomes (20- to 40-fold faster) than the other tetracyclines. Moreover, tigecycline blocks the efflux pump by the limited effect on the conformation of the repressor protein TetR (Barrenechea *et al*., 2021). Tigecycline shows increased antimicrobial activity compared to tetracycline, as well as overcoming the ribosome protection and efflux mechanism. Therefore, tigecycline is not affected by the classic tetracycline resistance mechanism (Jenner *et al*., 2013).

Moreover, tigecycline has the efficacy to combat MRCoNS like daptomycin, vancomycin, and minocycline. The efficacies of the antibiotics daptomycin, vancomycin, minocycline, and tigecycline against MRCoNS embedded in biofilm. The glycopeptides class, especially vancomycin, diffuses slowly into the deeper layers of bacterial biofilm and finally reduced the mass of pre-formed biofilms (Alter *et al*., 2019; Angelopoulou *et al*., 2020; Asai *et al*., 2020; Biedenbach *et al*., 2015; Chiquet *et al*., 2015; Decousser *et al*., 2015; Falcone *et al*., 2012; Morgenstern *et al*., 2016; Sader *et al*., 2016; Seng, Kitti, *et al*., 2017). Vancomycin reduces glycopeptide in bacterial biofilm since the biofilm is the virulence factor in CoNS infection. Furthermore, biofilm is an immune avoidance mechanism of CoNS. Moreover, metabolism and cell replication in the biofilm reduce the bactericidal activity of antibiotic agents leading to poor susceptibility to some antibiotic agents. Biofilm also plays an important role in facilitating the transfer of resistant genes (Rodriguez-guerineau *et al*., 2013). Overall, CoNS, especially *S. hominis* is susceptible to the glycopeptide class, for example, vancomycin, dalbavancin, and teicoplanin. Vancomycin is the standard antibiotic to treat CoNS infections, especially a methicillin-resistant staphylococci infection (Sader *et al*., 2021a).

In addition, linezolid was the most effective antibiotic in inhibiting staphylococci in the biofilm, without increasing the MIC. Linezolid affects the biofilm's structure and adhesion between the bacteria. Consequently, the biofilms grown were not well organized, as a result of low biofilms. Cell aggregation and cell-to-cell connections have been inhibited, resulting in loosely arranged cells that were easily disrupted (de Oliveira *et al*., 2016; Martinez *et al*., 2016).

Trimethoprim and fluoroquinolones have a unique mechanism of action that targets Deoxyribonucleic acid (DNA) synthesis. Trimethoprim is active against gram-positive bacteria and some gram-negative bacteria. This antibiotic inhibits bacterial DNA synthesis by binding to dihydrofolate reductase (DHFR) to prevent the conversion of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). Trimethoprim affinity to bacterial DHFR is 100,000 times stronger than human DHFR. The combination of trimethoprim with sulfamethoxazole has a synergistic effect to inhibit bacterial DNA synthesis through the folate pathway (Autmizguine *et al*., 2018). The addition of sulfamethoxazole provides an additional block in the folate biosynthesis pathway by inhibiting the synthesis of dihydrofolic acid (DHF). This combination improves the bactericidal effect of trimethoprim-sulfamethoxazole (Cassir *et al*., 2014; Fernández-Villa *et al*., 2019; Wróbel *et al*., 2019). Moreover, fluoroquinolones act by blocking two enzymes, DNA gyrase and topoisomerase IV that are involved in DNS synthesis, and thereby block DNA replication and transcription. However, a study at Bascom Palmer Eye Institute, Miami, Florida, reported that fluoroquinolones for the treatment of infection caused by CoNS have a poorer clinical outcome (Bassetti & Righi, 2015; Stringham *et al*., 2017).

Limitation of study

This study provides information on the susceptibility of *S. hominis* antibiotic agents of different drug classes. Evaluation in this review was conducted based on the MIC and percentage of resistance values. MIC values describe the bactericidal activity of antibiotics and how it relates to resistance using the MIC's breakpoint based on

EUCAST. However, Minimum Biofilm Eradication Concentration (MBEC) measures are more specific to assess the susceptibility of bacteria that produce biofilm (Mulla *et al*., 2016b). Further study is needed to determine *S. hominis* susceptibility using MBEC. Moreover, this review is a narrative review that has some weaknesses, for instance, the absence of an explicit determination to enlarge the scope or analyze data, and does not require any explanations of how the review process was conducted (Paré *et al*., 2015).

CONCLUSION

S. hominis is MDR and possible XDR bacteria that are resistant to some antibacterial. The choice of antibiotics against *S. hominis* should be based on local antibiotic resistance patterns. Obtaining appropriate cultures before antibiotic treatment is essential to confirm infection and susceptibility profiles. Antibiotic resistance profiles can be used as a reference in developing antibiotic use policies. Further study is needed to explore antibiotic resistance profile of *S. hominis* with PK/PD approach.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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