New Microbiologica, 43, 3, 133-135, 2020, ISSN 1121-7138

SHORT COMMUNICATION

Epidemiology and antimicrobial susceptibility of Staphylococcus lugdunensis in a Greek tertiary-care hospital

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SUMMARY

Staphylococcus lugdunensis is considered more pathogenic than other coagulase-negative Staphylococci (CoNS), with its virulence resembling that of *Staphylococcus aureus*. We report a retrospective study of all *S. lugdunensis* infection cases during a 3.5-year period in a large tertiary university hospital in Greece. *S. lugdunensis* was susceptible to most tested antibiotics, although a high resistance percentage was found to clindamycin (27%) and erythromycin (25%). The susceptibility rate to penicillin was 49%, much lower than previously reported elsewhere, indicating that penicillin may not be an optimal treatment choice for *S. lugdunensis* infections in our region.

Received January 29, 2020 *Accepted* May 05, 2020

Coagulase-negative Staphylococci (CoNS) are typically less virulent for healthy humans than *Staphylococcus aureus*. However, compared to other CoNS, *Staphylococcus lugdunensis* appears to be more virulent, implicated in severe infections such as native and prosthetic valve infective endocarditis, bloodstream, urinary tract, skin and soft tissue infections as well as device-related infections in both healthy and immunocompromised individuals (Frank *et al*., 2008). The incidence of *S. lugdunensis* infections to date is rising, and thus it is considered an emerging pathogen especially in hospital settings (Argemi *et al.,* 2017). The clinical importance of *S. lugdunensis* might be attributed to the severity of the aforementioned infections and to the presence of several virulence determinants such as adhesion factors, proteolytic enzymes and biofilm production (Archer *et al.,* 2011; Heilbronner *et al.,* 2013; Foster *et al.,* 2017).

S. lugdunensis isolates are usually susceptible to most anti-staphylococcal antibiotics, but show variable resistance levels to penicillin and oxacillin. Methicillin and β-lactam resistance in Staphylococci are mediated by the *mecA* and *mecC* genes, which encode for the PBP2a protein that has low affinity for β-lactam antibiotics. However, *S. lugdunensis* β-lactam resistance is more frequently due to the presence of a penicillinase encoded by the *blaZ* gene (Taha *et al.,* 2019). According to CLSI, *S. aureus* and *S. lugdunensis* have identical clinical breakpoints, higher than those of other CoNS. Regarding these two species, oxacillin MIC values of >2 mg/L are mostly indicative of methicillin resistance due to the presence of the *mecA* gene. The corresponding MIC for other CoNS is > 0.25 mg/L, because this breakpoint correctly indicates most CoNS with the *mecA* gene whereas it would overcall resistance for *S. lugdunensis* (Hussain *et al.,* 2000). Moreover, it has also been shown that commercial semi-automated systems are often problematic regarding the determination of penicillin and oxacillin MICs in *S. lugdunensis* (Mateo *et al.,* 2005) as well as for the detection of inducible clindamycin resistance in Staphylococci (Bohenchik *et al.,* 2014).

The purpose of the present study was to evaluate the incidence and microbiological aspects of *S. lugdunensis* infections at a tertiary university hospital. More precisely, we aimed to evaluate the incidence of *S. lugdunensis* infections over a 3.5-year period, to assess the susceptibility rates of 55 *S. lugdunensis* isolates to 19 antimicrobial agents and to review the clinical spectrum of these infections.

All 55 *S. lugdunensis* recovered from hospitalized patients at AHEPA University Hospital from January 2014 to July 2017 were included in the study. AHEPA is a 700-bed tertiary care teaching hospital that includes several surgical and internal medicine departments as well as three intensive care units (ICUs; general, surgical and cardio surgical). The information regarding the related infections was recovered retrospectively by reviewing the hospital's medical data.

Bacterial identification and antimicrobial susceptibility testing were performed using the VITEK2 automated system (bioMérieux, France). Isolates were defined as susceptible, intermediate or resistant according to the CLSI 2017 guidelines. MIC_{50} and MIC_{90} were calculated for each antibiotic using descriptive statistics on SPSS 21.0.

During the study period, *S. lugdunensis* were isolated from blood (55%); skin and soft tissues (24%); catheters (7%); sterile body fluids (9%) and urine (5%), representing 2.9% of all CoNS positive cultures (55 out of 1892). Twelve out

Key words:
Staphylococcus lugdunensis; CoNS; Greece.

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of 55 (22%), were polymicrobial infections (>1 organism isolated), whereas 43 out of 55 (78%) were monomicrobial with *S. lugdunensis* as the single isolated species. The average patient age was 62 years and 58% were male. Infections of *S. lugdunensis* were more frequent in the internal medicine departments and were mainly related to bloodstream infections.

All isolates were susceptible to vancomycin, teicoplanin, rifampicin, linezolid, tigecycline, and tetracycline. Ninety one percent were susceptible to ciprofloxacin, 89% to fosfomycin and imipenem and 82% to oxacillin. Higher resistance rates were found for clindamycin (27%) and erythromycin (25%). The susceptibility rate to penicillin was 49%.

MIC_{50} and MIC_{90} of penicillin, oxacillin, clindamycin, ciprofloxacin, vancomycin, teicoplanin and linezolid are presented in *Table 1*. This susceptibility pattern is quite different from that of other CoNS species isolated at our hospital (*Staphylococcus epidermidis*, *Staphylococcus haemolyticus* and *Staphylococcus hominis*), greater than 80% of which were resistant to penicillin, oxacillin and fluoroquinolones.

Among the 28 penicillin-resistant isolates, the majority (97%) presented penicillin MICs of ≥0.5 μg/ml, whereas only 3% had a MIC of 0.25 μg/ml. Conversely, oxacillin susceptibility was high (82%), also presenting low MICs (≤2 μg/ml) that indicate for susceptibility to both oxacillin and cefoxitin.

Frank *et al*. proposed that *S. lugdunensis* should be considered different from other CoNS, due to clinical, microbiological and genetic evidence that distinguish *S. lugdunensis* in terms of virulence and antimicrobial susceptibility (Frank *et al.,* 2008). Although CoNS tend to have a more latent pathogenicity, *S. lugdunensis* in particular is rather a pathogenic species with high virulence potential similar to *S. aureus* especially when involved in blood stream infections.

Since *S. lugdunensis* can be located to almost all cutaneous areas, skin and soft tissue infections are common sites for its isolation. On the contrary, in our study *S. lugdunensis* was mostly isolated from blood specimens, concerning bloodstream infections. Even though rates of true blood stream infections range from 10 to 25% in cases of CoNS isolation from blood cultures, with endocarditis being a rare event (Beekmann *et al.,* 2005), previous reports of *S. lugdunensis* isolated from the blood stream have emphasized the invasive potential of the species (Kleiner *et al.,* 2010).

Usually, *S. lugdunensis* present low resistance rates to aminoglycosides, macrolides, quinolones, tetracyclines, rifampicin, and fusidic acid (Taha *et al.,* 2019; Yen *et al.,* 2016). Although they are commonly susceptible to daptomycin, vancomycin, teicoplanin, and linezolid, constant surveillance of the antimicrobial resistance pattern of *S. lugdunensis* needs to be continuous. Overall, in our study the majority of the antimicrobials tested showed very good activity against *S. lugdunensis* with the exception of penicillin, oxacillin, clindamycin and erythromycin. Moreover, increased penicillin resistance was observed in blood isolates compared to that in isolates from skin, wound and tissue specimens. However, resistance levels reported from other parts of the world indicate the emergence of resistance. Yen *et al*., reported *S. lugdunensis* resistance to penicillin and oxacillin of 87% and 20%, respectively, in Taiwan (Yen *et al.,* 2016), while a study from the USA reported 45% resistance of *S. lugdunensis* to penicillin (Kleiner *et al.,* 2010). Resistance to macrolides is still rare and sporadically reported from other parts of the world (Herchline *et al.,* 1990; Liu *et al.,* 2012). However, previous studies from Greece reported a few resistant isolates in Athens (Papapetropoulos *et al.,* 2013) and an 18% resistance rate to erythromycin and clindamycin among 35 isolates collected from 2008 to 2013 in Athens and Patras (Giormezis *et al.,* 2014).

Our study has a limitation regarding the recovery of clinical data, since many medical records were unavailable by the time of its realization. This limitation could be addressed in the retrospective form of our study. Nevertheless, three documented cases of infective endocarditis and four others with significant underlying disease including renal failure and malignancy were identified. In one of the three infective endocarditis cases, *S. aureus* was also present, probably acting as a co-pathogen. Overall, ten patients died during their hospitalization; however, it was not possible to determine the exact role of *S. lugdunensis* infections in these deaths. Another limitation of our study is

Table 1 - *Antimicrobial susceptibility data of 55 S. lugdunensis isolates and cumulative susceptibility rates of all other CoNS during the study period.*

Antimicrobial agent	MIC_{50}	MIC_{90}	*MIC range (μg/mL)*	*Susceptibility rates*	*Susceptibility rates of other CoNS*
Penicillin	≤0.12	≥0.25	≤0.12 - ≥0.25	49%	6%
Oxacillin	≤2	≥4	≤2 - ≥4	82%	21%
Clindamycin	≤0.5	≥4	≤0.5 - ≥4	73%	36%
Ciprofloxacin	≤1	≤1	≤1 - ≥4	91%	45%
Vancomycin	≤4	≤4	≤4 - ≥32	100%	100%
Teicoplanin	≤8	≤8	≤8 - ≥32	100%	100%
Daptomycin	≤1	≤1	≤1 - ≥8	100%	100%
Linezolid	≤4	≤4	≤4 - ≥8	100%	97.5%
Tigecycline	≤0.12	≤0.12	≤0.12 - ≥2	100%	100%
Moxifloxacin	≤0.5	≤0.5	≤0.5 - ≥2	100%	85.4%
Erythromycin	≤0.5	≥8	≤0.5 - ≥8	75%	32.5%
Quinopristin-Dalfopristin	≤1	≤1	≤1- ≥4	100%	99%
Imipenem	1	1	≤0.12 - ≥4	82%	21%
Trimethoprim/sulfamethoxazole	≤2/38	≤2/38	≤2/38 - ≥4/76	95%	72%

the assessment of penicillin, oxacillin and clindamycin MICs by the Vitek2 system, which is not the optimal method for their determination (Mateo *et al.,* 2005; Bohenchik *et al.,* 2014) and could to some extent influence the importance of our findings. Especially for penicillin G, it has recently been shown that the disc diffusion method according to EUCAST is the best-performing method for *S. lugdunensis* isolates (Hagstrand *et al.,* 2020).

The pathogenic potential of *S. lugdunensis* and the recommendation of CLSI to use the same breakpoints with *S. aureus* underline the importance of its identification and the surveillance of its resistance rates to antibiotics. Our findings advocate the implementation of the EUCAST disc diffusion method for penicillin susceptibility testing of confirmed *S. lugdunensis* in our region before excluding penicillin as a treatment option. Prudent use of antibiotics is therefore essential to maintain enough treatment alternatives for *S. lugdunensis* in the long run.

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