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Staphylococcus aureus nasal carriage in hemodialysis centers of Fez, Morocco

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ABSTRACT

Background and objectives: *Staphylococcus aureus* (*S. aureus*) nasal carriage may be responsible for some serious infections in hemodialyzed patients. The main target of this study was to estimate the prevalence of *S. aureus* nasal carriage in hemodialysis outpatients and medical staff in hemodialysis centers specifically in Fez region. The second target is to identify the risks of colonization, resistance pattern of isolates and their virulence toxin genes.

Patients and Methods: Nasal swab specimens were obtained from 143 hemodialyzed outpatients and 32 medical staff from January to June 2012. Each participant completed a short questionnaire. Nasal carriage of *S. aureus* was demographically related (age, gender, hemodialysis duration), comorbidity (diabetes, malignancy) and exposure to health care (dialysis staff, hospitalization). PCR were used on all the isolates in the research of twelve staphylococcal enterotoxins genes. Also, PCR was used to investigate on the three factors epidermal cell differentiation inhibitors; three exfoliatin toxins; two leukotoxins; the toxic shock syndrome toxin-1 and the hemolysin beta genes.

Results: Nasal screening revealed 38.16%, 50% and 18.75% *S. aureus* carries in chronic, acute hemodialysis patients and medical staff, respectively. Only young participants were likely to be *S. aureus* carries ($p = 0.002$). There were no gender differences between the isolate carriers and non-carriers or some comorbidity factors such as viral hepatitis B and C, HIV infections, diabetes, chronic smoking, recent hospitalization or antibiotic therapy. Out of all isolates, only one (1.61%) was methicillin-resistant and Twenty-one (33.87%) had at least two virulence toxin genes.

Conclusions: Knowledge and monitoring of antibiotic resistance profile and virulence of *S. aureus* carriage are essential in the treatment of infections generated by this pathogen, as well as in the control of clonal dissemination and prevent the spread of *S. aureus* resistance.

Keywords: Nasal carriage, *Staphylococcus aureus*, hemodialysis, antimicrobial susceptibility, toxin genes

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INTRODUCTION

In Morocco, the number of patients with chronic hemodialysis (CHD) treated by machine has increased sharply during the past 30 years. Each year, around 4000 new cases are reported and prevalence was estimated at 300 per million inhabitants (1). This population of patients is at high risk of infection

with *Staphylococcus aureus* due to frequent vascular access, multiple hospital visits, immunosuppressant treatment, frequent use of antibiotics, increased strain skin colonization and central venous catheter use for vascular access (2, 3).

Nasal carriage of *S. aureus* in the anterior nares, present in over 42% of hemodialyzed (HD) patients, plays a major role in body expansion of this germ and consequently the HD patients infection risk (2, 4). Bacteria harboring in the nose passes to the hands and, from the hands, to the skin (5-7). From the skin, *S. aureus* may cause infection by any foreign substance such as a graft (introduced with venipuncture) or a dialysis catheter, either in HD patients (who mainly used fistula as their access) or peritoneal dialyzed (PD) patients. In fact, the entry into the blood in HD patients as well as to the peritoneum in PD patients may be from either touch contamination at the time of accessing the catheter, or from entry from exit site through the tunnel. On the other hand, Boelaert *et al.,* showed that 84% of nasal *S. aureus* patients carried these bacteria on their hands, against only 5% of patients who did not carry it in their nose (6). Even more, molecular typing revealed that strains from nares, skin and infectious sites are identical in 91% of cases (4, 8).

Several factors are likely to depress the immune system of HD patients, and thus, make them more susceptible to infection. Among those factors, there is old age, concurrent debilitating illnesses, long-term stay in hospital, repeated antibiotic treatment and specific immune defects associated with renal dysfunction (9). Therefore, recognition of persons colonized or infected with *S. aureus* is recommended for preventing the spread of the microorganism within the hospitals or in the communities. The emergence and dissemination of methicillin-resistant *S. aureus* (MRSA), which is also often multidrug-resistant, renders the treatment of staphylococcal infections more challenging.

Severity of *S. aureus* strains is associated with the production of a wide variety of extracellular toxins and virulence factors including staphylococcal enterotoxins (SEs), *like* enterotoxins (S*l*Es), Panton-Valentine leukocidin (PVL), toxic shock syndrome toxin-1 (TSST-1), exfoliative toxin (ET), hemolysins, and coagulase (10).

The purpose of this study was firstly, to determine *S. aureus* nasal carriage prevalence and associated risk factors in hemodialyzed patients and medical staff of 4 hemodialysis centers of Fez city (Morocco); to define antibiotic susceptibility for all *S. aureus* strains identified; and finally, to define isolates toxinic gene patterns.

MATERIALS AND METHODS

Patients and study period. This cross-sectional study involved two population types: MS and HD patients (chronic and acute) in four hemodialysis centers (two private clinics, Hassan II Academic Medical Center and the Al Ghassani Provincial Hospital Center) localized in Fez city (Morocco). Patients and staff consenting were recorded between January 2012 and June 2012. All patients and staff completed a health questionnaire before undergoing nasal swab. The questionnaire included data related to the identity (name, age, sex and address), some co-morbidities factors such as viral hepatitis B (HBV), hepatitis C (HCV) and Human Immunodeficiency Virus (HIV) infections, diabetes, recent hospitalization, chronic smoking and recent antibiotic therapy or other medical history. The specific questionnaire for dialyzed patients included issues about dialysis type (acute or chronic), dialysis duration, and dialysis method which are catheter (usually femoral) or intravenous fistula.

Sampling method and bacterial identification. Samples were collected by sterile swabs. The same swab was used for both nostrils. Sampling was performed by pressing swab at least 1 cm into nostrils and spin at least three times. Sterile physiological water was used to soak swab before sampling in case of dry nose. Immediately after sampling, swabs were transported directly to the laboratory at room temperature and inoculated into Chapman medium and incubated at 37°C for 24-48 hours. Species were identified by colony morphology, Gram staining, catalase test, coagulase activity on rabbit plasma (Coagulase Plasma, Liofichem, Roseta D.A (TE) -Italy) and production of clumping factor (Slidex staph® plus, bioMérieux, France).

Antimicrobial resistance. Susceptibility to penicillin G (PG), kanamycin (K), tobramycin (Tm), gentamicin (Gm), vancomycin (VA), erythromycin (E), lincomycin (L), fusidic acid (FA), pristinamycin (PT), chloramphenicol (C), rifampicin (RF), pefloxacin (Pef), tetracycline (Te), fosfomycin (Fos), cefoxitin (Fox) and

moxalactam (Mox) was determined by the standard disc diffusion technique in accordance with the guidelines of the French Society of Microbiology (11). Inhibition diameter around cefoxitin and moxalactam disks less than 27 mm and 24 mm, respectively, reflects MRSA suspicion. The MRSA were confirmed by polymerase chain reaction (PCR) detection of *mec*A gene. *S. aureus* ATCC 29213 and *S. aureus* ATCC 25923 were used as quality control organisms. Isolates were considered as multidrug resistant (MDR) when they were resistant to 3 or more of the antibiotics listed above.

Genomic DNA extraction. All *S. aureus* isolates were grown on ordinary medium agar for 18-24 hours at 37°C, bacterial cells were suspended in 500 µl of ultrapure water. Suspension was heated at 100°C for 10 min and immediately frozen at 0°C for 5 min. 300 µl of supernatant are then recovered after centrifugation of 20 000 g for 10 min. Supernatant containing DNA was stored at -20°C until further use.

***nuc* and *mecA* genes research by PCR.** Duplex PCR assay was performed for the detection of the 218 bp fragment *nuc* gene encoding specific thermonuclease of the *S. aureus* and the 309 bp fragment *mecA* gene encoding methicillin resistance, according to protocols previously defined (12, 13).

Detection of staphylococcal toxin genes. Different multiplex PCRs were performed to detect staphylococcal enterotoxins (SE) and SE-*like* (SE*l*) genes A, B, C, D, H, K, L, M, O, P, Q, and R (*sea, seb, sec, sed, seh, selk, sell, selm, selo, selp, selq,* and *ser*), exfoliative toxins A, B, and D genes (*eta, etb,* and *etd*), TSST-1 gene (*tst*), leukocidins genes (*lukS/F-PV* and *luk-M*), epidermal cell differentiation inhibitor genes (*edin A, B, C*) and beta-hemolysin gene (*hlb*), as previously described (14, 15). Control chromosomal DNA samples from standard laboratory controls of Pasteur Institute (Casablanca, Morocco) were used as positive control.

Statistical analysis. Statistical study was conducted in collaboration with Fez Laboratory of Epidemiology, Clinical Research and Community Health, Hassan II Academic Medical Center, Fez. Analyzes were performed using SPSS Version 17.0 statistics (IBM, Chicago, USA). A qualitative variable analysis was performed by nonparametric tests. For quantitative variables the Student's test (T) was used. A difference is considered statistically significant if p-value < 0.05.

RESULTS

A total of 175 nasal swabs were performed in the four hemodialysis centers conducted with 131 (74.86%) CHD, 12 (6.86%) acute hemodialyzed patients (ADH) and 32 (18.38%) in MS. Information collected from survey questionnaires allowed us to draw a summarizing table of demographic characteristics in population study (Table 1).

Out of all nasal swabs, sixty-two (35.43%) isolates were identified as *S. aureus*. Fifty (80.64%) and six (9.68%) of theme were found in CHD and AHD patients, respectively; whereas six (9.68%) were collected from the MS personnel.

The MS personnel mean age was 29.67 ± 6 years. The *S. aureus* nasal carriage was 33.33% (n = 2) in man and 66.67% (n = 4) in women, the sex ratio was 0.39. The AHD patients average age was 37 ± 26.94 years. Their average hemodialysis duration was 0.94 ± 1.54 months. For men *S. aureus* nasal carriage was 16.67% (one patient), it's 83.33% (five patients) for women, the sex ratio was 1. These populations were characterized by dialysis catheter carriage (usually femoral). No significant association on *S. aureus* carriage was observed.

We paid special attention to the CHD patients because of their greatest weaknesses (n = 131). 50 (38.16%) of them were carriers of *S. aureus* with the sex ratio of 1.25. No significant difference was observed in groups of patients (carriers and non-carriers *S. aureus*) by sex, hemodialysis duration (70.23 against 72.96 months), recent hospitalization (last 12 months), catheter harbor, smoking chronic, diabetes type 1, HIV, HCV, HBV infections and recent antibiotic therapy ($p > 0.05$). Regarding the age, the CHD patients were categorized into 3 classes, the first represented a relatively young population (age between 18 and 35 years), the second forming adult population (36 to 50 years) and finally the third with seniors (51 to 83 years). Comparing *S. aureus* carriers percentages of the three age groups, we interestingly found that the relatively young population tended to be colonized ($p = 0.002$), followed by the adult and old people ($p > 0.05$).

Review of antimicrobial susceptibility patterns in this study demonstrated that seven (11.29%) of all *S.*

Table 1. Demographics and characteristics of different study populations.

Caracteristic (n = 175)	MS (n = 32)	AHD (n = 12)	CHD (n = 131)
Sex:			
Male	9 (28.13%)	6 (50.00%)	70 (53.44%)
Women	23 (71.87%)	6 (50.00%)	61 (46.56%)
Age average (years)	31.87 ± 10.36	40.41 ± 23.69	51,45 ± 14.38
Diabete :			
Type 1	No	1 (8.33%)	11 (8.39%)
Type 2	No	No	3 (2.29%)
Dialysis duration average (months)	No	1.67 ± 3.45	71.27 ± 52.24
Catheter	No	12 (100%)	5 (3.81%)
Antibiotic treatment	1 (3.12%)	1 (8.33%)	14 (10.68%)
Last 12 months hospitalization	No	9 (75.00%)	21 (16.03%)
Average duration hospitalization (day)	No	8.11± 8.13	14 ±14.16
Patient shows :			
HCV	No	No	2 (1.53%)
HBV	No	No	2 (1.53%)
HIV	No	No	1 (0.76%)
Tuberculosis	No	No	3 (2.29%)
Urinary tract infection	No	1 (8.33%)	2 (1.52%)
Chronic angina	No	No	3 (2.29%)
Chronic smoking	No	No	10 (7.63%)

*MS: Medical staff, *AHD: Acute Hemodialysis, *CHD: Chronic Hemodialysis

aureus isolates had presented a wild phenotype, with sensitivity to all antibiotics tested. Two and five of them were isolated from AHD and CHD patients, respectively. Bacterial strains expressed a high level of sensitivity to macrolides and related antibiotics, aminoglycosides, pefloxacin, chloramphenicol, fosfomycine and glycopeptides (vancomycin) (Table 2). However, 16.13% of our strains showed resistance to tetracycline and 4.83% of them were resistant to rifampicin and fusidic acid. Interestingly, only one strain (1.64%) expressed an inhibition less than 27 mm and 24 mm around cefoxitin and moxalactam disks, respectively. It was confirmed as MRSA.

In this work, the resistance to penicillin G was

Table 2. Resistance pattern of 62 S. aureus strains.

Resistance pattern	Strain number	Origin isolats	(CHD) / (AHD) / (MS)	
Wild	7	5	2	0
P	43	34	4	5
P-RA	2	1	0	1
P-TE	3	3	0	0
FA-TE	1	1	0	0
P-C-TE	2	2	0	0
PEF-FA-TE	1	1	0	0
L-E-PEF-TE	1	1	0	0
K-FA-TE-RA	1	1	0	0
P-TE-FOX-MOX	1	1	0	0

P: Penicillin G, K: Kanamycin, TM: Tobramycin, TE: Tétracycline, E: Erythromycin, L: Lincomycin, C: Chloramphenicol, PEF: Pefloxacin, FOX: Cefoxitin, FA: Fusidique acid, RA: Rifampicin, MOX: Moxalactam.
AHD: Acute Hemodialysis, CHD: Chronic Hemodialysis, MS: Medical Staff.

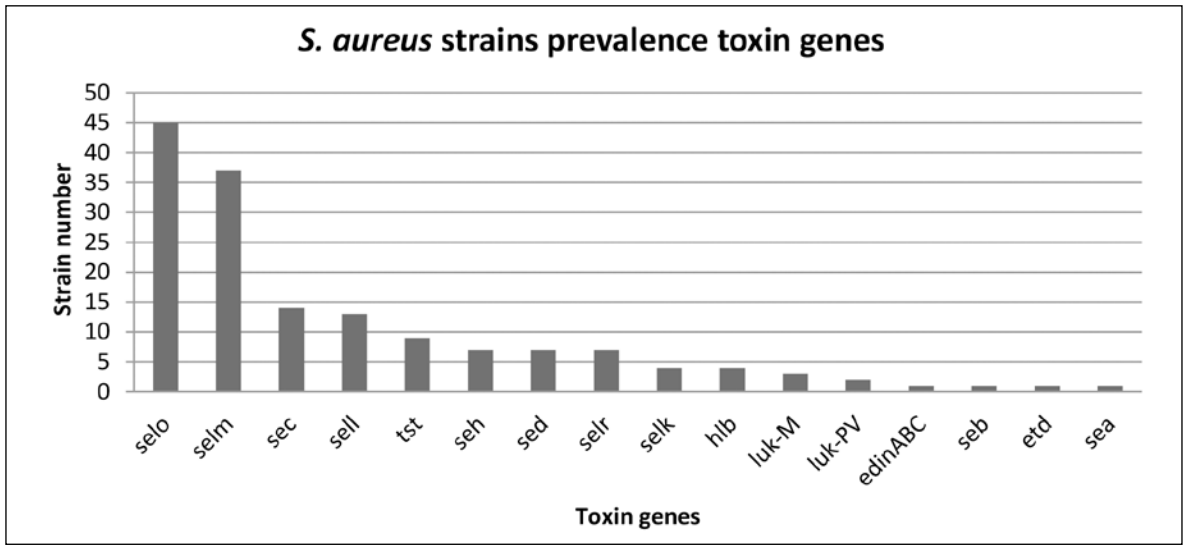

Fig1. toxin genes Prevalence of *S. aureus* stains isolated in the population study.

the dominant pattern phenotype (69.35%). Only six strains classified as multidrug resistant (MDR). These strains showed resistance to at least 3 antibiotics (Table 2) and contained *selm, selo, sed, selr, lukM*. We observed that the strains from AHD patients showed only "penicillin" (4/6) phenotype or wild type (2/6). Unlike in the CHD patient strains, the resistant rate is rather high with varying resistance patterns. All MDR strains were isolated from chronic hemodialyzed patients. Virulence genes study revealed sixteen toxin genes (*sea, seb, sec, sed, seh, ser, selk, sell, selm, selo, etd, hlb, tst, edinABC, lukM, luk-PV*) distributed in different profiles between strains isolated (Table 3).

Among these genes, we have nine *tst* genes (two in AHD and seven in CHD *S. aureus* isolates) and two *luk-PV* genes (one for each of AHD and CHD *S. aureus* isolate). In addition, 80.6% of strains (all populations combined) contained at least two toxin genes.

MDR isolates in this study harbored at least three toxin genes. Gene frequency was dispersed, the most frequent were *selo* gene with 72.6% (45 strains), followed by *selm* (n = 37, 60%) (Fig 1). It's interesting to note that none of the isolates undertaken in this study had any of *eta, etb* and *etd* genes.

DISCUSSION

S. aureus nasal carriage plays an important role in epidemiology and pathogenesis in chronic hemodialyzed patient infections, especially in

Table 3. Toxinic gene pattern of nasal carriage *S. aureus* strains in hemodialyzed patients.

Toxinic gene Pattern	Strains number (N = 62)
(Wild)	(9)
(*selo*)	(3)
(*selo-selm*) / (*selo-sell*) / (*selo-tst*) / (*selo-seh*) / (*selo-selk*) / (*selo-lukPV*) / (*selm-hlb*) / (*sell-seh*) / (*seh-hlb*)	(12) / (1) / (2) / (1) / (1) / (1) / (1) / (1) / (1)
(*selo-selm-sec*) / (*selo-selm-tst*) / (*selo-selm-lukM*) / (*selo-sell-sec*) / (*selo-seh-tst*)/ (*selo-sed-ser*) / (*selm-selk- tst*) / (*lukPV-tst-edinABC*)	(2) / (2) / (1) / (1) / (2) / (2) / (1) / (1)
(*selo-selm-sell-sec*) / (*selo-selm-sed-ser*) / (*selo-sell-seh-sec*) / (*selo-selk-seh-seb*)	(7) / (2) / (1) / (1)
(*selo-selm-sell-sec-hlb*) / (*selo-selm-sed-ser-lukM*) / (*selo-selm-sec-etd-sea*)	(2) / (2) / (1)
(*selo-selm-selk-sea-tst-ser*)	(1)

patients requiring vascular access for prolonged periods. A causal relation between *S. aureus* nasal carriage and infection is supported by the fact that the nasal *S. aureus* strain and the infecting strain share the same phage type or genotype (3, 16). These staphylococcal infections present a serious clinical problem in the routine management of hemodialyzed patients. That is why, a greater understanding of *S. aureus* colonization prevalence and microbiology is essential to guide efforts in reducing antibiotic resistant strains spread. Furthermore, nasal application of an antistaphylococcal drug temporarily decolonizes the nose and other body sites, which prevents infection (17).

The rate of *S. aureus* nasal carriage in this study was 35.43% (whole study population combined). It is 38.16%, 50.0% and 18.75% in CHD, AHD and MS patients, respectively. Nevertheless, the chronic or acute hemodialysis *S. aureus* carriage is quite high compared to medical personnel. This tells us that the hemodialysis incriminating factor is responsible in increasing of *S. aureus* carriage, as previously confirmed by Nouwen *et al.,* (18). Moreover, since the manpower of the CHD patients is more important, we have focused our work on this population. The rate of 38.16% in this study is comparable to other reported range (19). However, in previous reports, the *S. aureus* nasal carriage prevalence rate among patients receiving hemodialysis was relatively lower, between 11.25% and 31.4% (20-22) and the rate was between 44.0% and 84.0% in others studies (23-26). One explanation for this variability may be that factors in the host, such as nutritional status, HLA (human leukocyte antigen) system, race, sex, age, hormonal factors, anatomical alterations, bactericidal activity of nasal secretions, epithelial cells receptors and/or local immunity associated with IgA predispose some patients to be *S. aureus* nasal carriage. Other reasons may be related to bacteria and/or environment (27, 28).

In this work, no significant correlation was found regarding the nasal carriage of *S. aureus* and hemodialysis duration, diabetes, sex and recent hospitalization in patients on hemodialysis ($p > 0.05$). Publications differ on this issue; some authors have not found diabetes or hemodialysis duration as a risk factor (19-23) while others have found it as a risk factor (29). No additional significant risk factor was identified, either, among patients expressed HIV, HBV or HCV infections, or smoking patients or dialyzed with urinary disorders. Though, most recently Alexander et *al*., confirms an increased risk on *S. aureus* carriage with these factors (30). We can explain this result by the no representative patient number with these risk factors.

In our study, the young patients had a higher risk for *S. aureus* carriage ($p = 0.002$). Whereas, Saxena and coworkers (31) found a significant correlation between old age and nasal carrier state, they established that patients aged 75 to 84 years had the highest (84.6%) prevalence of *S. aureus* nasal carriage. Those aged 65 to 74 years had the next highest (49.0%) nasal carriage rates while patients aged 15 to 24 years had the lowest (12.8%) prevalence of nasal carriage.

Moreover, this study provides important data on current antimicrobial resistance, including methicillin-resistance. Resistance to tetracycline, widely used in Morocco, was found in ten HDC strains (16.13%). This rate remains very lower than one study reported in Poland (21). Nevertheless, four antibiotics (chloramphenicol, rifampicin, fusidic acid and pefloxacine) also actively used in Morocco, are more or less active (with 96%, 95.16%; 95.16% and 77% of sensitivity, respectively). All resistant strains have been developed in HDC patients except one person medical staff wearing a *S. aureus* resistant to rifampicin and penicillin. Such rates of resistance were lacking in most African countries (32, 33). We speculate that many factors may have contributed to the emergence of these resistances in Morocco, namely the self medication, the low costs, and availability of antibiotics without a prescription.

Throughout our study, particular attention has been focused for MRSA research. Methicillin resistance in staphylococci is conferred by the *mecA* gene, which is easily transferred horizontally and encodes for an altered penicillin-binding protein (PBP2a) that has a low binding affinity for all β-lactam antibiotics. One interesting finding to note was the high sensitivity rate (98.39%) of HD nasal carriage *S. aureus* to cefoxitin (MRSA) despite the worldwide reports of its high resistant rate to this drug (19, 23, 34). Our MRSA strain presented simultaneous resistance to only penicillin and tetracycline; it was isolated from a men chronic hemodialysis patient, tuberculosis, aged 32 years. He had not been hospitalized in the twelve months preceding organism isolation. The strain resistance pattern (P-TE-FOX) was very different from those reported in hospital-acquired (HA) or community-acquired (CA) MRSA. CA-MRSA

resistance is usually limited to β-lactams, and the strains remain susceptible to clindamycin, gentamicin, sulfamethoxazole-trimethoprim, vancomycin, rifampin, tetracycline, and linezolid compared with HA-MRSA isolates (35-37). Moreover, our strain does not possess *luk-PV* neither epidermolysin genes which are often associated with CA-MRSA (36, 38).

Besides the antibiotics resistance of *S. aureus*, it can be surprising how this bacterium is also armed to annihilate many defenses that his host could oppose him. In the current work, in agreement with Holtfreter and his teammates (14) *selo* and *selm* genes were more frequently detected in all isolates. Both genes belong to the recently described enterotoxin gene cluster (*egc*) that harbours 5 to 6 genes (*seg, sei, selm, seln, selo*, and sometimes *selu*), which cluster on a staphylococcal pathogenicity island type I γSaβ(10,39). this cluster will be found without all of the *egc* components (40, 41).

The *tst* gene is carried by a family of closely related pathogenicity islands that interact in highly specific way with certain staphylococcal phages. Most often associated with *sec, sell, selq or selk* genes (14), this gene encoding for TSST-1, was found in 14.5% of all isolates. Secreted toxin responsible of staphylococcal toxic shock syndrome can cause, on body spread, fever higher than 39°C, hypotension and generalized scarlatiniform, erythroderma followed by 7 until 14 days later by intense scaling and a multi-organs damage.

The gene encoding Panton-Valentine leukocidin (PVL) was present in two (3.22%) *S. aureus* isolates. PVL is cytotoxic to human polymorphonuclear cells, monocytes, macrophages and erythrocytes (42). It is also strongly associated with skin infections, such as furuncles, but also osteomyelitis (43) and necrotizing pneumonia mainly (44).

With low resistance rate to antibiotics tested, strains harboring these two toxin genes (*tst* and *luk-PV*) are not a direct danger to patients who wear them. But acquisition of any resistance antibiotic makes these strains a potential danger against hemodialyzed patients.

Another strain isolated from a female patient 66 old years, carries *sec, sea, seh* and *sell* genes. In literature, we find that *sec* and *sell* genes are localized with *tst* gene on pathogenicity islet of island SaPIm1/SaPIn1 family (10, 14). The most plausible explanation we can move forward to account for this pattern is that strain has probably kept genetic element (SaPIm1/SaPIn1) but lost the *tst* gene.

Regarding *lukM* gene, a leukocidin synergohymenotrope activity, was isolated from three strains. However, in literature, *lukM* gene is bovine native and is carried by mobile genetic element (45). Its presence in CHD patient strains may be due to contact with bovine, thus inducing a transfer of bovine strains to humans, or simply a mobile genetic element transfer from bovine strains to human strains, and by several other mechanisms *lukM* positive strains were colonizing our three dialyzed patients.

CONCLUSION

On the basis of all these data and investigation, and taking account hemodialysis as a major risk factor in *S. aureus* nasal colonization, only subtle balance between host defenses "immunocompetent" and *S. aureus* ability to express virulence factors, depending on environmental conditions, which will determine success or eradication infection.

These studies can therefore open way for prophylaxis or antibacterial therapy adapted according to each patient status. Thus, screening will allow to implement individual and collective hygiene directives, as well as clinical monitoring and *S. aureus* nasal carriage bacteriological in long-term in hemodialysis units.

Finally, multidrug resistance is not itself additional virulence factor in *S. aureus*. But infections associated with these strains exhibit frequently significant gravity related to environment, inefficiency to probabilistic treatment or initial therapeutic choice often restricted. In this way, *S. aureus* multi-resistant and multi-virulent lethality is significantly higher than identical wild germs infections.

Knowledge and monitoring of *S. aureus* sensitivity and virulence pattern are essential in the treatment of infections generated by this specie of bacteria, as well as control of clonal dissemination. Each hemodialysis center must make a periodic assessment of *S. aureus* antibiotics sensitivity currently used.

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