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Full Length Research Paper

Antibiotic susceptibility and toxins production of *Staphylococcus aureus* isolated from clinical samples from Benin

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A wide range of clinical samples were screened for identification of *Staphylococcus aureus*, their antibiotic sensitivity profile and the production of different leucotoxin and epidermolysins was evaluated. Out of 2,040 biological samples (collected from pus, urine, sperms, genital, catheter and blood of hospitalized and extra-hospital patients) screened, 123 pure cultures of *S. aureus* colonies were isolated. 48.78% of *S. aureus* were resistant to methicillin (MRSA), while 78% of them were isolated from extra-hospital patients. The *S. aureus* isolated from urines, pus and blood produced Panton and Valentine leukocidin (PVL) toxin, while the leucotoxin lukE-lukD was exclusively encountered by *S. aureus* isolated from pus samples. None of the bacterial colony isolated produced epidermolysin toxins A and B. In addition, 3.25% of MRSA and 8.13% of methicillin sensitive *S. aureus* (MSSA) produced PVL respectively. Our results indicated high frequency rate of MRSA in extra-hospital screened samples isolated from various types of infection. This high resistance rate combined with toxin production increases the virulence of *S. aureus* colonies and put therefore at risk the life of the patients in developing countries where auto-medication is not controlled. There is the need to instruct the population in order to avoid further widening of MRSA territory.

Key words: *Staphylococcus aureus*, Panton-Valentine leukocidin (PVL), antibiotic, infection, methicillin-resistant *Staphylococcus aureus* (MRSA), Benin.

INTRODUCTION

The animal organisms are often subject to various parasites. These microorganisms are generally viable at the expense of their hosts, while causing various diseases. The parasitic infectious agents are either diseases. The parasitic infectious agents are either specific pathogenic bacteria inducing clinically defined and physio-pathologically specific diseases, or opportunistic bacteria expressing their pathogenicity by exploiting the host physiological deficiency and by taking

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advantage of the modification of its environment. *Staphylococcus aureus* is one of the most frequently isolated human pathogenic bacteria in the community and hospital infections (Chambers, 1997; Deresinski, 2005; Friedman et al., 2002; Naimi et al., 2003). It is therefore one of the most devastating and widespread disease causing bacteria in hospital epidemiology due to its ability to produce a wide range of toxins and adhesion factors (Baba-Moussa et al., 2008; Foster and Höök, 1998).

The control of *S. aureus* causing diseases heavily relies on intensive use of antibiotic drugs. However, as a result of increasing use of antibiotics, the pathogenic bacteria become more easily resistant to a wide range of these drugs (Kim et al., 2004; Shittu and Lin, 2006). For instance, a year after the introduction of methicillin as an efficient antibiotic in 1960 (Durand et al., 2006), *S. aureus* has been reported to naturally resist this antibiotic (Deresinski, 2005; Ayliffe, 1997; Jevons, 1961). The emergence of methicillin-resistant *S. aureus* (MRSA) is greatly facilitated by the horizontal transfer of the bacterial virulence factors. Thus, MRSA have been reported in Europe, America (Deresinski, 2005; Ayliffe, 1997) and recently in Africa (Bell and Turnidge, 2002; Hayanga et al., 1997; Klugman, 1998). Later, MRSA cases have been reported in extra-hospital environments notably among the community with no contact to hospitals (Vandenesch et al., 2003; Zetola et al., 2005; Ho et al., 2007; Kuehnert et al., 2006). In contrast to the nosocomial colonies, the community acquired MRSA (CA-MRSA) are most sensitive to almost all antibiotics with the exception of the β-lactam antibiotics (O'Brien et al., 2005). In Benin (West Africa) for example, this case of CA-MRSA emergence has also been reported (Makoutodé et al., 1994). However, relatively few data exist from epidemiological studies on the variability of toxins produced by *S. aureus* colonies as well as their resistance profiles to a wide range of antibiotics in this country.

Therefore, in order to establish the trends of *S. aureus* resistance to antibiotics from clinical samples in Benin, we endeavored in this work to screen various clinical samples collected from Microbiology laboratory of the National Teaching Hospital Center, Hubert Koutoukou Maga (NTH-HKM), the biggest hospital center of Benin and subsequently characterize the isolated bacterial colonies. The ultimate objective of this study was to establish the toxin profile and the antibiotic resistance ability of the clinically isolated *S. aureus*.

MATERIALS AND METHODS

Sample collection and *S. aureus* identification

The sample collection was performed for a 4-month period (September 27, 2010 to January 27, 2011) from 2,040 hospitalized and extra-hospital patients admitted at the laboratory of Bacteriology of the National University Hospital Center (CNUH) of Cotonou (Benin). In this study, we focused our effort on isolating *S. aureus* in pure culture. In this regard, only samples more than 90% of bacterial colonies identified as *S. aureus* have been considered for further investigation. For epidemiological data analysis, we took into account every patient's clinical data (age, sex, site, hospitalization etc.) and the origin of the bacterial sample collection. The bacterial identification was done through morphological characterization. Gram stain test, catalase activity, production of DNase and coagulation of rabbit lyophilized plasma were tested according to the manufacturer instruction (Bio Mérieux, France).

Antibiotic susceptibility of *S. aureus* colonies

In order to study the effect of antibiotics on the isolated *S. aureus*, we tested the susceptibility or resistivity of *S. aureus* colonies on agar plates containing 20 different antibiotics. The disc diffusion method was employed on Mueller Hinton agar plates (Bio-Rad-Diagnostic Pasteur, Marnes la Coquette, France) according to the recommendations of the Antibiotic Committee of French Society of Microbiology (CA-SFM). Nitrofurantoin antibiotic were only tested against urine samples. Determination of methicillin resistance was performed by the disk diffusion method on Mueller Hinton agar with 5% (wt/v) NaCl at 37°C for 24 h.

Screening and characterization of bacterial toxins

S. aureus isolates are well known to produce different toxins. They were screened for the production of different leucotoxins such as Panton-Valentine leukocidin ((PVL: LukF-PV et LukS-PV)), leucotoxin LukE-LukD and epidermolysins A (ETA) and B (ETB) using the Ouchterlony method also known as radial gel immunodiffusion (Gravet et al., 1998) in the presence of specific purified anti-leucotoxins and anti-epidermolysin rabbit antibodies .

Statistical analysis

For statistical analysis, biological replicate experiments were conducted throughout this study. Software Microsoft office Excel 2007 was used for the treatment of data. Software Epi Info 6 versions 6.04 (Center for Disease Control and Prevention, Atlanta, GA, U.S.A.) easily allowed the statistical test of χ^2 used in the comparison studies to determine the meaning of every factor of bacterial virulence. The test was considered statistically significant at $P<0.05$.

RESULTS

Prevalence of *S. aureus* isolated according to samples origin

The 2,040 analyzed samples were composed of 30 urethral samples, 162 vaginal samples, 93 sperm samples, 89 pus samples, 17 catheter samples, 122 blood samples and 1527 urinal samples. In total, 123 colonies of *S. aureus* were isolated from the 2,040 independents samples analyzed. On the other hand, 24 colonies of *S. aureus* were co-isolated with other enterobacteria (*Escherichia coli*, *Klebsiella pneumoniae*, Enterococcus, *Pseudomonas aeruginosa*, Acinetobacter spp., *Enterobacter cloacae*, *Morganella morganii*, β hemolytic Streptococcus, hemolytic Bacillus Gram

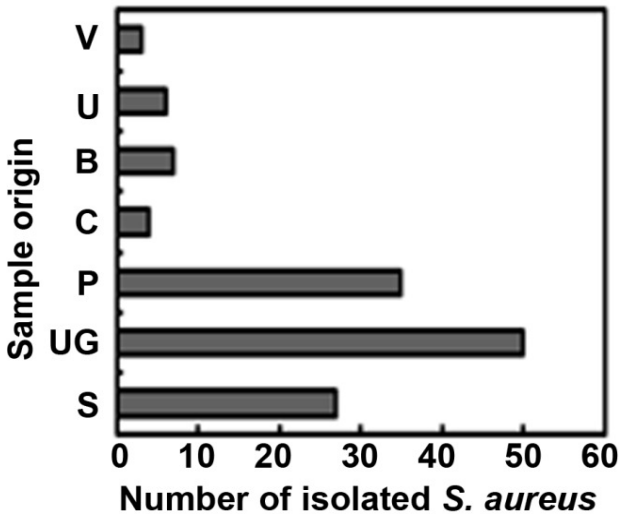

Figure 1. *S. aureus* distribution based on sample provenance. V, Vaginal sample; U, urinal sample; B, blood sample; C, catheter sample; UG, urogenital sample; S, sperm sample.

negative) and/or yeasts (*Candida albicans*). Since we needed to consider only pure cultures of *S. aureus* were not considered in this study.

A prevalence of 6% of *S. aureus* was observed from the entire samples collected. The patient concerned represented 61 and 21% of *S. aureus* isolates originated from hospitalized patients, while the rest (79%) were isolated from samples collected from the community (extra-hospital) patients. *S. aureus* were classified according to their biological provenance (blood, catheters, the pus, the urines, the vaginal samples, the urethral samples and the sperms) (Figure 1). Interestingly, we found the urine samples to be the most contaminated with 33.33% of *S. aureus* colonies followed by pus accounting for 28.45%. The vaginal samples proved to be the least contaminated with 2.44% of *S. aureus*. These infections are induced by the bacterial proliferation, invasion and destruction of local tissues resulting in local and systemic inflammatory response.

Susceptibility studies of *S. aureus* to antibiotics

The antibiotic tests revealed that 118 out of the 123 (95.93%) bacterial colonies were resistant to Penicillin G. Interestingly; the MRSA represented 48.78% of the whole isolates (Table 1). On the other hand, pristinamycin was found to have the greatest inhibiting effect on the *S. aureus* colonies with only 3.25% of bacterial resistance recorded for this antibiotic. In addition, nitrofurantoin antibiotic were specifically efficient against *S. aureus* originated from urinary infections with only 9.75% of bacterial resistance recorded for Nitrofurantoin treatment (Table 2). Out of the 60 *S. aureus* colonies resistant to methicillin (MRSA), 78% (47/60) were from community (extra-hospital) origin (Figure 2A). As depicted in Figure 2B, we represent the distribution pattern of the 60 MRSA based on their origin. Interestingly, out of the 41 *S. aureus* colonies isolated from urine samples, 22 (53.65%) of them were MRSA, 42.85% MRSA come from the pus, 59.26% from sperm samples, 33.33% from genital samples, 14.28% from blood samples and 75% from catheter samples.

Production of toxins by *S. aureus* colonies

Altogether, the PVL was produced by 14 *S. aureus* isolates out of the 123 bacterial colonies identified (11.38%). Among positive blood cultures, 57.14% (4/7) produced PVL, and 7.31% (3/39) urinal samples produced PVL. However, the leucotoxin lukE-lukD was leucotoxin lukE-lukD was produced by 28% (5/35) of the pus isolated colonies (Table 3). On the other hand, no *S. aureus* was isolated among produced epidermolysin ETA and ETB (Table 3).

DISCUSSION

Our study, revealed a prevalence of 6% of *S. aureus* isolated from various samples assessed from the laboratory of Microbiology of the CHU-HKM, Benin. These bacteria were isolated from almost all the types of samples considered in this study. This result is not surprising because of the opportunistic and ubiquitous nature of *S. aureus* (Nauciel and Vilde, 2005). *S. aureus* is the fourth most common hospital-acquired pathogen among older adults, following *E. coli, P. aeruginosa,* and Enterococci. The *S. aureus* isolates from genital samples represented 40.65% of the entire bacteria identified. This is similar to 43% (in Benin) and 40.71% (in Casablanca, Morocco) previously obtained results (Baba-Moussa et al., 1999; Elazhari et al., 2009). Surprisingly, these values are higher than those recorded in developed countries (~0.1 to 2%) (Foster and Höök, 1998). For instance, out of 15,074 infections of all origins, the frequency of urinary infections is 15% and only 2.5% are linked to *S. aureus* in Europe and USA (Fluit et al., 2001).

The strong percentage of *S. aureus* in urogenital infections in Benin can be explained by a passive presence of these germs in the urogenital region (Randrianirina et al., 2007). In addition, this can also be due to the lack of hygiene, the unfavorable climatic conditions and the lack of clean water. In our study, *S. aureus* was also isolated from blood sample. The presence of *S. aureus* in the blood confirms its capacity to provoke septicemia in human. *S. aureus* caused similar proportions of both community-onset (18%) and nosocomial (21%) bloodstream infections (Diekema et al., 2003). In a more recent series, staphylococcal species were the second most common pathogen

Table 1. *Staphylococcus aureus* resistance profile to a wide range of antibiotics

Antibiotics (AB)	Number of colony R (N = 123)	Percentage of AB resistance (%)
Penicillin (Pen G)	118	95.93
Oxacillin (OXA)	60	48.78
Amoxicillin (AMX)	85	69.10
AMX + clavulanate (AMC)	68	55.28
Cefotaxime (CTX)	112	91.05
Cefuroxime (CXM)	102	82.93
Cefixime (FOX)	98	79.67
Ciprofloxacin (CIP)	59	47.96
Ofloxacin (OFX)	51	41.46
Spiramycin (SP)	38	30.89
Lincomycin (L)	29	23.58
Pristinamycin (PT)	4	3.25
Erythromycin (E)	44	35.77
Trimethoprim sulfametoxazole (SXT)	78	63.41
Chloramphenicol (C)	38	30.89
Gentamicin (GEN)	52	42.27
Tobramycin (TM)	64	52.03
Kanamycin (K)	70	56.91
Netilmicin (NET)	51	41.46

Table 2. Antibiotic resistance profile of *S. aureus* according to the types of samples.

Antibiotic	Urine (%)	Pus (%)	Sperm (%)	Genital (%)	Blood (%)	Catheter (%)
Pen G	92.68	97.14	100	88.88	100	100
OXA	53.65	42.85	59.25	33.33	14.28	75.00
AMX	65.85	68.57	74.07	66.66	57.14	100
AMC	53.65	51.42	66.66	55.55	28.57	75.00
CTX	88.48	91.42	100	100	100	100
CXM	88.48	80.00	96.29	77.77	57.14	100
FOX	88.48	77.14	96.29	66.66	28.57	100
CIP	28.17	40.00	55.55	55.55	28.57	75.00
OFX	41.46	51.42	33.33	22.22	14.28	100
SP	19.51	42.85	25.92	11.11	71.42	50.00
L	17.07	40.00	14.81	0.00	14.28	75.00
PT	7.31	0.00	3.70	0.00	0.00	0.00
E	39.02	31.42	25.92	55.55	42.85	50.00
SXT	68.29	51.42	66.66	66.66	57.14	100
C	21.95	40.00	29.62	44.44	0.00	75.00
FT	9.75	NA	NA	NA	NA	NA
GEN	28.17	34.28	55.55	33.33	14.28	25.00
TM	53.65	40.00	62.96	66.66	42.85	50.00
K	63.41	45.71	66.66	66.66	28.57	50.00
NET	46.34	31.42	22.22	55.55	28.57	50.00

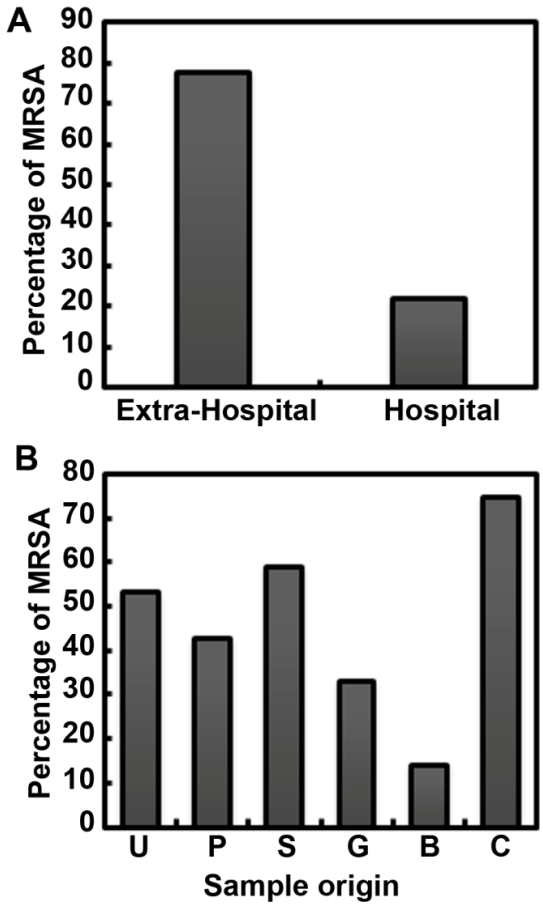

Figure 2. Distribution of methicillin-resistant *S. aureus* (MRSA) based on sample provenance. (A): MRSA registered from extra-hospital and hospital based samples. (B): MRSA registered according to the type of samples. U, Urinal sample; P, pus sample; S, sperm sample; G, genital sample; B, blood sample; C, catheter sample.

Table 3. Toxin profile of *S. aureus* according to the type of samples.

Toxins produced by *S. aureus*	Urine (41)*	Pus (35)*	Sperm (27)*	Genital (9)*	Blood (7)*	Catheter (4)*
PVL (%)	7.31	20	0	0	57.14	0
ETA (%)	0	0	0	0	0	0
ETB (%)	0	0	0	0	0	0
LukE-LukD (%)	0	14.28	0	0	0	0

*Number in parenthesis represents the number of *S. aureus* isolated from indicated biological samples.

(after *E. coli*) reported among older patients hospitalized with bacteremia that was acquired either in the community or hospital (McBean and Rajamani, 2001).

As revealed in Table 1, the *S. aureus* isolates displayed a wide range of antibiotic susceptibility to antimicrobial. Our findings are in agreement with previously reported data on the effects of antibiotics on clinically isolated *S. aureus* (Shittu and Lin, 2006; Denton et al., 2008, Elahari et al., 2009). The bacterial colonies were highly resistant to the AMC, AMX, FOX, CTX and CXM antibiotic family. This might be due to the fact that certain classes of antibiotics are easily accessible and frequently used by

the patients without medical prescription in Benin. The self medication mediating bacterial resistance to antibiotics has been widely reported in Africa (Sow et al., 1993; Kesah et al., 2003; Randrianirina et al., 2007; Diekema et al., 2001; Elazhari et al., 2009). Several MRSA colonies were lately described in France, but the epidemiology of MRSA is poorly understood (Dauwalder et al., 2008). We observed about 48.78% of MRSA from hospitalized patients and about 78% of MRSA from community patients. This high antimicrobial resistance profile might be due to auto-medication of the community patients. This bacterial resistance occurrence is highly reduced (36% in Ireland in 1999, with only 14.28% of MRSA from blood sample) where auto-medication is not allowed (McDonald et al., 2003).

The pathogenicity of *S. aureus* colonies has been related to a wide range of toxin productions. In agreement with our previous report, 11.3% of *S. aureus* isolated in this study produced PVL (Baba-Moussa et al., 1999). The PVL producing *S. aureus* are classically associated with primitive skin infections, notably the furuncles (Couppie et al., 1994; Durupt et al., 2007). In our study, only 4.06% of bacterial colonies tested produced the leucotoxin lukE-lukD (Table 3). These lukE-lukD producing *S. aureus* were all isolated from the pus. This weak rate of lukE-lukD production is not surprising if we assume that lukE-lukD plays an important role in the occurrence of diarrheic infections (Gravet et al., 1998). In fact, 93.6% of *S. aureus* isolated from older patient concerned by post-antimicrobial diarrhea produced lukE-lukD toxin (Gravet et al., 2001). In our study, no *S. aureus* colony produced epidermolysins A and B (ETA and ETB). However, sample screening studies done in Guyane proved that 93% of *S. aureus* originating from impetigo infections produced epidermolysin (Couppie et al., 1998). In addition, 3.25% of *S. aureus* tested produced PVL as well as leucotoxin lukE-lukD. The PVL and lukE-lukD producing *S. aureus* were only isolated from pus samples, suggesting that these toxins target different cell types such as the polynuclears, neutrophils, the monocytes and the macrophages that can easily be found in this type of infection (Gravet et al., 1998).

Until recently, cases of *S. aureus* resistant to penicillin M and sometimes to other antibiotics have been rarely recorded outside the hospitals or medical centers. Our study shows a strong prevalence of community based *S. aureus* colonies that are resistant to methicillin. Evidently, this bacterial germ has nowadays widened its infectious territories. The infections linked to MRSA outside hospital environment have been frequently reported in the USA (Fridkin et al., 2005). However, a screening study conducted at the Centers for Disease Control and Prevention (CDC) appearing in the New England Journal of Medicine, revealed that MRSA infections have been frequently reported among people that have never been admitted in hospital or in contact with hospital environment in a period of one year. Our study shows a variability of toxins produced by *S. aureus* isolated from various types of infections. Interestingly, the production of toxins combined with antibiotic resistance of the bacteria can easily result into disease complication or even death of the patients if appropriate antibiotics are not administered in time.

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