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Full Length Research Paper

Antimicrobial resistance of *Staphylococcus aureus* isolated from human and food against Linezolid, Quinupristin-Dalfopristin, Quinolones and Imipenem

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Staphylococcus aureus **is a versatile pathogen of humans and animals that has evolved resistance to all classes of antimicrobials. A total of 293** ***S. aureus*** **isolates including 71 obtained from human and 222 recovered from food against crucial antimicrobial agents used in human and veterinary practice were examined for the antimicrobial resistance profiles. The** ***in vitro*** **activities of new agents (linezolid and quinupristin-dalfopristin), quinolones (ofloxacin, norfloxacin, levofloxacin, moxifloxacin) and imipenem against the isolates were performed by standard disk diffusion method. The 293 isolates demonstrated very low levels of resistance to imipenem (0.7%), followed by quinupristin-dalfopristin (1.7%) but had the highest activity against linezolid (6.8%) and moxifloxacin (5.5%). Over 9.9% of clinical isolates showed resistance to three or more antimicrobial agents. Only 1.8% of food isolates were multidrug resistant (≥3 antibiotics). The differences between clinical and food isolates in the results of antimicrobial resistance were statistically significant. Besides, comparing the resistance to each antimicrobial agent between the two group isolates, there were statistically significant differences (*** P **<0.05). Because** ***S. aureus*** **has a remarkable propensity to develop or acquire resistance to antimicrobial agents, it is important to continually monitor antimicrobial susceptibilities of isolates from clinical and food sources.**

Key words: *Staphylococcus aureus*, antimicrobial resistance, clinical and food isolates, linezolid, quinupristin-dalfopristin, quinolones, imipenem.

INTRODUCTION

Staphylococcus aureus causes a wide variety of diseases in humans, ranging from clinical to food-borne infections in varying degrees of severity (De Buyser et al., 2001; Enright, 2003; Le Loir et al., 2003). The primary habitat of *S. aureus* is animal skin and nasal mucosae of humans. It is a significant cause of wide range of infectious diseases in humans which involves the skin, and they include furuncules, cellulitis, impetigo, and postoperative wound infections of various sites. Some of the more serious infections produced by *S. aureus* are bacteremia, pneumonia, toxic shock syndrome, osteomyelitis, endocarditis and food poisoning (Murray et al., 1999). Staphylococcal food poisoning (SFP) is a very common disease which is a widespread cause of gastroenteritis worldwide. Some isolates of *S. aureus* produce staphylococcal enterotoxins (SEs) that may cause food poisoning if food containing one or more preformed SEs is ingested (Dinges et al., 2000; Le Loir et al., 2003). Symptoms of SFP emerge within a few hours (from 30 min to 8 h) and may include vomiting, nausea, diarrhea and abdominal cramps (Le Loir et al., 2003).

In recent decades, antimicrobial resistance has been a major public health problem. The use and misuse of

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antimicrobial agents in human medicine and food producing animals has led to a relentless rise in the number and types of resistant microorganisms to the antimicrobial agents (WHO, 2001). The resistance may also be due to the persistent circulation of resistant strains of bacteria in the environment and the possible contamination of water and food (Enright, 2003).

Among the Gram-positive microorganisms, staphylococci are the most frequently resistant ones to antibiotics. *S. aureus* may develop resistance to various antimicrobial agents through different ways. Since *S. aureus* is genetically versatile, it plays an important role in the formation of this resistance. The spread of multidrug-resistant staphylococci in the community or hospital is a great threat to public health (Enright, 2003; Lina et al., 1999). Therefore, there is an urgent need for novel antimicrobial agents as alternatives in the treatment of infections caused by these multidrug-resistant Gram-positive bacteria (Von Eiff et al., 2000; Luh et al., 2000; Betriu et al., 2001).

Linezolid is a member of a new class of synthetic agents known as oxazolidinones, which it has excellent activity against a variety of Gram-positive bacteria (Luh et al., 2000; Jevitt et al., 2003). Quinupristin-dalfopristin is a new streptogramin and used for the treatment of infections caused by Gram-positive cocci including multidrug-resistant isolates of staphylococci, streptococci, and *Enterococcus faecium* (Von Eiff et al., 2000; Betriu et al., 2000; Jevitt et al., 2003). Quinolones exhibit potent antibacterial activity by targeting DNA gyrase and topoisomerase IV. These enzymes are essential to all bacterial species for their growth and survival. It has been reported in recent years that resistance of staphylococci to quinolones has increased at extraordinary rate (George et al., 1990; Roychoudhury et al., 2001). Carbapenems such as imipenem have the broadest spectrum of all β-lactams. Carbapenem resistance remains extremely rare but increasing resistance to other β-lactams promotes increasing carbapenem usage (Livermore and Woodford, 2000).

Antimicrobial resistance pattern of *S. aureus* to quinolones and new agents has been investigated in *S. aureus* in various clinical studies (Sader et al., 2001; Jevitt et al., 2003; Madhusudhan et al., 2003; Jorgen et al., 2007; Hidalgo et al., 2008; Jacobs et al., 2009; Japoni et al., 2010), whereas less information has been reported on antimicrobial activity of these agents in food isolates (White et al., 2003; Baek et al., 2009).

The objective of this study was to evaluate the *in vitro* antimicrobial activities of new agents (linezolid and quinupristin-dalfopristin), quinolones (ofloxacin, norfloxacin, levofloxacin, and moxifloxacin) and imipenem, commonly used crucial antimicrobial agents in human medicine and veterinary practice, against clinical and food isolates of *S. aureus.* The study also aims to compare the antimicrobial resistance profiles between the isolates of human and food origins and to monitor the antimicrobial resistance both in food and clinical isolates.

MATERIALS AND METHODS

Bacterial isolates

In the study, a total of 293 *S. aureus* isolates including 222 isolates recovered from cheese samples and 71 isolates obtained from various clinical specimens were used to examine for the antimicrobial resistance profiles against crucial antimicrobial agents. The clinical isolates were collected from a wide range of infections. They were from throat and nasal swabs, wounds, urine, blood, and catheters. All of the clinical and food isolates tested were derived from our stock culture collection stored at -80°C in the glycerol. The *S. aureus* isolates were grown aerobically at 37°C for 24 h in Brain Heart Infusion (BHI, Merck, Darmstadt, Germany) broth and maintained on BHI agar.

Antimicrobial susceptibility testing

Antimicrobial susceptibility tests were performed by the Kirby-Bauer disc diffusion method following the recommendations of the Clinical and Laboratory Standards Institute (CLSI, 2006) on Mueller-Hinton agar plates (Merck). Two or three identical colonies were picked from the plate and transferred to the Mueller Hinton broth (Merck). The inoculum density was adjusted according to a 0.5 McFarland standard turbidity. Then a cotton swab dipped in the inoculum suspension was swabbed over the entire surface of agar. After incubation at 37°C for 24 h, zone diameter around the disk was measured and isolates were classified as susceptible, intermediately resistant and resistant as defined in CLSI. Specifically, disks used for determination of susceptibility of *S. aureus* isolates were new agents; linezolid (30 µg) and quinupristin-dalfopristin (15 µg), quinolones; ofloxacin (5 µg) and norfloxacin (10 µg) as the second generation, levofloxacin (5 µg) as the third generation, moxifloxacin (5 µg) as the fourth generation and imipenem (10 µg). All antibiotic disks used were provided from Oxoid (Basingstoke, Hampshire, UK). *S. aureus* ATCC 6538 (MicroBiologics, St. Cloud, Minnesota, USA) was used as reference strain.

Data analysis

Differences in antimicrobial resistance profiles between the isolates of food and clinical origin and comparison of resistance to each antimicrobial agent between these two groups were assessed by the Chi-square test. Differences were considered to be statistically significant for $P < 0.05$.

RESULTS

A total of 293 *S. aureus* isolates, 222 obtained from food samples and 71 recovered from various clinical specimens, were tested to determine the antimicrobial resistance profiles to clinically crucial antimicrobial agents including new agents (linezolid and quinupristin-dalfopristin), quinolones (ofloxacin, norfloxacin, levofloxacin, and moxifloxacin) and imipenem. The 293 *S. aureus* isolates generally demonstrated very low levels of resistance to imipenem (0.7%), followed by quinupristin-dalfopristin (1.7%). Overall, the results of the

antimicrobial susceptibility of food and clinical isolates which were interpreted as resistant, intermediate or susceptible to antibiotics are summarized in Table 1.

The results of the present study indicated that a total of 23.9% of 71 clinical *S. aureus* isolates were resistant to at least one or more antimicrobial agents, but 9.9% of clinical isolates showed multiple resistances (≥3 antibiotics). Among 222 isolates of food origin, 8.6% were seen individual resistance (≥1 antibiotics). The multiple resistances to three or more antimicrobial drugs were also found in 1.8% of food isolates (Table 2). Furthermore, the distribution of the number of resistant *S. aureus* isolated from different origins against one or more antimicrobial agents tested were represented in Table 3.

According to the results of statistical analysis, the antimicrobial resistance rates in *S. aureus* isolated from two different origins (human and food) were significantly different ($P<0.05$). In other words, the clinical *S. aureus* isolates had a significantly more resistance to the antimicrobial agents tested compared to the resistance of the food isolates. Besides, comparing the resistance to each antimicrobial agent between the isolates of food and clinical origin, significant differences were found statistically ($P<0.05$). In fact, the frequencies of resistance of *S. aureus* to linezolid, quinupristin-dalfopristin, and imipenem between these two groups were statistically similar ($P>0.05$), but the resistance of quinolones was significantly different, which clinical isolates to quinolones demonstrated a higher resistance frequency ($P<0.05$).

DISCUSSION

Bacterial resistance to antimicrobial agents is an increasing problem in the treatment of bacterial infections. Antimicrobial resistance among Gram-positive bacteria, particularly staphylococci, has complicated the treatment of infections due to these organisms. As a result of the increase in antimicrobial resistance, new chemical compounds have been developed. Linezolid and quinupristin-dalfopristin are important new antimicrobials that possess enhanced activity against multidrug-resistant Gram-positive pathogens which cause infections (Livermore, 2000; Allen et al., 2002). In the present study, linezolid showed *in vitro* activity against 7.0% of clinical isolates and 6.8% of food isolates. Quinupristin-dalfopristin, the other new agent tested, had an excellent activity (100%) against all staphylococcal clinical isolates whereas 2.3% of food isolates were resistant to quinupristin-dalfopristin. But, there was no statistically significant difference between the isolates of food and clinical origin related to the resistance to both linezolid and quinupristin-dalfopristin ($P>0.05$).

In the clinical *S. aureus* isolates, the activities of the new agents were reported in different studies. The susceptibility rates of *S. aureus* recovered from nosocomial infections to linezolid and quinupristin-dalfopristin were 100% and 99.8% (Sader et al., 2001). Jevitt et al. (2003) noted that 87 (99%) staphylococcal isolates were susceptible to linezolid, and quinupristin-dalfopristin showed the best activity against all staphylococcal isolates. In a previous study, all clinical *S. aureus* isolates were susceptible to linezolid and quinupristin-dalfopristin (Jorgen et al., 2007). Gales et al. (2009) also reported linezolid was very active against all isolated *S. aureus* from various clinical specimens in the Brazilian hospitals. A report from Germany showed that no *S. aureus* isolate from clinical samples appeared to be resistant to quinupristin-dalfopristin (Von Eiff et al., 2000). Nonetheless, resistance to quinupristin-dalfopristin in 6.9% of clinical *S. aureus* isolates has been reported in France (Lina et al., 1999). Our antimicrobial resistance results to quinupristin-dalfopristin are similar to the results of previously published studies mentioned above, but slightly different to linezolid, with 7% of resistant isolates.

Antimicrobial susceptibility of *S. aureus* isolated from various food samples to new agents (linezolid and quinupristin-dalfopristin) has been investigated only in several countries. New agents showed good activity against *S. aureus* isolated from frozen food samples collected in Korea (Baek et al., 2009). White et al. (2003) also reported that all *S. aureus* isolated from commercial broilers in northeastern Georgia were susceptible to linezolid and quinupristin-dalfopristin. The results of our study indicated that the new agents also exhibited good activity against the *S. aureus* isolates from food samples.

Quinolones are important antimicrobials for the treatment of a variety infections caused by Gram-positive pathogens. In our study, the susceptibility rates of quinolones such as levofloxacin and moxifloxacin against *S. aureus* recovered from clinical specimens were similar to the results of the study of Jacobs et al. (2009) which indicated considerably high susceptibility levels to moxifloxacin (89.4%) and levofloxacin (89.2%) in *S. aureus* isolates. A report noted that resistance rate of *S. aureus* isolates to moxifloxacin was 52.6% whereas it was 87.5% in methicillin-resistant *S. aureus* isolates (Hidalgo et al., 2008). Our findings are dissimilar to the results of study published in USA (Madhusudhan et al., 2003) in which the ineffectiveness of fluoroquinolones for treating coagulase-positive *S. aureus* was demonstrated by poor *in vitro* susceptibility rates with levofloxacin (52%) and moxifloxacin (57%). The quinolone antimicrobials are one of the most useful drugs used in human and animal medicine because of their high potency, broad spectrum of activity and potentially low incidence of side effects. But, recently concerns have been aroused over the possible emergence of quinolone-resistant strains and the effects on the environment if such drugs are over-used. The problem of quinolone resistance is trying to be solved with the help of the newly developed quinolone derivatives which exhibits enhanced activity against Gram-positive bacteria (Roychoudhury et al., 2001;

Table 1. Antimicrobial susceptibility patterns of new antimicrobial agents, quinolones and imipenem against the isolates of *S. aureus* originating from clinical and food samples.

Antimicrobial agents	Clinical isolates (n=71)			Food isolates (n=222)		
	R	I	S	R	I	S
Linezolid	5 (7)	0 (0)	66 (93)	15 (6.8)	0 (0)	207 (93.2)
QD	0 (0)	3 (4.2)	68 (95.8)	5 (2.3)	9 (4.1)	208 (93.7)
Ofloxacin	6 (8.5)	3 (4.2)	62 (87.3)	3 (1.4)	3 (1.4)	216 (97.3)
Norfloxacin	7 (9.9)	2 (2.8)	62 (87.3)	4 (1.8)	2 (0.9)	216 (97.3)
Levofloxacin	6 (8.5)	1 (1.4)	64 (90.1)	4 (1.8)	1 (0.5)	217 (97.7)
Moxifloxacin	11 (15.5)	1 (1.4)	59 (83.1)	5 (2.3)	1 (0.5)	216 (97.3)
Imipenem	2 (2.8)	0 (0)	69 (97.2)	0 (0)	0 (0)	222 (100)

n, number of isolates tested; R, resistant; I, Intermediate; S, susceptible; QD, Quinupristin-dalfopristin.

Table 2. Resistance percentages of new antimicrobial agents, quinolones and imipenem against all *S. aureus* isolates of clinical and food samples (n=293).

Antimicrobial agents	Number of resistant isolates	Percentage
Linezolid	20	6.8
Quinupristin-dalfopristin	5	1.7
Ofloxacin	9	3.1
Norfloxacin	11	3.8
Levofloxacin	10	3.4
Moxifloxacin	16	5.5
Imipenem	2	0.7
Resistance to ≥1 antibiotic	19[b]	8.6
Multi-resistance[a]	4[b]	1.8
Resistance to ≥1 antibiotic	17[c]	23.9
Multi-resistance[a]	7[c]	9.9

n, number of the isolates tested; [a], resistance to at least 3 different antimicrobial agents; [b], number of resistant food isolates; [c], number of resistant clinical isolates.

Table 3. Antimicrobial resistance profiles of 293 *S. aureus* isolates of clinical and food samples.

Antimicrobial resistance profile	Number of antimicrobials	No. (%) of isolates with a specific profile	
		Clinical (n=71)	Food (n=222)
OFX-NOR-LEV-MXF-IPM	5	2 (2.8)	
OFX-NOR-LEV-MXF-LZD	5		2 (0.9)
OFX-NOR-LEV-MXF	4	1 (1.4)	1 (0.5)
NOR-MXF-LZD	3	1 (1.4)	
NOR-LEV-MXF	3	1 (1.4)	1 (0.5)
OFX-NOR-MXF	3	1 (1.4)	
OFX-LEV-MXF	3	1 (1.4)	
OFX-NOR	2	1 (1.4)	
LZD-QD	2		2 (0.9)
NOR-QD	2		1 (0.5)
MXF-QD	2		1 (0.5)
LEV	1	1 (1.4)	
MXF	1	4 (5.6)	
LZD	1	4 (5.6)	10 (4.5)
QD	1		1 (0.5)

OFX, ofloxacin; NOR, norfloxacin; LEV, levofloxacin; MOX, moxifloxacin; LZD, linezolid; QD, Quinupristin-dalfopristin; IPM, imipenem.

Schmitz et al., 2002). In our study, the resistance rates between the quinolone antimicrobials to *S. aureus* isolates originating from food and clinical samples were comparable and low levels. Even, interestingly, one of the newer generations of fluoroquinolones, moxifloxacin had slightly low activity to clinical isolates of *S. aureus* among quinolones tested in the present study.

Carbapenems remain the most powerful beta-lactams and carbapenemase-mediated resistance remains extremely rare. According to our results, imipenem showed excellent activity to a total of clinical and food isolates of *S. aureus*, only with a rate of 0.7% of resistant isolates. Carbapenems are stable and retain activity against various pathogens bacteria. Imipenem is one of the most reliable antimicrobial drugs for treatment of infections today, since there was virtually no development of antimicrobial resistance to it (Livermore and Woodford, 2000; Ishihara et al., 2002).

In conclusion, resistance to antimicrobial agents is an increasing and serious problem. This problem may partly be solved promoting the prudent use of antimicrobials for therapeutic or prophylactic purpose in human and animals. The present study is significant that it indicates and compares the antimicrobial resistance profiles of *S. aureus* isolates originating from food and clinical samples to new agents such as linezolid and quinupristin-dalfopristin, quinolones and imipenem. In this research, despite we have found low levels of the antimicrobial resistance or multidrug resistant isolates among the food and clinical isolates to crucial antimicrobial agents, a possible monitoring of antimicrobial susceptibilities of important pathogen *S. aureus* may be important in helping the choice of antibiotic to control infections in human medicine and veterinary practice.

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