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Daptomycin susceptibility of clinical isolates in invasive *Staphylcoccus aureus* infections in Korean hospitals: can resistance to daptomycin occur without previous exposure?

Joo-Hee Hwang[1], Eun Young Nam[1,2] Soo-Jin Yang,[3] Eu Suk Kim[1,2], Kyung-Hwa Park,[4] Sook-In Jung,[4] Nara Yoon,[5] Dong-Min Kim,[5] Chang-Seop Lee,[6] Hee-Chang Jang,[7] Yoonseon Park,[8] Kkot Sil Lee,[9] Yee Gyung Kwak,[10] Jae Hoon Lee,[11] Seong Yeon Park,[12] Moonsuk Kim,[1,2] Kyoung-Ho Song,[1,2] Hong Bin Kim,[1,2] and Korea INfectious Diseases (KIND) study group

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea [2]Department of Internal Medicine, National University College of Medicine, Seoul, Republic of Korea [3]SeoulSchool of Bioresources and Bioscience, Chung-Ang University, Anseong, Republic of Korea [4]Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Republic of Korea [5]Department of Internal Medicine, Chosun University Hospital, Gwangju, Republic of Korea [6]Department of Internal Medicine, Chonbuk National University Hospital, Jeonju, Republic of Korea [7]Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea [8]Department of Internal Medicine, National Health Insurance Corporation Ilsan Hospital, Goyang, Republic of Korea [9]Department of Internal Medicine, Seonam University Myongji Hospital, Goyang, Republic of Korea [10]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Republic of Korea [11]Department of Internal Medicine, Wonkwang University Hospital, Iksan, Republic of Korea [12]Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang, Republic of Korea

Contact Information
Eu Suk Kim, MD
Seoul Nat'l Univ. Bundang Hospital.
173 Gumi-ro, Bundang-gu, Seongnam.
463-707, Republic of Korea
Tel: 82-31-787-7021,
Fax: 82-31-787-4052
E-mail: eskim@snu.ac.kr

Abstract

BACKGROUND
It was suggested that daptomycin non-susceptibility in *Staphylococcus aureus* can be induced by vancomycin exposure in vitro and in vivo without daptomycin exposure. To prove this, we conducted a multicenter study in a large scale to evaluate whether daptomycin non-susceptibility can occur in the isolates from Korean patients with invasive *S. aureus* (ISA) infection who have never been exposed to daptomycin.

METHODS
We selected potential daptomycin-resistant isolates from *S. aureus* collection in the previous prospective study for ISA infections which was performed from July 2009 to June 2011 at 10 hospitals in Korea. Potential daptomycin resistant *S. aureus* isolates were defined as follows: 1) heteroresistant vancomycin-intermediate *S. aureus* (h-VISA), 2) *S. aureus* strain with vancomycin minimal inhibitory concentration (MIC) more than 1.5 ug/mL by Etest or brothmicrodilution (BMD), 3) persistent *S. aureus* bacteremia for 7 days or more. Vancomycin MICs were determined by the BMD and Etest, and daptomycin MICs by Etest. Clinical characteristics were collected and multilocus sequence typing was performed for the daptomycin non-susceptible *S. aureus* strains.

RESULTS
A total of 208 non-duplicate *S. aureus* isolates from the cases of ISA infections, of which 171 was MRSA were screened for daptomycin non-susceptibility by Etest. Among these, 124 showed vancomycin MICs more than 1.5 ug/mL, 93 persistent bacteremia, and 42 h-VISA with overlaps. Five *S. aureus* isolates with daptomycin non-susceptibility (MIC >1 ug/mL) were detected. These were isolated from patients without previous vancomycin exposure. All of them had healthcare associated (HA) infections and underwent surgery within recent one year. All but one of these patients had catheter-associated bloodstream infections or surgical site infections (Table).

CONCLUSION
Daptomycin non-susceptible *S. aureus* is extremely rare in Korea where daptomycin is not commercially available yet. However, this study showed that daptomycin resistance in HA-ISA infections can develop without previous exposure to daptomycin or vancomycin.

Introduction

- **Daptomycin**
  - a cyclic lipopeptide
  - has potent bactericidal effects against gram positive organisms including MSSA or MRSA
  - Indicated in Skin and soft tissue infection (SSTI, bacteremia including endocarditis, bone and joint infection (BJI)
- **daptomycin non-susceptibility in *Staphylococcus aureus***
  - can be induced by vancomycin exposure
  - in vitro and in vivo without daptomycin exposure
- we conducted a multicenter study in a large scale to evaluate whether daptomycin non-susceptibility can occur in the isolates from Korean patients with invasive *S. aureus* (ISA) infection who have never been exposed to daptomycin.

Methods

- Performed from July 2009 to June 2011 at 10 hospital in Korea
- Potential daptomycin resistant *S. aureus* isolates were defined

1) heteroresistant vancomycin-intermediate *S. aureus* (h-VISA)
2) *S. aureus* strain with vancomycin minimal inhibitory concentration (MIC) more than 1.5 ug/mL by Etest or brothmicrodilution (BMD)
3) persistent *S. aureus* bacteremia for 7 days or more

- Vancomycin MICs were determined by
  - the BMD
  - Etest
- daptomycin MICs by
  - Etest
- Clinical characteristics were collected
- multilocus sequence typing was performed for the daptomycin non-susceptible *S. aureus* strains

Conclusion

Daptomycin non-susceptible *S. aureus* is extremely rare in Korea where daptomycin is not commercially available yet. However, five *S. aureus* isolates with daptomycin non-susceptible (0.48%) were detected by Etest in our study. This showed that daptomycin resistance in HA-ISA infections can develop without previous exposure to daptomycin or vancomycin.

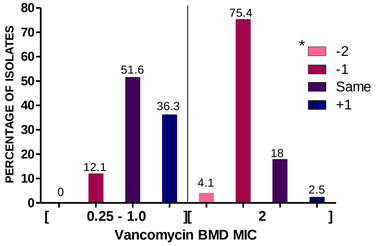

Figure 2. Percentage of discrepant Etest MICs stratified according to the MICs values * Differences ($\pm$ $\log_2$ dilution)

Results

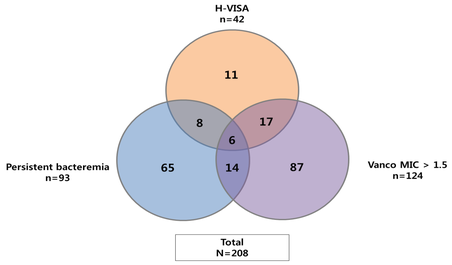

Figure 1. Distribution of invasive *Staphylococcus aureus* isolated from blood

Table. Clinical and microbiological characteristics of daptomycin non-susceptible invasive *Staphylococcus aureus* infections in Korea

Patient	Age (y) /sex	h-VISA	Persistent bacteremia (>7 days)	Vancomycin MIC >1.5 ug/mL BMD	Vancomycin MIC >1.5 ug/mL Etest	Daptomycin MIC Etest	ST	Location	Previous vancomycin exposure (<1 m)	Operation (<1 y)	Primary foci	Underlying disease(s)	Treatment	30-day mortality
1	39/M	Yes	Yes	2	3	1.5	5	HA	No	Yes	Mediastinitis (SSI)	Chronic liver disease	vancomycin and rifampin	Yes
2	57/M	No	Yes	1	1.5	1.5	72	HA	No	Yes	BJI (SSI)	Malignancy	vancomycin and rifampin	No
3	70/F	Yes	No	2	1.5	2	5	HA	No	Yes	CA-BSI	DM	vancomycin	No
4	75/M	Yes	No	2	1.5	1.5	5	HA	No	Yes	Unknown	Malignancy	teicoplainin and piperacillin-tazobactam	Yes
5	59/F	No	No	2	1.5	2	5	HA	No	Yes	CA-UTI	Malignancy	vancomycin	No

h-VISA, heteroresistant vancomycin-intermediate *Staphylocccus aureus*; MIC, minimal inhibitory concentration; BMD, broth microdilution; ST, sequence type; HA, healthcare-associated; SSI, surgical site infection; BJI, bone and joint infection; CA-BSI, catheter-associated blood stream infection; DM, diabetes mellitus; CA-UTI, catheter-associated urinary tract infection