International Journal of Antimicrobial Agents 41 (2013) 578–581

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Short communication

Glycopeptide minimum inhibitory concentration creep among meticillin-resistant *Staphylococcus aureus* from 2006–2011 in China

Chao Zhuo[a,*], Ying-chun Xu[b], Shu-nian Xiao[a], Guang-yan Zhang[c], Nan-Shan Zhong[a]

[a] *State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou, China*
[b] *Peking Union Medical College Hospital, Beijing, China*
[c] *Chengdu 7th People's Hospital, Chengdu, China*

ARTICLE INFO

Article history:
Received 30 April 2012
Accepted 11 February 2013

Keywords:
Staphylococcus aureus
Teicoplanin
Vancomycin
Linezolid
Minimum inhibitory concentration
Creep

ABSTRACT

Vancomycin minimum inhibitory concentration (MIC) creep has recently been demonstrated by many countries but is rarely reported in China. In this study, a total of 1411 meticillin-resistant *Staphylococcus aureus* (MRSA) isolates were collected from six hospitals in China during the period 2006–2011 and the MICs of vancomycin, teicoplanin and linezolid were determined by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) guidelines. MIC_{50} and MIC_{90} values (MICs required to inhibit the growth of 50% and 90% of organisms, respectively) as well as geometric mean (GM) MICs were calculated for all isolates in each year, and MIC creep for the drugs was evaluated. All of the MRSA isolates were susceptible to vancomycin and linezolid. Overall, the vancomycin GM MIC of MRSA isolates was 0.906, 0.952, 0.956, 0.947, 1.013 and 1.040 mg/L, with a significantly increasing trend over the years ($P < 0.001$). Percentages of MRSA isolates with a vancomycin MIC above 1 μg/mL (2 μg/mL ≥ MIC > 1 μg/mL) were 26.0%, 23.5%, 21.6%, 27.8%, 30.6% and 42.8% from 2006–2011, respectively, and increased over time ($P < 0.005$). The teicoplanin GM MIC increased rapidly from 0.749 mg/L in 2008 to 0.973 mg/L in 2011, and ca. 5% of isolates were resistant to teicoplanin in the period according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. MIC shifts were not found for linezolid ($P > 0.05$). In conclusion, a tendency towards decreasing susceptibility to glycopeptides in MRSA has emerged in China.

1. Introduction

Glycopeptides such as vancomycin remain a front-line drug for the treatment of meticillin-resistant *Staphylococcus aureus* (MRSA) infections. However, loss of susceptibility, characteristically involving an increase in vancomycin minimum inhibitory concentrations (MICs) to above 1.5 mg/L, is associated with treatment failure [1]. Several studies have demonstrated that the mean vancomycin MIC in MRSA has increased in recent years, referred to as 'MIC creep' [2–5]. To the best of our knowledge, no studies have examined the MIC creep phenomenon in China, although the incidence of heterogeneous vancomycin-intermediate *S. aureus* (hVISA) correlating with an increase of vancomycin MIC was reported by Chen et al. in 2011 [6]. Thus, the aim of this study was to analyse the vancomycin MIC distribution in MRSA isolates obtained from six hospitals over a 6-year period in southern China and to determine MIC trends of these isolates to teicoplanin and linezolid.

2. Materials and methods

2.1. Micro-organisms

A total of 1411 clinical MRSA isolates collected from six hospitals were submitted to the MOH National Antimicrobial Resistance Investigation Net (Mohnarin) programme from January 2006 to December 2011. Only the first isolate per patient was tested in this study. Isolates were recovered from various clinical sources, including the respiratory tract ($n = 947$), secretions ($n = 212$), blood ($n = 106$), pus and wounds ($n = 54$), drainage ($n = 25$), urine ($n = 16$), abdominal fluid ($n = 15$) and other sources ($n = 36$). All isolates were stored at −80 °C until MIC testing was performed.

2.2. Antimicrobial susceptibility testing

MICs were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [7] with some modifications. For vancomycin and teicoplanin, the precise incremental dilutions method reported by Sader et al. [4] was used, comprising 15 dilution steps of vancomycin ranging from 0.125 mg/L to 8 mg/L (0.125, 0.25, 0.50, 0.625, 0.75, 0.875, 1, 1.125,

* Corresponding author. Present address: 1 Kangda Road, Guangzhou 510230, China. Tel.: +86 20 3429 5505; fax: +86 20 3429 5505.
E-mail addresses: chao_sheep@263.net, chaosheep@sina.com (C. Zhuo).

0924-8579/$ – see front matter © 2013 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.
http://dx.doi.org/10.1016/j.ijantimicag.2013.02.014

Table 1
Susceptibility of meticillin-resistant *Staphylococcus aureus* (MRSA) in China, 2006–2011.

Antimicrobial agent	Year	No. of isolates	MIC (mg/L)				Susceptibility (%)	
			GM	MIC_{50}	MIC_{90}	Range	CLSI	EUCAST
Vancomycin	2006	192	0.906	1	1.5	0.25–2.0	100	100
	2007	284	0.952	1	1.5	0.25–2.0	100	100
	2008	305	0.956	1	1.5	0.25–2.0	100	100
	2009	187	0.947	1	1.5	0.375–2.0	100	100
	2010	242	1.013	1	1.5	0.375–2.0	100	100
	2011	201	1.040	1	1.5	0.125–2.0	100	100
	Total	1411	0.968	1	1.5	0.125–2.0	100	100
Teicoplanin	2006	192	0.712	0.5	1	0.5–2	100	100
	2007	284	0.739	0.5	2	0.5–4	100	100
	2008	305	0.749	0.5	2	0.5–4	100	96.4
	2009	187	0.743	0.5	2	0.5–4	100	96.8
	2010	242	0.768	0.5	2	0.5–4	100	95.0
	2011	201	0.973	1	2	0.5–4	100	94.5
	Total	1411	0.773	0.5	2	0.5–4	100	96.8
Linezolid	2006	192	1.461	2	2	0.5–4	100	100
	2007	284	1.414	1	2	0.5–4	100	100
	2008	305	1.422	1	4	0.5–4	100	100
	2009	187	1.386	1	2	0.5–4	100	100
	2010	242	1.41	1	2	0.5–4	100	100
	2011	201	1.221	1	2	0.125–4	100	100
	Total	1411	1.388	1	2	0.125–4	100	100

MIC, minimum inhibitory concentration; GM, geometric mean; $MIC_{50/90}$, MICs required to inhibit the growth of 50% and 90% of organisms, respectively; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

1.25, 1.375, 1.5, 1.75, 2.0, 4.0 and 8.0 mg/L) and 14 dilution steps of teicoplanin ranging from 0.06 mg/L to 16 mg/L (0.06, 0.12, 0.25, 0.50, 0.625, 0.75, 0.875, 1, 1.125, 1.25, 1.5, 2.0, 4.0 and 8.0 mg/L). For linezolid, the two-fold dilutions method with a concentration range of 0.25–16 mg/L in seven dilutions was employed. Differences in aggregate susceptibility were evaluated between 2010 European Committee on Antimicrobial Susceptibility Testing (EUCAST) and CLSI M100-S20 criteria [7,8]. Quality controls were performed by each testing site on each day of testing using *S. aureus* ATCC 29213 according to CLSI guidelines.

2.3. Data analysis

MIC_{50} and MIC_{90} values (MICs required to inhibit the growth of 50% and 90% of organisms, respectively), the MIC range, the geometric mean (GM) MIC, MIC distribution, and percentage susceptible and resistant were evaluated using WHONET 5.4 software (http://www.who.int/drugresistance/whonetsoftware/en/).

2.4. Statistical analysis

Statistical analysis was carried out using SPSS v.17.0 software (SPSS Inc., Chicago, IL). For analysis of MIC trends over time, non-parametric correlation (Spearman's *r*) was used. For comparison of GM MICs among groups, the Kruskal–Wallis test was employed. Statistical significance was defined a priori as $P < 0.05$.

3. Results and discussion

3.1. Minimum inhibitory concentration population distribution of three antibiotics

As shown in Table 1, the overall GM MICs were 0.968 mg/L for vancomycin, 0.773 mg/L for teicoplanin and 1.388 mg/L for linezolid. Vancomycin MICs were around 1 mg/L (range 0.75–1.25 mg/L) for 79.4% of the isolates, which is similar to a previous report in the USA [2], and the incidence of isolates with a MIC of 2 mg/L remained relatively low (<5%). Teicoplanin MICs were around 0.5 mg/L for 54.6% of the isolates. Linezolid MICs were 1 mg/L and 2 mg/L for 41.7% and 40.3% of the isolates, respectively, which is higher than 0.46 mg/L reported by Steinkraus et al. [2] and lower than 3.3 mg/L reported by Golan et al. [9]. All isolates were categorised as susceptible to vancomycin and linezolid according to EUCAST and CLSI breakpoints. For teicoplanin, all isolates were susceptible according to CLSI criteria and 96.8% of isolates were susceptible according to EUCAST criteria.

3.2. Assessment of minimum inhibitory concentration creep

Two methods were employed to assess MIC creep for the three antibiotics. First, as seen from the annual change of GM MICs shown in Table 1, the GM MIC increased 1.15-fold over the study period for vancomycin, from 0.906 mg/L in 2006 to 1.040 mg/L in 2011 ($P < 0.001$). For teicoplanin, the GM MIC increased 1.37-fold from 0.712 mg/L in 2006 to 0.973 mg/L in 2011 ($P < 0.001$), whilst the GM MIC for linezolid decreased 0.84-fold from 1.461 mg/L in 2006 to 1.221 mg/L in 2011. Second, different MIC intervals shown in Fig. 1 were divided as described previously [2]. For vancomycin, there was a decrease in the percentage of isolates with a MIC $\leq$ 0.5 mg/L from 5.7% (11/192) in 2006 to 1.0% (2/201) in 2011, whilst there was a sharp increase in isolates in the MIC range >1.0 mg/L to $\leq$1.5 mg/L from 18.2% (35/192) in 2006 to 38.3% (77/201) in 2011; the percentage of isolates in the MIC range from >0.5 mg/L to $\leq$1.0 mg/L and the range from >1.5 mg/L to $\leq$2.0 mg/L remained relatively stable.

For teicoplanin, there was a small fluctuation in the percentage of isolates with a MIC of 2 mg/L in the period 2006–2010, ranging from 7.9% to 10.2%, but there was a dramatic increase in 2011, up to 15.9%; moreover, there was a slow growth in the percentage of isolates with a MIC of 4 mg/L from 2006 to 2011. For linezolid, there were a downward trend in the percentages of isolates with a MIC of 1 mg/L and a MIC of 4 mg/L from 2006 to 2011, respectively.

Vancomycin MIC creep has recently been reported worldwide, although relevant data in China are lacking. There are a number of factors accounting for the inconsistent results in the available literature [10]. For instance, the precise incremental dilution method, but not the doubling dilution method, has enabled differences in MICs to be more precisely assessed for susceptibility to