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Methicillin resistant *S. aureus* in German university hospitals: Changes in Resistance 2002-2005

P 463

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Revised Abstract

Objectives

During the 1990s, the prevalence of methicillin resistant *S. aureus* (MRSA) increased in German hospitals while resistance phenotypes changed with a decrease in the number of resistance markers. We want to examine the changes in resistance in MRSA during recent years using the dataset of the GENARS project (German Network for Antimicrobial Resistance Surveillance), a prospective multi-center surveillance study designed to provide epidemiological data for German university hospitals.

Methods

Analysis was based on non-duplicate isolates of MRSA from five laboratories with continuous data collection from January 2002 to December 2005. Antimicrobial susceptibility was determined as minimal inhibitory concentrations by broth microdilution method performed by automated quality controlled test systems for antibiotics of various classes. Resistance rates were evaluated by using breakpoints according to DIN guidelines.

Results

The percentage of *S. aureus* isolates (n=24,152) tested as resistant to oxacillin increased from 9.4% in 2002 to 13.5% in 2005 with considerable variation between hospitals. A total of 3,048 MRSA isolates was analysed. Resistance rates to ciprofloxacin (CIP), erythromycin (ERY) and clindamycin (CLI) remained on a very high level with little fluctuation, whereas the already low rates for doxycycline (DOX), rifampicin (RAM) and quinupristin/dalfopristin (SYN) tended to decline. For gentamicin (GEN) there was a significant decrease from 31.3% in 2002 to 18.1% in 2005 with extreme variation between hospitals. No resistance was observed against teicoplanin, vancomycin or linezolid. Analysis of resistance patterns including CIP, ERY, CLI, GEN, DOX, RAM and SYN resulted in six main patterns accounting for about 90 percent of the strains. The two most frequent patterns showed a reverse trend: While the frequency of OXA-CIP-CLI-ERY increased (2002: 37.6% to 2005: 51.4%) OXA-CIP-CLI-ERY-GEN decreased (2002: 20.7% to 2005: 11.6%). On the hospital level results are heterogeneous: In two centres the pattern OXA-CIP-CLI-ERY-GEN is still predominant with a proportion of more than 40% of all MRSA strains in 2005.

Conclusions

Data from the GENARS project show that changes in resistance phenotypes of MRSA reported for the 1990s continue in the observed period from 2002 to 2005 with a remarkable decrease of resistance to gentamicin as the main feature. However, findings from pooled data mask substantial diversity on the local level.

Introduction

During the 1990s, the prevalence of methicillin resistant *S. aureus* (MRSA) increased in German hospitals. At the same time the German national reference centre for staphylococci observed that the range of antimicrobials to which MRSA were resistant decreased, this trend was mainly due to the emergence of new epidemic strains in which resistance to gentamicin and oxytetracycline is rare (1).

We want to explore resistance phenotypes in MRSA during recent years using the dataset of the GENARS-project (German Network for Antimicrobial Resistance Surveillance).

Methods

GENARS is a prospective multi-center surveillance study of German university hospitals: Since 2002 six laboratories have been collecting routine data for all clinical relevant pathogens in a widely standardized and quality controlled way (2). Antimicrobial susceptibility is determined as minimal inhibitory concentrations (MICs) by broth microdilution method performed by automated test systems. Unvalidated MIC values are submitted to a central database, these results are evaluated by using breakpoints according to DIN guidelines (3).

From 2002 to 2005 five laboratories with continuous participation have collected data of 24,152 non-duplicate isolates of *S. aureus*. 3,137 of these were classified as MRSA showing an MIC > 1 for oxacillin. Further analysis was based on 3,048 strains with complete MIC results for ciprofloxacin (CIP; for one centre replaced by levofloxacin), erythromycin (ERY; for one centre replaced by roxithromycin), clindamycin (CLI), gentamicin (GEN), doxycycline (DOX; for one centre replaced by tetracycline), rifampicin (RAM) and quinupristin/dalfopristin (SYN).

Results

The percentage of *S. aureus* isolates (n=24,152) tested as resistant to oxacillin increased from 9.4% in 2002 to 13.5% in 2005. A total of 3,048 MRSA isolates was analysed. Resistance rates to selected antimicrobials by year are shown in table 1. Resistance to ciprofloxacin (CIP), erythromycin (ERY) and clindamycin (CLI) remained on a very high level with little fluctuation, whereas the already low rates for doxycycline (DOX), rifampicin (RAM) and quinupristin/dalfopristin (SYN) tended to decline. No resistance was observed against teicoplanin, vancomycin or linezolid.

Results

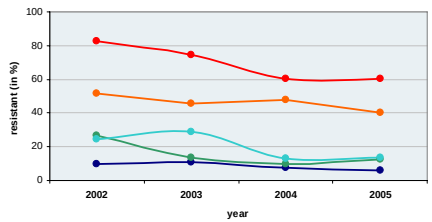
Table 1: Percentage of MRSA strains with resistance to selected antibiotics by year

Antibiotic	2002	2003	2004	2005
	(n=511)	*(n=710)*	*(n=879)*	*(n=948)*
Ciprofloxacin	86.9	90.8	91.1	93.2
Erythromycin	70.8	73.8	74.4	72.6
Clindamycin	66.3	67.3	70.8	65.7
Gentamicin	31.3	31.3	20.6	18.1
Doxycycline	5.9	3.9	3.2	1.4
Rifampicin	4.3	3.2	2.4	3.0
Quinupristin/Dalfopristin	2.6	1.0	0.6	0.8
Linezolid *	0.2	0.2	0.0	0.2
Teicoplanin	0.0	0.0	0.0	0.0
Vancomycin	0.0	0.0	0.0	0.0

* retests did not confirm resistance to linezolid

For gentamicin (GEN) there was a significant decrease from 31.3% in 2002 to 18.1% in 2005 (Chi^2=58.75; p<=0.001). Besides this overall trend there was substantial variation between hospitals as shown in figure 1:

Figure 1: Resistance rates of MRSA to Gentamicin by year and centre



Analysis of resistance patterns including CIP, ERY, CLI, GEN, DOX, RAM and SYN resulted in six main patterns accounting for about 90 percent of the strains. The two most frequent patterns were OXA-CIP-CLI-ERY and OXA-CIP-CLI-ERY-GEN. According to the overall decline in MRSA strains with resistance to GEN these two phenotypes show a reverse trend: The proportion of OXA-CIP-CLI-ERY increased from 37.6% in 2002 to 51.4% in 2005 while OXA-CIP-CLI-ERY-GEN decreased from 20.7% in 2002 to 11.6% in 2005. Results are given in table 2 and illustrated by figure 2.

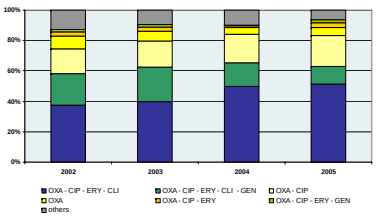
On the hospital level, results reflect the differences mentioned above: In two centres the pattern OXA-CIP-CLI-ERY-GEN is still the most frequent phenotype, accounting for more than 40% of all MRSA strains in 2005.

Results

Table 2: Resistance patterns of MRSA strains by year (in percent)

Resistance pattern	2002	2003	2004	2005
	(n=511)	*(n=710)*	*(n=879)*	*(n=948)*
OXA - CIP - ERY - CLI	37.6	39.9	49.9	51.4
OXA - CIP - ERY - CLI - GEN	20.7	22.8	15.2	11.6
OXA - CIP	16.0	17.2	19.0	20.4
OXA	8.6	6.1	4.3	5.1
OXA - CIP - ERY	2.5	3.1	1.1	3.3
OXA - CIP - ERY - GEN	1.8	1.4	0.5	1.9
others	12.7	9.6	9.9	6.4

Figure 2: Proportions of resistance patterns of MRSA by year



Conclusions

Data from the GENARS project confirm changes in resistance phenotypes of MRSA reported for the 1990s. Within the observed period from 2002 to 2005, the decrease of MRSA strains carrying resistance to gentamicin has been continuous. However, the situation at the local level may differ substantially from the overall trend.

References

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