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REVISED ABSTRACT

Objectives Since the end of 2001, six laboratories for medical microbiology at German university hospitals have been taking part in the GENARS-project (German Network for Antimicrobial Resistance Surveillance). These laboratories regularly send data obtained in the laboratory routine to the central office of GENARS in Bonn. Here they are merged in the database and analyzed. The goal of this investigation was to find out, if significant trends in the development of antimicrobial resistance in GENARS hospitals are detectable.

Methods MIC values from species listed were determined for 25 antibiotics, considering all relevant antibiotic classes: *E. coli*, *E. cloacae*, *K. pneumoniae*, *P. mirabilis* (ciprofloxacin, gentamicin, ampicillin, piperacillin and cefotaxime), *P. aeruginosa* (ciprofloxacin, imipenem, ceftazidime, gentamicin and piperacillin) and *S. aureus* (penicillin, oxacillin, erythromycin, doxycycline and linezolid). Only the values of non-copy strains of five GENARS hospitals entered the statistics.

Results For many antibiotic-species-pairs no obvious trends could be detected. However some species show continuous changes in their resistance rates. A highly significant increase in ciprofloxacin resistant strains of *E. coli* and *P. aeruginosa* as well as for piperacillin with *K. pneumoniae* could be observed. Detailed percentages of resistant strains for the 1st half of 2002 to the 1st half of 2004 are shown in table 1. For *S. aureus* strains resistant to oxacillin (MRSA) increased significantly to a level of 11.6 % (table 1). In means for all GENARS hospitals the resistance rate to oxacillin increased. Nevertheless, in two of these hospitals a clear decrease was observed. The level of resistance and resistance development for all species evaluated can vary considerably from hospital to hospital.

Conclusions In the time under observation, in GENARS hospitals for most of the selected species and antibiotics no significant changes in antimicrobial resistance could be detected. Nevertheless, as shown for *E. coli* and *P. aeruginosa* resistance to ciprofloxacin and for *S. aureus* resistance to oxacillin increased significantly. This demonstrates that an early detection of any alterations in antimicrobial resistance by a continuous surveillance is of great importance.

INTRODUCTION AND PURPOSE

Since the end of 2001, six laboratories for medical microbiology at German university hospitals have been taking part in the GENARS-project (German Network for Antimicrobial Resistance Surveillance). These laboratories regularly send data obtained in the laboratory routine to the central office of GENARS in Bonn. Here they are merged in the database and analyzed. The goal of this investigation was to find out whether significant trends in the development of antimicrobial resistance in GENARS hospitals are detectable.

METHODS

GENARS – funded by the German Federal Ministry of Health and Social Security – is a national network for antimicrobial resistance surveillance. At present, six laboratories affiliated to university hospitals are collecting data continuously for all clinical relevant pathogens in a widely standardized and quality controlled way (1).

Susceptibility tests are performed by determination of minimal inhibitory concentrations (MICs) by broth microdilution method according to DIN guidelines (2), one center provides data achieved by the automated system VITEK 2.

Analysis was based on first isolates of *E. coli*, *E. cloacae*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa* and *S. aureus* from five centers, collected from January 2002 to June 2004. For each species, analysis was focussed on five selected antimicrobials: Enterobacteriaceae: ampicillin (AMP), cefotaxime (CTX), ciprofloxacin (CIP), gentamicin (GEN) and piperacillin (PIP); *P. aeruginosa*: ceftazidime (CAZ), CIP, GEN, PIP and imipenem (IMP); *S. aureus*: penicillin (PEN), oxacillin (OXA), erythromycin (ERY), doxycycline (DOX) and linezolid (LIZ). Resistance rates were calculated for half year periods, using breakpoints according to DIN (3). Data analysis was executed by WHONET software (4), significance tests were computed by Epi Info™ (5).

RESULTS

All species samples are composed of isolates from any patient type as well as from all kinds of specimens. The number of isolates collected per center varied due to differences in size and structure of the hospitals. Table 1 gives a summary of the resistance rates over time in GENARS hospitals for the selected species and antimicrobial agents:

Species	Antibiotic	2002 1 st half		2002 2 nd half		2003 1 st half		2003 2 nd half		2004 1 st half	
		No.	% R	No.	% R	No.	% R	No.	% R	No.	% R
<i>E. coli</i>	Ampicillin	2287	43.9	2472	40.9	3009	42.9	3188	42.7	3068	44.5
	Cefotaxime	2288	1.0	2996	1.1	3154	1.0	3181	1.3	3066	1.8
	Piperacillin	2285	26.2	2475	25.8	3101	28.1	3184	24.7	3065	26.0
	Ciprofloxacin	2367	9.6	3087	11.5	3228	11.6	3065	12.8	3740	13.8
	Gentamicin	2379	4.5	3078	4.6	3226	5.2	3080	4.8	3157	5.1
<i>E. cloacae</i>	Ampicillin	335	90.4	814	89.5	499	83.0	634	81.2	498	77.9
	Cefotaxime	342	26.9	609	24.7	506	26.5	634	24.0	499	29.5
	Piperacillin	338	25.1	612	21.6	496	24.6	634	21.5	500	25.8
	Ciprofloxacin	346	2.0	617	1.3	512	1.8	638	2.0	502	1.8
	Gentamicin	347	4.3	618	1.5	513	1.9	639	1.6	502	1.6
<i>K. pneumoniae</i>	Ampicillin	471	92.4	570	88.2	609	88.5	798	86.1	890	84.3
	Cefotaxime	476	4.8	688	4.1	600	2.4	786	6.1	690	4.5
	Piperacillin	473	15.4	673	15.0	609	15.4	787	21.0	689	19.9
	Ciprofloxacin	487	3.3	706	2.7	692	3.0	794	4.2	699	4.6
	Gentamicin	487	3.9	707	3.1	693	2.1	795	4.7	699	4.6
<i>P. mirabilis</i>	Ampicillin	372	28.0	491	32.2	611	28.2	686	26.7	645	30.2
	Cefotaxime	375	0.8	454	1.3	614	1.1	688	0.9	647	1.1
	Piperacillin	371	7.8	492	5.7	611	6.5	687	7.5	646	5.4
	Ciprofloxacin	385	2.6	446	4.0	633	3.8	678	3.7	688	6.2
	Gentamicin	384	7.8	445	10.1	632	6.9	676	8.6	686	8.5
<i>P. aeruginosa</i>	Cefotaxime	1143	9.0	1777	6.2	1908	6.8	1810	6.0	1815	7.2
	Ciprofloxacin	1143	11.5	1775	10.9	1808	14.9	1809	14.4	1816	18.8
	Imipenem	886	23.1	1738	20.0	1603	16.9	1799	16.2	1609	22.0
	Gentamicin	1143	25.9	1775	21.0	1810	23.2	1811	20.4	1818	21.8
	Piperacillin	1134	10.6	1432	10.1	1880	9.7	1810	8.6	1814	8.2
<i>S. aureus</i>	Penicillin	3030	75.0	3788	72.9	3658	73.1	4338	72.9	4272	73.3
	Oxacillin	3010	9.0	3793	10.0	3662	10.8	4319	10.9	4259	11.8
	Erythromycin	3008	19.2	3020	18.6	3161	21.2	3484	21.6	3297	21.8
	Doxycycline	2282	4.3	2693	2.2	3166	2.6	3607	2.2	3554	2.5
	Linezolid	1931	0.0	2881	0.0	3165	0.0	3607	0.0	3893	0.0

Table 1: Resistance rates of selected species and antimicrobials in GENARS hospitals

The summary table shows that there are no significant changes in resistance rates for the majority of the selected species-antibiotic-combinations within the period of observation.

The highlighted results will be investigated more closely as they indicate increases of resistance:

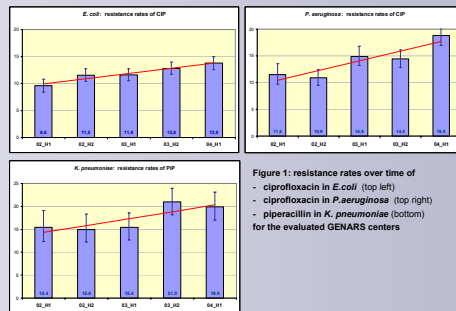


Figure 1: resistance rates over time of
- ciprofloxacin in *E. coli* (top left)
- ciprofloxacin in *P. aeruginosa* (top right)
- piperacillin in *K. pneumoniae* (bottom)
for the evaluated GENARS centers

Ciprofloxacin resistance increases in *E. coli* and *P. aeruginosa* (Fig.1). The difference in the resistance rates are significant ($\chi^2 = 52.15$; $p \leq 0.001$ for *P. aeruginosa*, $\chi^2 = 25.9$; $p \leq 0.001$ for *E. coli*). The increase of the resistance rates is highly significant for *E. coli*, but not for *P. aeruginosa* ($\chi^2 = 24.34$; $p \leq 0.001$), where the rates tend to vary from period to period. The resistance rates for *Klebsiella pneumoniae* and piperacillin (Fig.1 bottom) differ significantly ($\chi^2 = 14.66$; $p = 0.005$) and the increase also is significant ($\chi^2 = 9.98$; $p \leq 0.005$).

The difference in the resistance rates are significant ($\chi^2 = 14.8$; $p = 0.005$) for methicillin resistant *S. aureus*. This holds true for the increase as well ($\chi^2 = 13.88$; $p \leq 0.001$) (Fig.2 top left).

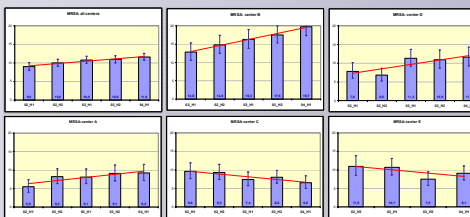


Figure 2: resistance rates of oxacillin in *S. aureus* over time for complete sample (top left) and by center

Oxacillin resistance increases in *S. aureus* if all centers are taken into consideration (Fig.2). However, the trend for all centers is dominated mainly by center B. The difference in the resistance rates for center B are highly significant ($\chi^2 = 18.7$; $p \leq 0.001$). The increase of the resistance rates is highly significant as well ($\chi^2 = 17.92$; $p \leq 0.001$). All figures for the tests for significance are listed in table 2

Center	variation of rates		linear trend	
	χ^2	p	χ^2	p
Center A	8.95	n.s.		
Center B	18.70	<=0.001	17.92	<=0.001
Center C	7.27	n.s.		
Center D	17.40	<=0.005	11.97	<=0.001
Center E	6.68	n.s.		
All	14.80	<=0.005	13.88	<=0.001

Table 2: Significance of resistance rates and trends for MRSA

CONCLUSIONS

- Within the period of observation from January 2002 to June 2004, for most of the selected species and antibiotics no significant changes in antimicrobial resistance could be detected in GENARS hospitals.
- Significant increases of resistance rates were found for ciprofloxacin in *E. coli* and *P. aeruginosa*, for piperacillin in *K. pneumoniae* as well as for oxacillin in *S. aureus*.
- The level of resistance as well as changes in resistance rates may vary considerably from hospital to hospital.
- A prolonged study period is necessary to establish nationwide trends.

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