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funded by
Federal Ministry of Health and Social Security

REVISED ABSTRACT

Objectives Clones of *K. pneumoniae* were involved in nosocomial infections with fatal consequences in the late 1960ies. They became rare with the introduction of 3rd and 4th generation cephalosporins. Today this species again seems to play a major role in nosocomial infection due to resistance to the modern drugs. The GENARS-project (German Network for Antimicrobial Resistance Surveillance) is designed to provide epidemiological data for German university hospitals. Since 2002 resistance data are collected for all clinical relevant pathogens.

Methods Analysis was based on first isolates of *K. pneumoniae* from six laboratories, collected from January 2002 to June 2004. Minimal inhibitory concentrations (MICs) were determined by broth microdilution method (DIN) for ceftazidime (CAZ), cefotaxime (CTX), ciprofloxacin (CIP), gentamicin (GEN), meropenem (MER) and piperacillin (PIP). Resistance patterns were evaluated by using breakpoints according to DIN, grouping susceptible and intermediate as non-resistant; multi-drug resistance was defined as resistance to at least four of the six agents.

Results A total of 3,077 isolates was analysed. 19% of these isolates were resistant to at least one agent: The most common pattern was a mono-drug resistance to PIP (10.1%) followed by co-resistance to PIP, CAZ and CTX (1.5%) and co-resistance to PIP and CAZ (1.1%). 71 isolates (2.3%) were classified as multi-resistant. The resistance rate of PIP with tazobactam was 5.4% but increased to 63.4% in multi-resistant strains.

Conclusions The relevance of multi-resistance in *K. pneumoniae* as a major clinical problem is proven by an overall rate of 2.3 percent for German university hospitals and an even higher proportion for ICU patients. Among the agents tested piperacillin plays an eminent role in regard to its mono-resistant rate as well as a component of the most frequent resistance patterns. Resistance to the combination of PIP with tazobactam however is rare in respect to the overall PIP resistance but high in multi-resistant strains.

INTRODUCTION AND PURPOSE

Clones of *K. pneumoniae* were involved in nosocomial infections with fatal consequences in the late 1960ies. They became rare with the introduction of 3rd and 4th generation cephalosporins. Today this species again seems to play a major role in nosocomial infections due to resistance to the modern drugs. Using the GENARS database (German Network for Antimicrobial Resistance Surveillance) we want to see how common multi-resistant strains of *K. pneumoniae* are in German hospitals.

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 provided data achieved by the automated system VITEK 2.

Analysis was based on first isolates of *K. pneumoniae* from six centers, collected from January 2002 to June 2004. MICs were determined for the following five class representatives: ceftazidime (CAZ), cefotaxim (CTX), ciprofloxacin (CIP), gentamicin (GEN), meropenem (MER) and piperacillin (PIP). Resistance patterns were evaluated by using breakpoints according to DIN (3); multi-drug resistance was defined as resistance to at least four of the six agents. Data analysis was executed by WHONET software (4), significance tests were computed by Epi Info™ (5).

RESULTS

A total of 3,077 isolates was analysed. The number of isolates collected per center varied from 130 to 777 due to differences in size and structure of the hospitals. With regard to patient type the sample is composed as follows: 25.8% isolates from patients of intensive care units, 53.5% from non-ICU inpatients and 12.9% from outpatients, for the remaining 7.8% information was missing. Of the isolates, 33.4% were from the respiratory specimens, 26.9% from urine, 6.0% from blood, and 33.7% from other sites or unknown origin.

Basic information about susceptibility of the *K. pneumoniae* isolates tested is given in terms of SIR proportions (table 1) and more detailed as distributions of MICs (figure 1):

Antimicrobial	MIC breakpoints		S%	I%	R%
	S (<=)	R (>)			
Piperacillin	1	4	48.7	32.9	17.4
Ceftazidime	4	16	93.8	1.2	5.0
Cefotaxime	2	8	92.8	2.6	4.6
Gentamicin	4	16	92.9	3.1	4.0
Ciprofloxacin	1	2	94.9	1.8	3.1
Meropenem	4	32	99.9	0.1	0.1

Table 1: MIC breakpoints according to DIN and susceptibility rates of *K. pneumoniae* (N=3,077)

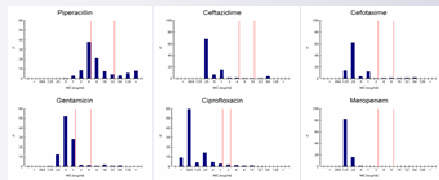


Figure 1: Distributions of MICs for *K. pneumoniae* (red lines indicate DIN breakpoints)

Rates of susceptibility were highest with meropenem (99.9%) followed by ciprofloxacin (94.9%). In contrast, piperacillin showed the highest rate of resistance (17.4%) as well as a very high proportion of intermediate strains (32.9%, see table 1).

Table 2a shows the results of the analysis of resistance patterns. 2,491 isolates (81%) were not resistant to any of the selected antibiotics, for the remaining 586 isolates 26 different resistance patterns were detected. The most common pattern was a mono-drug resistance to PIP (10.1%) followed by co-resistance to PIP, CAZ and CTX (1.5%) and co-resistance to PIP and CAZ (1.1%). Resistance to cephalosporins in most cases occurs combined with resistance to other agents, mainly with PIP. The proportions of strains resistant to PIP, CAZ and CTX sum up to 3.2%.

71 isolates (2.3%, see table 2b) were classified as multi-resistant according to our definition – resistance to at least four agents – including one strain resistant to all six antibiotics.

a) resistance pattern	No.	%	b) Patient type	%	sample size
none	2491	81.0	icu patients	4.4	793
PIP	310	10.1	inpatients	1.8	1647
CIP	29	0.9	outpatients	0.0	396
GEN	9	0.3	total	2.3	2836
CTX	6	0.2			
CAZ	2	0.1			
PIP - CAZ	34	1.1			
PIP - CIP	18	0.6			
PIP - GEN	17	0.6			
PIP - CTX	8	0.3			
GEN - CIP	3	0.1			
GEN - CTX	1	<0.1			
GEN - CAZ	1	<0.1			
PIP - CTX	1	<0.1			
PIP - CTX - CAZ	47	1.5			
PIP - GEN - CAZ	12	0.4			
PIP - GEN - CTX	8	0.3			
PIP - GEN - CIP	5	0.2			
PIP - CIP - CTX	2	0.1			
PIP - CIP - CAZ	2	0.1			
PIP - GEN - CTX - CAZ	28	0.9			
PIP - GEN - CIP - CTX	14	0.5			
PIP - CIP - CTX - CAZ	5	0.2			
PIP - GEN - CIP - CAZ	3	0.1			
PIP - GEN - CIP - CTX - CAZ	19	0.6			
PIP - GEN - CIP - CTX - MER	1	<0.1			
PIP - GEN - CIP - CTX - CAZ - MER	1	<0.1			

Table 3: multi-resistance rates in *K. pneumoniae*
a) by patient type
b) by center

Many of the piperacillin resistant strains are sensitive towards piperacillin with tazobactam (17.4% and 5.4%). However, 63.4% of all multi-resistant strains are also resistant to the combination piperacillin/tazobactam. This is an indication for the effective spread of extended spectrum AmpC β-lactamases.

b) number of resistances	No.	%
none	2491	81.0
one	356	11.6
two	83	2.7
three	76	2.5
four to six = multi-resistant	71	2.3
total no. of isolates	3077	

Table 2: resistance patterns and number of resistances in *K. pneumoniae*

Significant differences in multi-drug resistance rates were associated with patient type (table 3a): While 4.4% of the isolates from ICU patients were resistant to four or more drugs the rate was 1.8% for inpatients and there were no multi-resistant strains detected among outpatients (Chi²=26.86, df=2, p<0.001).

Furthermore, multi-resistance rates varied between the centers involved (table 3b) with a range from 0.6% to 4.7%. Finally, the development of multi-resistance within four centers was analyzed by cross-tabulation of the number of multi-resistant strains by month (see figure 2): For center 5, which is the center with the highest proportion of multi-resistant strains, the accumulation of those strains within a 9 month period may indicate an outbreak of a clone.

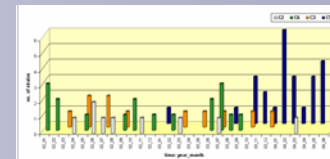


Figure 2: Multi-resistance in *K. pneumoniae* over time in four centers

CONCLUSIONS

The relevance of multi-resistance in *K. pneumoniae* as a major clinical problem is proven by an overall rate of 2.3 percent for German university hospitals and an even higher proportion for ICU patients. Among the agents tested piperacillin plays an eminent role in regard to its mono-resistant rate as well as a component of the most frequent resistance patterns. Resistance to the combination of PIP with tazobactam is rare among mono-resistant strains, however prominent in multi-resistant strains.

The data demonstrate, that multi-resistant *Klebsiella* strains again are a threat in respect to their ability to cause hospital infections.

REFERENCES

- Huppertz K., Noll I., Wiedemann B. and the GENARS-group (2003). Antibiotic Resistance Surveillance on the Basis of High Quality Routine Data: German Network for Antimicrobial Resistance Surveillance. *Clinical Microbiology and Infection*, Vol. 9, Suppl. 1: 386.
- Deutsches Institut für Normung e.V. Empfindlichkeitsprüfung von mikrobiellen Krankheitserregern gegen Chemotherapeutika (2002). Teil 6: Mikrobiologie – Allgemeine methodenspezifische Anforderungen. DIN 58940-6. Berlin: Beuth Verlag.
- Deutsches Institut für Normung e.V. Empfindlichkeitsprüfung von mikrobiellen Krankheitserregern gegen Chemotherapeutika (2004). Teil 4: Bewertungskriterien für die minimale Hemmkonzentration – MHK-Grenzwerte von antibakteriellen Wirkstoffen. DIN 58940-4. Teil 1. Berlin: Beuth Verlag.
- World Health Organization. WHONET Software. WHO.int/drugresistance/whonetsoftware/en.
- Centers for Disease Control and Prevention. Epi Info™. CDC.gov/epiinfo.

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