Epidemiology of Ceftazidime-Resistant *Klebsiella pneumoniae* in a Large University Hospital in Tel Aviv

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Abstract

Background: An increase in multiple drug-resistant *Klebsiella pneumoniae* due to extended spectrum β-lactamase production has recently been reported from many centers around the world. There is no information in the literature regarding this problem in Israel. A high prevalence of ceftazidime-resistant *K. pneumoniae* was noted in our Intensive Care Unit in the first few months of 1995.

Objective: To describe the epidemiology of ceftazidime-resistant *K. pneumoniae* in our medical center, as representing the situation in tertiary care hospitals in Israel.

Methods: We vigorously restricted the use of ceftazidime in the ICU and enforced barrier precautions. The susceptibility rate of *K. pneumoniae* was surveyed in the ICU and throughout the hospital before and after the intervention in the ICU.

Results: Following the intervention, the susceptibility rate of *K. pneumoniae* increased from 11% (3/28) to 47% (14/30) ($P<0.01$) among ICU isolates, from 55% (154/280) to 62% (175/281) ($P=0.08$) among total hospital isolates, and from 61% (50/82) to 74% (84/113) ($P<0.05$) among total hospital blood isolates, although no additional control measures were employed outside the ICU.

Conclusions: The epidemiology of ceftazidime-resistant *K. pneumoniae* in our medical center is similar to that reported from other centers around the world. Early awareness to the emergence of this resistance, identification of the source of the epidemic, and prompt action at the putative source site may reduce the rate of acquisition and spread of such resistance inside and outside of the source unit.

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The increasing resistance of gram-negative bacilli to broad-spectrum antibiotics constitutes an alarming problem in hospital epidemiology. One of these emerging problems with a potential for a dramatic spread among hospitalized patients is the resistance of *Klebsiella pneumoniae* to all cephalosporins [1]. Outbreaks of extended spectrum β-lactamase producing *K. pneumoniae* have been reported since the mid-1980s, initially from Western Europe and the USA [2–9] but more recently from almost all over the world [10–13]. This resistance phenotype is due to the production of transmissible plasmid-mediated extended spectrum β-lactamases, which have been widely studied and speciated as various TEM, SHV, YOU and CTX types [14–17].

Since we are not aware of any reports of the extent of this problem in Israel, we describe here our experience with an "outbreak" of ceftazidime-resistant *K. pneumoniae* in a large tertiary care hospital in Israel.

Materials and Methods

The Tel Aviv Sourasky Medical Center is a 1,100 bed tertiary care and teaching hospital, with an 8 bed general Intensive Care Unit. During the first months of 1995 a high rate of *K. pneumoniae* resistant to ceftazidime was noted in the ICU. To combat this increasing resistance, two interventions were undertaken in May 1995: a) enhancement of infection control measures including barrier precautions and hand washing, and b) restriction of the use of ceftazidime in the ICU as much as possible, and reducing its use throughout the hospital by alerting all infectious disease consultants to the "outbreak."

Concomitantly, ceftazidime susceptibility of *K. pneumoniae* isolates from all types of clinical material from the entire hospital was recorded systematically for the 16 month period between January 1995 and April 1996. Specimens from ambulatory, pediatric, and rehabilitation departments were excluded. Repeated isolates from the same patient with identical susceptibility to ceftazidime, even from different sites, were excluded, unless 2 months had elapsed between dates of recovery. The 16 month study period was arbitrarily divided into three consecutive parts: period I (before intervention, January until May 1995), period II (immediately following intervention, June until November 1995) and period III (a follow-up period, December 1995 to April 1996).

Identification and antibiotic susceptibility testing of *K. pneumoniae* were performed using an automated system

ICU = Intensive Care Unit

(Baxter/Micro Scan) with MIC breakpoint plates in accord with NCCLS criteria (ceftazidime susceptible ≤ 8 μg/ml, intermediate 16 μg/ml, resistant ≥ 32 μg/ml). Information on the amounts of ceftazidime (in grams) used in the ICU and throughout the hospital during each of the three study periods was collected from the hospital pharmacy.

Statistical analysis was performed using the chi-squared test for contingency tables or for a trend as applicable. A P value of ≤ 0.05 was considered significant.

Results

The consumption of ceftazidime in the ICU decreased dramatically following the decision to restrict its use. The total amounts used during each of the three study periods I, II and III were 461, 156 and 63 g respectively, while in the entire hospital there was no significant change [Table 1]. Concomitantly, the rate of susceptibility of *K. pneumoniae* isolated from the ICU increased from 11% (3 of 28) in period I to 47% (14 of 30) in periods II and III combined ($P<0.01$) [Table 2].

A total of 909 unique *K. pneumoniae* isolates were recovered from the entire hospital (excluding the ICU) during the study period. Of these, 337 (37%) were resistant to ceftazidime, 41 (5%) were of intermediate susceptibility and 531 (58%) were susceptible. There was a slight trend for increasing susceptibility during the three study periods from 55% (154 of 280) though 58% (202 of 348) to 62% (175 of 281) (P for linear trend = 0.08) [Table 2]. However, the susceptibilities of the same 909 *K. pneumoniae* isolates to gentamicin, ceftriaxon and imipenem during the same three study periods did not show any significant change (not shown).

The main body sites from which these 909 isolates were recovered, as well as the site-specific ceftazidime susceptibility of *K. pneumoniae* are listed in Table 3. The lowest susceptibility rate was noted in *K. pneumoniae* isolated from intravenous line tips (11%), while the susceptibility rate of blood, urine and sputum isolates was 61%. The susceptibilities of *K. pneumoniae* from blood cultures were also available for the rest of 1996 (May to December) and for all of 1997. These were 70% (61 of 88 unique *K. pneumoniae* blood isolates) and 74% (84 of 113) respectively (P for linear trend for blood isolates during 1995–97 was <0.001).

Table 1. Total and monthly ceftazidime consumption (in grams) in the intensive care unit and throughout the hospital in each study period

	Study period I January–May 1995		Study period II June–November 1995		Study period III Dec 1995–April 1996	
	Total	**Per month**	**Total**	**Per month**	**Total**	**Per month**
Intensive care unit	461	92.2	156	26.0	63	12.6
Entire hospital	5,199	1,040	7,163	1,194	6,268	1,254

Table 2. Number of *K. pneumoniae* isolates and percent susceptibility to ceftazidime in the ICU and throughout the hospital (excluding ICU) in each study period

	Study period I January–May 1995		Study period II June–November 1995		Study period III Dec 1995-April 1996	
	No. of isolates	**Susceptible**	**No. of isolates**	**Susceptible**	**No. of isolates**	**Susceptible**
ICU*	28	3 (11%)	18	9 (50%)	12	5 (42%)
Entire hospital**	280	154 (55%)	348	202 (58%)	281	175 (62%)

* $P<0.01$ for the difference between 11% (3/28) in period I and 47% (14/30) in periods II and III combined.

** No statistical difference between the periods.

Table 3. Ceftazidime susceptibility among 909 *K. pneumoniae* isolates according to body site (during the 16 month study period).

Specimen site	No. of isolates	Susceptible
Urine	442	271 (61%)
Wound	200	105 (52%)
Blood	82	50 (61%)
Sputum	65	40 (61%)
IV line tip	36	4 (11%)
Other	84	60 (71%)
Total	909	530 (58%)

Discussion

Shortly after the introduction of the third-generation cephalosporins in the late 1970s and early 1980s, resistance to these new agents began to emerge [18]. Since then, outbreaks of highly resistant *K. pneumoniae* have been reported [Table 4]. A collaborative study of 12 university hospitals in France found ceftazidime resistance among *K. pneumoniae* isolates in the range of 12.6%–15.8% during 1988–90, and one U.S. hospital experienced a dramatic rise from 1.0% to 40% approximately at the same time [1]. Epidemics of extended spectrum β-lactamases producing *K. pneumoniae* have been described from acute care hospitals [4,8,9,10,13], chronic care facilities [4,7], pediatric departments [5,6,12], and ICUs [2]. Isolates have been recovered from all types of clinical material. Increased use of ceftazidime and prolonged hospitalization and stay in ICUs have been implicated as risk factors for the emergence of the resistant strains [9].

The "outbreak" reported here seemed to have originated from the ICU, where ceftazidime consumption was high, the patients were seriously ill, and the physical conditions were sub-optimal (all the patients were in one large

Table 4. Some aspects of several outbreaks of ceftazidime-resistant *K. pneumoniae* from the literature

Type of facility and location [ref]	Period	No. of isolates	Rate of resistance*	Identified β-lactamase
ICU Clermont-Ferrand, France [2]	July 1984–Dec 1987	74	0–15%	CTX-1=TEM-3
Chronic care facility Boston, MA, USA [3]	Aug 1988–Jan 1989	22	Not available	YOU-1, YOU-2
General hospital Flushing, NY, USA [4]	Oct 1988–0ct 1989	432	17.3%	TEM-26 [17]
Pediatric Oncology Unit Stanford, CA, USA [5]	Jan 1988–Mar 1990	12	Not available	TEM-26
Pediatric hospital Paris France [6]	Aug 1989–July 1990	43	Not available	SHV-1 SHV-2
Geriatric department Nimes, France [7]	Aug 1991–Mar 1993	12	Not available	TEM-2, TEM-3, SHV-1
General hospital Chicago. IL, USA [8]	Apr 1992–Nov 1994	21**	18–27%	TEM-10
General hospital Cleveland, OH, USA [9]	1993–94	180	6–28%	TEM-6, TEM-26
General hospital Tel Aviv, Israel	Jan 1995–Apr 1996	337	37%	Not done

* Percent resistant among all *K. pneumoniae* isolates
** Blood isolates only.

room). Resistance at the peak time of the epidemic was the highest ever described (25 of 28 isolates, 89%). Ceftazidime is well known for its ability to induce β-lactamases in Enterobacteriaceae, and its increased use was implicated as an important factor in the emergence of ceftazidime-resistant *K. pneumoniae* in many of the outbreaks reviewed here [3,4,9]. Therefore, it is not surprising that restriction of ceftazidime use is an effective control measure in addition to enhancement of barrier precautions. This was true in our experience as well as in others [3,4,9].

The effectiveness of the measures undertaken was demonstrated by the significant increase in ceftazidime susceptibility in the ICU following the intervention. More interesting is the increasing susceptibility in blood isolates throughout the hospital (61%, 70%, 74%), even though there was no change in the total consumption of ceftazidime.

Unfortunately, we had neither the tools for analyzing the types and varieties of β-lactamases that prevailed during this "outbreak," nor any fingerprinting methods to identify the isolates. Nonetheless, susceptibilities to all other antimicrobials were not identical among the different isolates. Thus, although not proved, it seems that the origin of the outbreak was a multiple source rather than a single-strain "epidemic."

In conclusion, the data presented here are similar to those reported from other medical centers confronted with the problem of ceftazidime-resistant *K. pneumoniae*. The high prevalence of the resistant strain in the ICU was probably associated with a high consumption of ceftazidime. Reducing the antibiotic pressure and implementing infection-control measures were associated with an increase in the susceptibility to ceftazidime not only in the ICU but also throughout the hospital. Early awareness of an increase in ceftazidime resistance among *K. pneumoniae* isolates and a prompt response may slow the spread of the epidemic and reduce the rate of *K. pneumoniae* isolates acquiring such resistance.

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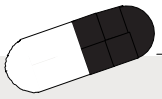
It was once said that the moral test of government is how that government treats those who are in the dawn of life, the children; those who are in the twilight of life, the elderly; and those who are in the shadows of life, the sick, the needy and the handicapped.

Hubert Humphrey, American Democratic Vice-President (1911–78)

Capsule



The future of research into rotavirus vaccine

The future of a potentially lifesaving vaccine for developing countries has been imperiled by its recent withdrawal from the United States market. In August 1998, tetravalent rhesus rotavirus vaccine was licensed for routine vaccination in the United States on the basis of randomized controlled trials there and in Finland. The trials showed that the vaccine had an efficacy of 49–68% in preventing rotavirus diarrhea overall and, importantly, 69–91% efficacy in preventing severe disease.

In July 1999 the U.S. Centers for Disease Control and Prevention reported a clustering of cases of intussusception in the weeks alter vaccination with tetravalent rhesus rotavirus vaccine, representing an additional risk of 1 in 10,000 for this complication. On the basis of this finding they recommended "postponing administration of tetravalent rhesus rotavinus vaccine to children," and in October 1999 the manufacturer voluntarily withdrew the product from the U.S. market. This leaves researchers with a moral quandary: should randomized controlled trials of tetravalent rhesus rotavirus vaccine proceed in developing countries?

Assuming a worst case scenario of a 25% fatality rate from intussusception in developing countries, widespread use of tetravalent rhesus rotavirus vaccine could cause 2,000–3,000 deaths a year. For some, the prospect of causing this many deaths, perhaps even any deaths, is morally untenable. The context of developing countries differs starkly from North America. Despite efforts to prevent death with programs of oral rehydration therapy, about three million children die of diarrhea annually. Of these deaths approximately 600,000 to 800,000 are caused by rotavirus. Tetravalent rhesus rotavirus vaccine may prevent 80% of these deaths. If the next vaccine in development takes three to five years to get to the stage where tetravalent rhesus rotavirus vaccine is now, the choice to wait must be weighed against the cost of waiting: 1.4 to 3.2 million preventable deaths.

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