ORIGINAL ARTICLE

Antimicrobial Resistance of Nosocomial Infections in Children

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Abstract. A 9-month prospective study, from August 1988 to April 1989, was performed at the Department of Child Health, Medical School, Padjadjaran University, Hasan Sadikin Hospital Bandung. The aim of the study was to identify the pattern of sensitivity of bacteria causing nosocomial infections. It was revealed that among 4328 hospitalized pediatric patients, a total number of 342 patients had one or more nosocomial infections, yielding 411 episodes. Twenty-five per cent of isolated *S. aureus* was resistant to either ampicillin or oxacyllin. Higher percentages of resistance were observed in *S. albus*, i.e., to penicillin (53.3%) and oxacyllin (46.7%), and to cefuroxime, erythromycin and clindamycin (each in 40.0% of isolate). *E. coli* was in 86.3% resistant to ampicillin, 78.4% to chloramphenicol (and thiamphenicol), 56.8% to tobramycin and 48.2% to gentamicin. The isolated *Salmonella sp* was almost 100% resistant to ampicillin and chloramphenicol (and thiamphenicol) but was highly sensitive to amikacin, cefotaxime and netilmicin, arround 100%. *Pseudomonas sp* was 92.9% resistant to ampicillin, 85.7% to chloramphenicol (and thiamphenicol) and 78.6% to cefuroxime; on the contrary it was 92.9% sensitive to amikacin. It can be concluded that gram-negative microorganisms were in general showed highly resistant to ampicillin, chloramphenicol (and thiamphenicol), tobramycin, and gentamicin; on the other hand more than 90% were sensitive to netilmicin, cefotaxime and amikacin. **[Paediatr Indones 1993; 33:133-41].**

Introduction

Antimicrobial therapy has a major impact on the changing ecology of nosocomial infections. In the preantibiotic era, streptococci and staphylococci were the dominant nosocomial pathogens. The introduction of penicillin abated infections caused by streptococci but had only a temporary effect on staphylococci; most strains of staphylococci are resistant to penicillin and a number of more recent antibiotics. For reasons that are still poorly defined, aerobic gram-negative bacilli have emerged as the major nosocomial pathogens in the past two decades. Concurrent with the introduction and widespread use of potent aminoglycosides, multiresistant nosocomial pathogens have emerged.[1] Many organisms are multiple drug-resistant, defined as resistance to two or more antibiotics to

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which the bacteria are usually susceptible.[2] The purpose of this study was to identify the pattern of sensitivity of bacteria causing nosocomial infections.

Materials and Methods

This was a 9-month prospective study, performed at the Department of Child Health, Medical School, Padjadjaran University, Hasan Sadikin Hospital Bandung, from August 1, 1988 till April 30, 1989. Patient's records and case finding by trained nurses were used as the basis for detecting nosocomial infections. During the study period, none of the selected and already trained nurses were transferred either from one ward to another in the Department or to any other Department in the hospital.

During the study a careful and strict monitoring record of all patients' movements was kept in a special book and completed by the trained nurses in every ward. Clinical samples for bacteriological examination were collected by the trained nurses in every ward from all patients at the onset of clinical signs of the suspected nosocomial infection and transported to the Department of Microbiology, Medical School, Padjadjaran University, Bandung. The isolated microorganisms were stored and regularly sent to the Department of Microbiology Academisch Ziekenhuis-Vrije Universiteit Brussel (VUB), Belgium, for quality assurance, where the results were generally reliable.

The collection of data was conducted as follows. First, every trained nurse reported a new suspected nosocomial infection case in her ward to the investigator. The investigator then immediately examined the patient and checked the patient's record. If a nosocomial infection was suspected the nurse completed all forms needed. These forms were then rechecked and corrected when necessary by the investigator together with the nurse. Every two weeks a meeting with the microbiologists was held to discuss the microbiological results, and the results were checked again together with the microbiology form. After all forms were completed, data cleaning and completed questionnaires verification were done by the investigator to ensure that no data had been missed or had escaped from the attention before computerization.

Results

It was revealed that among 4,328 hospitalized pediatric patients, a total number of 342 patients had one and or more nosocomial infections, yielding 411 episodes. The overall nosocomial infection rate was 9.5%. Tables 1 and 2 present the antibiograms of the isolated microorganisms, those of the gram-positive separated from the gram-negative.

Tables 1a and 1b show clearly that in this study *Staphylococcus aureus* was resistant to ampicillin and oxacyllin, each in 25.0% of isolates. Higher percentages of resistance were observed in *Staphylococcus albus* to penicillin (53.3%) and oxacyllin (46.7%), whereas to cefuroxime, erythromycin and clindamycin each in 40.0% of isolates.

The antibiogram of gram-negative microorganisms can be seen in Tables 2a and 2b. Eighty-six per cent of *Escherichia coli* was resistant to ampicillin, 78.4% to chloramphenicol (and thiamphenicol), 56.8% to tobramycin, and 48.2% to gentamicin. *Salmonella species* were almost 100% resistant to ampicillin and chloramphenicol (and thiamphenicol) but were highly sensitive to amikacin, cefotaxime, and netilmicin. *Pseudomonas species* was 92.9% resistant to ampicillin, 85.7% to chloramphenicol (and thiamphenicol), and 78.6% to cefuroxime. On the contrary they were 92.9% sensitive to amikacin. Similar results were obtained with *Klebsiella species*; in addition it was also resistant to cotrimoxazole and tobramycin, i.e., in 76.5% and 58.8% of isolates, respectively. However, *Klebsiella* were 100% sensitive to amikacin, 94.1% to netilmicin, and 85.3% to cefotaxime.

Discussion

The evolution of antimicrobial resistance continues to hamper the efforts to control the impact of infectious diseases in an increasingly compromised patient population, especially nosocomial infections. Multiresistant infections continue to occur both in isolated instances and in epidemics. In the hospital multiresistant nosocomial isolates of gram-negative bacilli require the use of amikacin, trimethoprim-sulfamethoxazole, and cephalosporins to achieve clinical success.[3]

Mechanisms of antibiotic resistance may be divided into three categories: (1) changes in permeability of the cell wall or outer membrane to the antimicrobial agent, (2) alteration of the antimicrobial binding or target site, and (3) inactivation or modification of the drug by bacterial enzymes. One or more of these mechanisms may be present in a single bacterial isolate. The genetic coding for these mechanisms may be chromosomal, plasmid, or transposon mediated. Unlike chromosomal resistance that is spread only by means of cell division to genetically identical progeny, plasmids and transposons can jump from one organism to another, thereby facilitating the spread of resistance. These transmissible genetic fragments are capable of conveying single or multiple drug resistance, as well as other factors important for cell survival or virulence.[3]

In this study large variations in antimicrobial efficacy are most dramatically illustrated by the high resistance of almost all gram-negative bacilli to ampicillin and chloramphenicol (and thiamphenicol), i.e., 80%. Resistance to tobramycin, gentamicin, and cotrimoxazole was also high (around 40-60%). On the contrary, resis-

Table 1a. Antibiogram of gram-positive microorganism isolated from specimens of suspected nosocomial infection

Species of microorganisms and resistancy	ampicillin			cefrox			gentamicin			netilmycin			tobramycin		
	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S
S. aureus	-	3	9	-	1	11	-	1	11	-	2	10	-	2	10
% resistant		25.0			8.3			8.3			16.7			16.7	
S. albus	2	5	8	2	6	7	3	3	9	-	2	13	2	2	11
% resistant		33.3			40.0			20.0			13.3			13.3	
S. pneumoniae	-	-	1	-	-	1	-	1	-	-	1	-	1	-	-
% resistant		0			0			100.0			100.0			100.0	
Enterococcus	-	-	1	-	1	-	-	1	-	-	1	-	1	-	-
% resistant		0			100.0			100.0			100.0			0	
Overall	2	8	19	2	8	19	3	6	20	-	6	23	3	5	21
% resistant		27.6			27.6			20.7			20.7			17.2	

Table 1b. Antibiogram of gram-positive microorganism isolated from specimens of suspected nosocomial infection

Species of microorganisms and resistancy	co-trimoxazole			penicillin			oxacillin			erythromycin			clindamycin		
	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S
S. aureus	-	2	10	1	2	9	-	3	9	-	1	11	-	-	12
% resistant		16.7			16.7			25.0			8.3			0	
S. albus	1	5	9	1	8	6	-	7	8	1	6	8	-	6	9
% resistant		33.3			53.3			46.7			40.0			40.0	
S. pneumoniae	1	-	-	-	-	1	-	1	-	-	1	-	-	1	-
% resistant		100.0			0			0			0			100.0	
Enterococcus	1	-	-	-	-	1	-	1	-	-	1	-	-	1	-
% resistant		0			0			100.0			100.0			100.0	
Overall	2	8	19	2	10	17	-	11	18	2	8	19	-	8	21
% resistant		27.6			34.5			37.9			27.6			27.6	

Table 2a. Antibiogram of gram-negative microorganisms isolated from specimens of suspected nosocomial infection

Species and resistancy	ampicillin			cefrox			gentamicin			netilmycin			tobramycin		
	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S
E. coli	-	120	19	10	15	114	49	67	63	1	2	136	10	79	50
% resistant		86.3			10.8			48.2			1.4			56.8	
Salmonella sp.	-	56	1	3	9	5	1	40	16	1	1	55	1	52	4
% resistant		98.2			15.8			70.2			1.8			91.2	
Pseudomonas sp.	-	13	1	-	11	3	1	9	4	-	8	6	-	9	5
% resistant		92.9			778.6			64.3			57.1			64.3	
Klebsiella sp.	-	32	2	3	13	18	-	17	17	-	2	32	-	20	14
% resistant		94.1			38.2			50			5.9			58.8	
Enterobacter sp.	-	19	5	1	7	16	5	7	12	1	2	21	4	9	11
% resistant		79.2			29.2			29.2			8.3			37.5	
Serratia sp.	-	7	-	-	5	2	2	3	2	1	1	5	-	7	-
% resistant		100			71.4			42.9			14.3			100	
Citrobacter sp.	-	6	-	1	2	3	2	4	-	1	2	3	2	4	-
% resistant		100			33.3			66.77			33.3			66.7	
Proteus sp.	-	4	-	-	3	1	-	2	2	-	-	4	-	2	2
% resistant		100			75			50			0			50	
Shigella flex.	-	-	3	-	-	3	-	-	3	-	-	3	-	2	1
% resistant		0			0			0			0			66.7	
Providencia sp.	-	-	2	-	1	1	-	-	2	-	-	2	-	-	2
% resistant		0			50			0			0			0	
Non-ferm gram (-)	-	-	2	-	-	2	-	-	2	-	1	1	-	1	1
% resistant		0			0			0			50			50	
Arizona	-	1	-	-	1	-	-	1	-	-	-	1	-	1	-
% resistant		100			100			100			0			100	
Overall	-	258	35	18	67	208	20	150	123	5	19	269	17	186	90
% resistant		88.1			22.9			51.2			6.5			63.5	

Table 2b. Antibiogram of gram-negative microorganisms isolated from specimens of suspected nosocomial infection

Species and resistancy	co-trimoxazole			amikacin			cefotaxime			chlorampenicol			thiampenicol		
	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S
E. coli	8	43	88	1	3	135	5	3	131	1	109	29	2	109	28
% resistant		30.9			2.2			2.2			778.4			78.4	
Salmonella sp.	2	17	38	-	-	57	1	-	56	-	56	1	-	56	1
% resistant		29.8			0			0			98.2			98.2	
Pseudomonas sp.	-	12	2	1	1	12	1	3	10	1	12	1	1	12	1
% resistant		85.77			7.1			21.4			85.7			85.7	
Klebsiella sp.	2	26	6	-	-	34	-	5	29	1	276	6	1	27	6
% resistant		76.5			0			14.7			79.4			79.4	
Enterobacter sp.	1	12	11	-	-	24	1	2	21	-	14	10	-	14	10
% resistant		50			0			8.3			58.3			58.3	
Serratia sp.	-	5	2	-	-	7	-	-	77	-	5	2	-	5	2
% resistant		71.4			0			0			71.4			71.4	
Citrobacter sp.	-	5	1	-	-	6	1	2	3	-	6	-	-	6	-
% resistant		83.3			0			33.3			100			100	
Proteus sp.	-	3	1	-	-	4	-	2	2	-	2	2	-	2	2
% resistant		75			0			50			50			50	
Shigella flex.	-	-	3	-	-	3	-	-	3	-	1	2	-	1	2
% resistant		0			0			0			33.3			33.3	
Providencia sp.	-	-	2	-	-	2	-	-	2	-	1	1	-	1	1
% resistant		0			0			0			50			50	
Non-ferm gram (-)	-	-	2	1	-	1	-	-	2	-	1	1	-	1	1
% resistant		0			0			0			0			0	
Arizona	-	1	-	-	1	-	-	1	-	-	1	-	-	1	-
% resistant		100			0			100			100			100	
Overall	13	124	156	3	4	286	9	18	266	4	234	55	5	234	54
% resistant		42.3			1.4			6.1			79.9			79.9	

tance to netilmicin and amikacin remained low (6.5 and 1.4%). Resistance to the third generation cephalosporin, cefotaxime, was 6.1%; the use of cefotaxime in Hasan Sadikin General Hospital has been very limited since this agent is very expensive.

In the United States the frequency of resistance to gentamicin of *P. aeruginosa* causing nosocomial infections increased from approximately 10% in 1980 to approximately 22% in 1985. During the same period, the frequency of resistance of *P. aeruginosa* to tobramycin and amikacin increased less rapidly.[4] Gentamicin resistance is much more common among *P. aeruginosa* isolates in Japan and Greece than in isolates from Switzerland, UK or USA.[5] Garcia et al. also reported an outbreak of *P. aeruginosa* infection in a neonatal unit that is resistant to ticarcillin, piperacillin, mezlocillin, gentamicin, netilmicin, tobramycin, amikacin, cefotaxime, ceftazidime in six out of eight patients.[6] Infection due to Klebsiella species resistant to many kinds of antibiotics was mentioned by Morgan et al.[7] Ampicillin is usually not effective to Klebsiella, as was also shown in this study (94.1% resistance).

Outbreaks due to antibiotic multiresistant salmonellae of serotypes other than *S. typhi* were also reported frequently.[8] In this study the *Salmonella species* was more than 70% resistant to gentamicin, ampicillin, tobramycin and chloramphenicol (and thiamphenicol). Janas et al. from Jakarta, Indonesia, showed that *Salmonella species* and *Enteropathogenic E. coli* were 100% resistant to ampicillin, chloramphenicol and tetracylin, whereas 30% to trimethoprim-sulfamethoxazole and 27% to gentamicin.[9]

Murray et al. investigated resistance to trimethoprim-sulfamethoxazole among strains of *E. coli* isolated during 1983-1984 in Chile, Thailand, Honduras, Costa Rica, and Brazil (developing countries) and found that the prevalence of resistance to this agent ranged from 38% to 50%, while in the United States during the same period it was 4-6%.[10] In our study it was 30.9%.

In a study of 176 strains of enterotoxigenic *E. coli* from the Philippines, Korea, Taiwan and Indonesia, 126 (72%) were found to be resistant to one or more antibiotics, and 44% were resistant to at least four drugs.[8] In our study at least 56.8% of *E. coli* was resistant to three drugs (ampicillin, chloramphenicol/thiamphenicol, and tobramycin).

According to NEU, penicillin G remains the most useful antibiotic for the treatment of a number of important gram-positive infections.[11] In our study more than 30% gram-positive bacteria were resistant to penicillin. Resistance to aminoglycosides, trimethoprim-sulfamethoxazole, and cephalosporins requires a completely different approach to the choice of empiric therapy for the treatment of infections caused by such microorganisms at different institutions. Factors that account for such differences include severity of patient's illness and length of stay, extent of immunosuppression, instrumentation, clustering of patients in specialty services, and overcrowding in poorly designated patient care units.[3]

In several patients with life threatening infections, it is still prudent to use a second agent, such as an aminoglycoside, until the clinical status becomes stabilized because of the significant morbidity associated with *P. aeruginosa* infection and the emergence of resistant Enterobacter species in many centers.[12] In general there is a relation between antibiotic use (or overuse) and the development of resistance; therefore it is imperative to have an accurate antibiotic policy in the hospital.

Conclusion

It can be concluded that in this study gram-negative microorganisms causing nosocomial infections showed high resistance to ampicillin, chloramphenicol (and thiamphenicol), tobramycin, and gentamicin. On the other hand more than 90% of them were sensitive to netilmicin, cefotaxime, or amikacin.

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