PATTERNS OF RESISTANCE TO ANTIBIOTICS AT KING FAHD HOSPITAL OF THE UNIVERSITY

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هدف الدراسة: لوحظ مؤخرا وفي جميع أنحاء العالم ارتفاعا مطردا في نسبة مقاومة البكتيريا لمضادات الجراثيم مما قد يؤدي إلى الفشل في علاج الأخماج أو زيادة تكاليف العلاج. لذلك فانه من الأهمية بمكان دراسة نمط مقاومة البكتيريا للأنواع المستعملة من مضادات الجراثيم بانتظام على مستوى الإقليم أو الدولة.

طريقة الدراسة: لقد تم تحليل نمط سلوك البكتيريا التي عزلت في مستشفى الملك فهد الجامعي بالخبر على مدار سنة كاملة تجاه مضادات الجراثيم المستعملة في المستشفى.

نتائج الدراسة: لقد تم عزل 3679 كائن جرثومي حي ينتمون إلى 35 نوعا وكانت أجناس البكتيريا العقدية هي الأكثر شيوعا (25.5 %) يليها العنقودية الذهبية (16.1 %)، الاشريكية القولونية (12.7 %)، أجناس الزائفة (9.3 %)، و أجناس الكبسيلة (7.0 %).

لقد كان اكثر من 50 % من أجناس البكتيريا المعوية وكذلك المستديمة النزلية مقاوم لدواء الامبسلين ومركب الامكسيسلين + الكالفونيت بينما كان نحو 60 % و 38.1 % من بكتيريا الاشريكية القولونية مقاوم للدواءين السابقين على التوالي. أما بالنسبة للبكتيريا العنقودية الذهبية فقد كان نحو 98.1 % منها مقاوم للبنسلين فيما 91.1 % مقاوم لمركب الامكسيسلين + الكالفونيت و 25.5 % مقاوم للمثيسلين ولكنها بقيت حساسة لدواء الفنكوميسين.

لقد لوحظ مقاومة عالية لدواء التتراسيكلين (> 53 % من 2830) وخاصة بكتيريا المستديمة النزلية 80.5 % ، البكتيريا العقدية 72.9 % و الاشريكية القولونية 54.5 %، كما كان هناك مقاومة عالية لمركب السلفاميثيكسازول + الترايميثوبريم من قبل هذه البكتيريا وبالنسب التالية 75.5 %، 80.4 % و 48.1 % لكل منها على التوالي. لقد كانت المقاومة العامة لدواء الجنتاميسين متوسطه (26.0 % من 1567) ولكن من المهم ملاحظة ان البكتيريا السالبة بقيت حساسة لهذا الدواء. ومن الجدير ملاحظة ان نحو 24.3 % من 839 تم تحليلها لتعدد مقاومتها لمركب الامكسيسلين + الكالفونيت ولدواء الجنتاميسين.

الاستنتاجات: إن هذه الدراسة تبين أن نمط مقاومة البكتيريا لمضادات الجراثيم عالية جدا وتنذر بالخطر وربما كان ذلك يعكس سوء استعمال هذه المضادات في المنطقة الشرقية من المملكة العربية السعودية.

التوصيات: نوصي بان يكون لكل مستشفى سياسة خاصة تعتمد على التحليل المستمر لنمط مقاومة البكتيريا في المنطقة التي يقع بها، كما نؤكد على أهمية إنشاء مركز في كل منطقة من مناطق المملكة لمكافحة أمراض الأخماج وكذلك لحفظ وتبادل المعلومات وصياغة الاستراتيجية اللازمة لشراء وصرف واستعمال مضادات الجراثيم

الكلمات المرجعية: مضادات الجراثيم ، مقاومة مضادات الجراثيم ، كائنات حية دقيقه ممرضه ، المملكة العربية السعودية.

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Introduction and Aim*: A sharp worldwide rise in bacterial resistance to antimicrobial agents in both nosocomial and community acquired pathogens has recently been observed. This may complicate treatment of infectious disease or increase the cost of its management. It is, therefore, important to regularly investigate the patterns of resistance to antimicrobial agents at both local and national levels.*

Methods: *The antibiograms of organisms isolated over a one-year period in King Fahd Hospital of the University were analyzed.*

Results*: Of the 3679 microbial isolates of 35 types of organisms identified, the most common were Streptococcous spp (25.5%), S. aureus (16.1%), E. Coli (12.7%), Psueudomonas spp (9.3%) and Klebsiella spp (7%) High resistance rates (>50%) to ampicillin and to amoxycillin + clavulanate (AMX+CLV) were encountered in Enterobacter spp., and H. influenzae while in E. coli, the resistance was higher to ampicillin (60.0%) than to AMX+CLV (38.1%). With regard to S. aureus, 98.3%, 91.1% and 25.5% of isolates were resistant to penicillin, AMX+CLV and methicillin respectively but all were sensitive to vancomycin. High resistance (53% of 2830 isolates) to tetracycline was also observed especially in H. influenzae (80.5%), Streptococcous spp (72.9%) and E. Coli (54.5%). The same organisms were also highly resistant to trimethoprim/sulphamethoxazole with rates of 75.5%, 80.4% and 48.1% respectively. Moderate resistance (26% of 1567 isolates) to gentamicin was noted but the drug remained very effective against most tested gram-negative organisms. In addition, multiple resistance to gentamicin and AMX+CLV was also detected in 24.3% of 839 isolates.*

Conclusions and Recommendations*: It is concluded that the alarmingly high pattern of bacterial resistance to antibiotics may reflect the extent of use of each antibiotic in the eastern province of Saudi Arabia. It is recommended that hospital antibiotic policies (purchasing, prescribing and dispensing) be based on, and regularly reviewed in accordance with hospital antibiogram results. A center for infectious disease control should also be established in each region of the Kingdom to disseminate information and coordinate antibiotic policies among hospitals.*

Key Words*: Antibiotics, resistance, pathogenic organisms, Saudi Arabia*

INTRODUCTION

Over the last several years, the incidence of bacterial resistance to antimicrobial agents has risen sharply in both nosocomial and community acquired pathogens.[1] The resistance to antibiotics may result in therapeutic failure, relapse of infections or increase in the cost of their management.[2] Many factors contribute to the increase in the incidence of bacterial resistance to antibiotics, particularly, the misuse of antibiotics by physicians and the easy acquisition of antibiotics via non-physicians.[3] In addition, the feeding of farm animals with subtherapeutic levels of antimicrobial agents may cause the development of resistant strains that may spread to humans.[3]

The mechanisms by which bacterial resistance to antibiotics arise may be natural or acquired through chromosomal mutation or transfer of plasmids between bacterial cells by conjugation, transformation and transduction.[4] Resistance to individual antibiotics differs

according to bacterial species and antibiotic policies adopted by different countries. One of the most important mechanisms of resistance to β-lactam antibiotics is the production of β-lactamase enzymes. The incidence of development of strain-producing enzymes together with that of those with extended spectrum β-lactamases has been increasing rapidly.[5] Most of these strains show cross-resistance to different types of antibiotics.[5] Among the isolates which exhibit these characteristics are E. coli and Klebsiella spp. Resistance to the new fluoroquinolones is also increasing especially in some nosocomial pathogens such as Serratia spp., Acinetobacter spp., and methicillin-resistant S. aureus.[6]

Our study aimed at analyzing the antibiograms of the organisms isolated during a one-year period in the laboratories of King Fahd Hospital of the University, Al-Khobar, in order to provide the basis for updating the current antibiotic policy in our hospital and serve as base data for future review.

METHODOLOGY

The results of all microbiological susceptibility tests performed at King Fahd Hospital of the University (KFHU) were collated over a period of one year, between 1st January 1995 and 31st December 1995. Organisms were isolated and identified according to standard laboratory methods.[7] Each organism was tested against the recommended antimicrobial agents using single-disc antibiotic-sensitivity testing method. Susceptibility tests were performed using BBL® Sensi-Disc® antimicrobial susceptibility test discs (Becton Dickinson Microbiology Systems, Cockeysville, USA). The criteria for interpretation were those recommended by the National Committee for Clinical Laboratory Standards (NCCLS)[8] and quality control was performed on a regular basis. Control culture of S. aureus (ATCC 25923), E. coli (ATCC 25922) and P. aeruginosa (ATCC 27853) were used and zone diameters were measured in parallel with susceptibility tests performed on clinical isolates. The zone diameters given by the control studies were compared with the standard zone diameters recommended by NCCLS. Patient's number, type of specimen, organism detected and its antibiogram were recorded and later entered in a database for analysis using SPSS/PC software.

RESULTS

Over the one-year period, 3679 isolates of 35 types of organisms were isolated from 2484 patients (Table 1). The most frequently isolated organisms (939 – 25.5%) were streptococcus groups (552 Streptococcus B, 199 Streptococcus D, 124 Streptococcus A, 57 Streptococcus pneumoniae and 7 Viridans streptococci), S. aureus 594 (16.1%), E. coli 469 (12.7%) and Pseudomonas spp. 342 (9.3%).

The overall resistance rate to ampicillin was 36.4%. Streptococcus groups showed the lowest resistance rate (1.6%) while the highest rates were observed with Enterobacter spp. (92.8%), H. influenzae (61.9%) and E. coli (60.2%) (Table 2). S. aureus, Enterobacter spp., H. influenzae and E. coli organisms were also highly resistant to amoxycillin + clavulanate with rates of 91.1%, 80%, 50% and 38.1% respectively (Table 3). All B. fragilis, 98.3% of S. aureus and 92% of S. epidermidis isolates were resistant to penicillin G while streptococci remained the most sensitive to the drug with a resistance rate of only 5.6% (Table 4).

The resistance rates of Pseudomonas spp., isolates to piperacillin, aztreonam, imipenem and ceftazidime were 8.5%, 16%, 12.4% and 6.8% respectively; 15.2% of 407 S. aureus and 25.7% of 74 S. epidermis isolates were resistant to cefoxitin.

Table 1:*Organisms isolated from patients treated in KFHU*

Organisms Detected	Frequency	%
Streptococci	939	25.5
S. aureus	594	16.1
E. coli	469	12.7
Pseudomonas spp.	342	9.3
Klebsiella spp.	258	7.0
Candida spp.	172	4.7
Enterobacter spp.	145	3.9
S. epidermidis	119	3.2
Salmonella spp.	118	3.2
H. influenzae	90	2.4
H. aegyptius	80	2.2
Serratia spp.	64	1.7
Proteus spp.	40	1.1
Acinetobacter spp.	39	1.1
Citrobacter spp.	30	0.8
B. fragilis	29	0.8
Peptococcus spp.	21	0.6
S. saprophyticus	19	0.5
M. catarrhalis	17	0.5
M. morganii	17	0.5
Shigella spp.	16	0.4
G. vaginalis	13	0.4
N. gonorrhoeae	12	0.3
Providencia spp.	9	0.2
H. pylori	7	0.2
X. maltophilia	6	0.2
B. melentesis	3	0.1
C. perfringens	2	0.1
Aspergillus spp.	2	0.1
Bacillus spp.	2	0.1
Campylobacter spp.	1	0.0
Corynebacteria spp.	1	0.0
Aeromonas sobria	1	0.0
Flavobacterium spp.	1	0.0
C. tetani	1	0.0
Total	**3679**	**100**

Table 2*: Patterns of resistance to ampicillin*

Microorganisms	No. of tests	No. resistant	% Resistance
E. coli	455	274	60.2
Enterobacter spp.	139	129	92.8
H. aegyptius	72	44	45.8
H. influenzae	84	52	61.9
Salmonella spp.	117	26	22.2
Streptococci	925	15	1.6
Others	315	227	72.1
Total	**2107**	**767**	**36.4**

Table 3: *Patterns of resistance to amoxicillin + clavulanate (AMX + CLV)*

Micro-organisms	No. of tests	No. Resistant	% Resistant
E. Coli	197	75	38.1
Enterobacter spp	110	88	80.0
H. aegyptius	72	33	45.8
H. influenzae	84	42	50.0
Klebsiella spp	149	36	14.5
Salmonella spp	118	7	5.9
S. aureus	146	133	91.1
Streptococci	412	4	1.0
Others	208	119	57.2
Total	**1496**	**537**	**35.9**

Table 4: *Patterns of resistance to penicillin G*

Micro-organisms	No. of tests	No. Resistant	% Resistant
B. fragilis	28	28	100
G. vaginalis	13	2	15.4
Peptococcus spp	18	2	11.1
S. aureus	517	508	98.3
S. epidermidis	100	92	92.0
Streptococci	568	32	5.6
Others	67	48	71.6
Total	**1311**	**712**	**54.3**

Table 5: *Patterns of resistance to tetracycline*

Micro-organisms	No. of tests	No. Resistant	% Resistant
E. Coli	418	228	54.5
Enterobacter spp	131	36	27.5
H. aegyptius	65	50	76.9
H. influenzae	82	66	80.5
Klebsiella spp	130	49	37.8
Salmonella spp	114	24	21.1
S. aureus	507	179	35.3
S. epidermidis	102	29	19.4
Streptococci	872	636	72.9
Others	409	192	46.9
Total	**2830**	**1489**	**52.3**

Table 6: *Patterns of resistance to gentamicin and multiple resistance to gentamicin and amoxycillin + clavulanate*

Micro-organisms	Resistance to gentamicin		Resistance to gentamicin & AMX+CLV	
	No. tested	No. Resistant (%)	No. tested	No. Resistant (%)
E. Coli	211	38 (18.0)	168	12 (7.10)
Enterobacter spp	120	26 (21.7)	106	20 (18.9)
H. aegyptius	71.0	8 (11.3)	66	3 (4.50)
H. influenzae	69.0	11 (15.9)	63	3 (4.80)
Klebsiella spp	167	27 (16.2)	139	16 (11.5)
Pseudomanas spp	328	60 (18.3)	6	1 (16.7)
S. aureus	239	130 (54.4)	124	110 (88.7)
Others	321	120 (37.4)	167	39 (23.4)
Total	**1568**	**411 (26.2)**	**839**	**204 (24.3)**

Table 7: *Patterns of resistance to trimethoprim/sulphamethoxazole*

Micro-organisms	No. of tests	No. Resistant	% Resistant
E. Coli	455	219	48.1
Enterobacter spp	143	28	19.6
H. aegyptius	69	62	89.9
H. influenzae	85	64	75.5
Klebsiella spp	248	64	25.8
Salmonella spp	115	15	13.0
S. aureus	533	111	20.8
S. epidermidis	100	26	26.0
Streptococci	929	742	80.4
Others	295	117	39.7
Total	**2972**	**1448**	**48.7**

Sensitivity of 2830 isolates to tetracycline is presented in Table 5. The overall resistance rate was 52.3%. In ranking order, the higher resistance rates were 80.5%, 76.9%, 72.9% and 54.5% for H. influenzae, H. aegyptius, streptococci and E. coli respectively, while S. epidermidis had the lowest rate of resistance (19.4%).

Table 6 summarizes the resistance patters of 1568 isolates to gentamicin. The highest rate of resistance (54.4%) was observed with S. aureus and the lowest (11.3%) with H. aegyptius. In addition, a high resistance pattern to amikacin was exhibited by S. aureus, 135 (71.1%) while 33 (10%) of 331 Pseudomonas spp. and only 1 (1.1%) of 93 S. epidermidis isolates showed resistance to it. All the 146 (25.5%) methicillin resistant S. aureus isolates were sensitive to vancomycin and teicoplanin but 11.3% of them were resistant to lincomycin.

Sensitivity of 2972 isolates to trimethoprim/sulphamethoxazole is shown in Table 7. The overall resistance rate was 48.7%, the highest rate (89.9%) was observed with H. aegyptius, streptococci (80.4%), H. influenzae (75.5%), and E. coli (48.1%) while Salmonella spp. sowed the lowest resistance rate (13%).

Nalidixic acid, norfloxacin and nitrofurantoin showed high efficacy against E. coli with resistance rates as low as 15.8%, 10.5% and 7.4% respectively. Only 7 (4.3%) of 163 Klebsiella spp. and 6 (5%) of 119 Enterobacter spp. isolates were resistant to ciprofloxacin.

Amoxycillin + clavulanate and chloramphenicol were the most effective drugs against Salmonella spp. isolates with resistance rates of 5.9% and 8.7% respectively, while resistance rates to erythromycin were relatively high in streptococci (41.5%) and S. aureus (33.9%).

DISCUSSION

The data in this study include community and nosocomial infections at King Fahd Hospital of the University (KFHU) in the eastern province of Saudi Arabia. The most frequently isolated pathogens were strepto-

cocci (25.5%) of which streptococcus B was the most common group, S. aureus (16.1%) and E. coli (12.7%). However, another study carried out in a general hospital in the same region[9] showed that the most frequently isolated nosocomial pathogens were Pseudomonas spp., S. aureus, Klebsiella spp., and E. coli. Similar patterns of prevalence were observed in Danish, Spanish and Canadian hospitals while P. aeruginosa and methicillin resistant coagulase-negative staphylococci and S. aureus were found to be the most frequent nosocomial pathogens in some other European hospitals.[10-14]

The antibiograms of isolated organisms showed great variation between types of antimicrobial agents tested and types of isolates. Very low rates of resistance were observed with streptococci to all the investigated penicillins (range 1.0-5.6%), thus penicillins remain the most effective agents in the treatment of streptococcal infections which constitute 26% of all infections. In contrast, very high rates of resistance (>90%) were encountered with S. aureus to both penicillin and AMX+CLV suggesting that the likely mechanism of resistance to penicillin and AMX+CLV is in the change in the target of action of penicillin and not the production of beta-lactamases since AMX+CLV contains a beta lactamase inhibitor, clavulanic acid. Similarly, enterobacter isolates in our hospital were highly resistant to both ampicillin (92.8%) and AMX+CLV (80.0%), again, suggesting that the mechanism of enterobacter resistance to beta lactam antibiotics is not via the production of β-lactamase. These results are in agreement with those of Andersen et al[15] who reported that 46 enterobacter isolates showed a high resistance to both extended spectrum penicillins and third generation cephalosporins. Resistance of E. coli to ampicillin (60.2%) and AMX+CLV (38.1%), however, suggests that production of β-lactamase and extended – spectrum β-lactamase are the most likely mechanisms of resistance by these organisms. Similar findings have been reported for both E. coli and Klebsiella spp., by several investigators.[5,16-18]

Resistance to tetracycline (Table 5) was generally high or moderate with all isolated organisms including Haemophilus spp., streptococci, E. coli and staphylococci. However, tetracyclines are not considered among the drugs of choice for infections caused by all of these organisms. Nevertheless, our data reflects the impact of extensive use of these antibiotics in primary health clinics and as additives to animal feed in the eastern province of Saudi Arabia. It is well established that cross-resistance between the various tetracycline compounds is common and probably plasmid mediated. The mechanisms by which organisms acquire resistance to tetracyclines possibly involve decreased drug penetration through cell membranes, reduced binding to bacterial ribosomes or by enzymatic inactivation of the drug.[19]

The good activity of gentamicin against all gram-negative organisms investigated (Table 6) in our study confirms the fact that aminoglycosides are known to be mostly effective against gram negative species. The relatively low resistance rates observed with gentamicin suggest that aminoglycosides are not misused since their use is restricted mainly to hospitalized patients. Multiple resistance to both gentamicin and AMX+CLV was observed with some gram-negative organisms, such as E. coli (7.1%), Enterobacter spp., (18.9%) and Klebsiella spp., (11.5%). Such findings were previously reported by French et al[18] who isolated an extended-spectrum β-lactamase producing Klebsiella strains which were resistant to

aminoglycosides and both cephalosporins and β-lactam β-lactamase inhibitor combinations. Although, P. aeruginosa isolates were not investigated for the combination of aminoglycosides and extended spectrum β-lactams in our study, other investigators reported an outbreak of these organisms which were highly resistant to aminoglycosides, extended spectrum β-lactams and quinolones in a Brazilian hospital.[20]

Trimethoprim is a bacteriostatic agent commonly used in combination with sulphamethoxazole (Co-trimoxazole, TMP-SMX) or as a single agent to treat urinary tract infections.[21-23] Our data suggest an emergence of high resistance to this drug combination especially, in E. coli and streptococci which are the main infecting agents of the urinary tract. The mechanism of acquired resistance to trimethoprim in gram negative bacteria is suggested to be plasmid – mediated alteration of the target enzyme, dihydrofolate reductase.[24]

In contrast to the observation of Asensi et al[25] who reported an outbreak in Brazil of Salmonella agona that was resistant to ampicillin, TMP-SMX, tetracycline, chloramphenicol, cephalosporins and aminoglycosides. Amoxycillin + clavulanate, chloramphenicol and trimethoprim were still highly effective against Salmonella spp.

The results of the investigated quinolones showed that nalidixic acid and norfloxacin had good activity against E. coli while ciprofloxacin was highly effective against enterobacteriaceae. Similar results were reported by Acar et al[6] who concluded that resistance to fluoroquinolones was still rare in common pathogens in France.

In conclusion, the antibiograms of pathogenic organisms in the eastern province of Saudi Arabia show alarmingly high resistance patterns especially to these essential antibiotics. This may be due to the fact that these drugs are available to patients without prescription[26,27] inspite of laws which classify them as non-over-the-counter (non-OTC) drugs. However, in comparison to those published in other countries our results show a great variation owing to a number of factors, such as antibiotic policies, the extent of use of broad spectrum antibiotics, abuse of antibiotics and the absence of global standard method for performing the sensitivity test or interpreting the results.[28]

We, therefore, recommend that antibiogram studies of nosocomial and community pathogens should be carried out periodically on national or regional levels. The results would be of great value in optimizing treatment strategies and national drug policies as well as in measuring the success of these policies. Furthermore, the results of such studies could be used to educate policy-makers, prescribers, health care professionals, and the general public in order to reduce misuse of antibmicrobial agents.

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