Antibiotic use and resistance in public-sector hospitals in KwaZulu-Natal

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Objective. To investigate a possible association between level of care, antibiotic use and antimicrobial resistance in 16 public-sector hospitals providing different levels of care in KwaZulu-Natal.

Design. A multicentre surveillance study was undertaken in 16 hospitals at three progressive levels of health care (district, regional, tertiary) where each hospital submitted 100 consecutive, non-repetitive isolates judged in the laboratory to be of potential clinical significance. Isolates were identified and susceptibility testing was undertaken using the Kirby-Bauer disc diffusion method with minimum inhibitory concentrations (MICs) extrapolated on an automated reading system. Isolates were grouped according to their natural resistance profiles, and percentage susceptibility, mean percentage susceptibility and standard deviation to each antibiotic were stratified within and across hospital levels. Antibiotic use data were expressed as the number of daily divided doses (DDDs) per 1 000 patient-days.

Setting. Two tertiary, 9 regional and 5 district public hospitals in KwaZulu-Natal.

Outcome measures. Percentage susceptibility.

Results. There was a general trend among the 1 270 isolates of highest susceptibility in district hospitals, followed by regional and then tertiary hospitals. This is consistent with the referral system where health conditions become increasingly severe/complex requiring greater antibiotic use and broader-spectrum agents at progressive hospital levels, with statistical significance ($p < 0.05$) evident where sample numbers were relatively large. Trend variations could be associated with the qualitative and quantitative differences in antibiotic use, albeit without statistical corroboration. Three per cent of the total number of isolates were sensitive to all antibiotics tested and 6% were resistant to a single agent only. The remaining 91% showed acquired resistance to more than one drug. The standard deviation ranged from 0% to 55%.

Conclusions. This study showed that resistance profiles among bacteria varied greatly within and across hospital levels. While antibiotic use varied as much, a statistically significant correlation between use and resistance could not be established. It was therefore postulated that the effect of selection pressure was obscured by other resistance determinants apparent in public hospitals in resource-poor settings. On a clinical level, the study showed that resistance profiles among bacteria vary too much to allow a national antibiotic policy as proposed in the standard treatment guidelines. Rather, such guidelines should be directed to specific profiles found in different hospitals and at different levels of health care. Regular surveillance to adjust such guidelines is essential.

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Antimicrobial resistance is currently the greatest challenge to the effective treatment of infections globally. Resistance adversely affects both clinical and financial therapeutic outcomes, with effects ranging from the failure of an individual patient to respond to therapy and the need for expensive and/or toxic alternative drugs to the social costs of higher morbidity and mortality rates, longer duration of hospitalisation, and the need for changes in empirical therapy.[1,2]

It is generally accepted that antimicrobial consumption in a population is one of the main driving forces for the development of resistance. Several epidemiological studies have shown that the type and frequency of resistance mechanisms varies in different settings and such differences have been related to qualitative and quantitative differences in antibiotic use.[3-5]

We investigated the association between antibiotic use and resistance in public-sector hospitals in KwaZulu-Natal.

Materials and methods

Setting

Since 1998 referral in the South African public health care system has involved three hospital levels, viz. district, regional and tertiary, with services ranging progressively from general medical services to highly specialised care. KwaZulu-Natal has 2 tertiary, 9 regional and 35 district hospitals. The study included both tertiary, all 9 regional and 5 randomly chosen but geographically representative district hospitals (Fig. 1).

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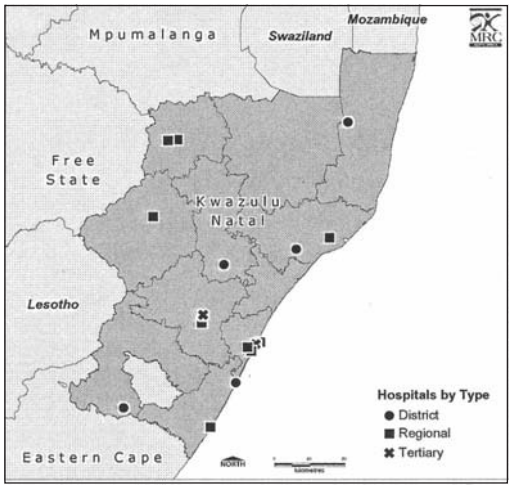

Fig. 1. Location of hospitals that participated in the study.

Isolates

The microbiology laboratory at each of the 16 hospitals was requested to submit a maximum of 100 consecutive, non-repetitive isolates during the study period. All isolates were considered by the laboratory staff to be of potential clinical significance based on specimen type and clinical information.

Antibiotics

The antibiotic test panel for Gram-negative organisms included ampicillin, amoxicillin-clavulanate, piperacillin, piperacillin-tazobactam, cephalothin, cefuroxime, cefotaxime, ceftazidime, cefepime, cefoxitin, meropenem, gentamicin, amikacin, nalidixic acid, ciprofloxacin, chloramphenicol, cotrimoxazole and nitrofurantoin. Benzylpenicillin, ampicillin, amoxicillin-clavulanate, oxacillin, cephalothin, cefepime, amikacin, chloramphenicol, clindamycin, cotrimoxazole, erythromycin and vancomycin made up the test panel for Gram-positive organisms.

Identification

Identification methods included standard in-house laboratory procedures[6] for Gram-positive isolates and the applicable API (bioMérieux sa, Lyon, France) systems for Gram-negatives.

Susceptibility testing

Susceptibility testing was performed using the Kirby-Bauer agar diffusion method following the National Committee for Clinical Laboratory Standards (NCCLS) guidelines.[7] Discs were obtained from Mast Diagnostics, Merseyside, UK. Minimum inhibitory concentrations (MICs) were extrapolated using the BIOMIC automated reading system and software (Giles Scientific, New York). MICs were confirmed using the agar dilution method on a selected sample.[7] Methicillin-resistant staphylococci (MRSA) were detected by means of oxacillin screening plates (6 μg/ml of oxacillin plus 2% NaCl in Mueller Hinton agar) and confirmed using the E-test.[8]

Extended-spectrum β-lactamases (ESBLs) were detected using the double-disc test,[9] while cefoxitin resistance was presumed to be indicative of ampC production.

All tests were performed in the laboratories of the Department of Medical Microbiology of the Nelson R Mandela School of Medicine, which participates in the UK National External Quality Assessment Scheme for Microbiology (NEQAS).

Susceptibility data analysis

NCCLS breakpoints for resistance were used to differentiate between susceptibility and resistance. Each organism was categorised as susceptible or resistant for drugs potentially relevant for treatment of infections with such species. Isolates were grouped according to their natural resistance profiles, and percentage sensitivity to each antibiotic was stratified according to hospital level. The mean percentage sensitivity and standard deviation (SD) were determined within hospital levels. Percentage susceptibility for each drug was also calculated by combining all species but excluding those with inherent resistance to a particular drug.

Antibiotic use data

Antibiotic use data were obtained from hospital pharmacy records and expressed as usage density rate. The total number of grams of each antibiotic used was divided by the number of grams per daily dose for the specific antibiotic, then divided by the patient-days, and multiplied by 1 000 to give the number of daily divided doses (DDDs) per 1 000 patient-days.[10]

Statistical methods

Categorical data were reported as per cent of specimens examined by hospital level of care (tertiary, regional, district). An overall chi-square test was used to compare percentages of isolates, susceptibility and antibiotic use by subgroups. If the overall chi-square was significant ($p < 0.05$), pairwise comparisons were explored. Where more than one comparison was significant, the most conservative p-value was reported.

Analysis of variance was used to compare average antimicrobial use and prevalence of antibiotic use. Overall significance was reported where the differences were not significant. Where significant, the overall p-value was not reported. Instead the Duncan multiple range test was used to test pairwise comparisons. Where multiple pairwise comparisons were significant, the most conservative p-value was reported.

Comparison of sensitivity by health facilities was limited to organisms with more than 30 specimens. Data were analysed using SAS V8 statistical software.

Results

The number of organisms received from the different hospital laboratories varied from 21 to 100, resulting in a total of 1 270 isolates. Twenty-four different species were identified, viz. *Escherichia coli* (24%), *Staphylococcus aureus* (22%), *Proteus* spp. (14%), *Klebsiella* spp. (10%), *Pseudomonas* spp. (9%), *Streptococcus* spp. (5%), *Acinetobacter* spp. (4%), *Enterobacter* spp. (3%), *Citrobacter* spp. (2%) and *Enterococcus* spp. (2%). The remaining 5% (not shown) was made up of *Aeromonas* spp., *Alcaligenes faecalis*, *Erwinia* spp., *Hafnia alvei*, *Haemophilus influenzae*, *Kluyvera* spp., *Morganella morganii*, *Neisseria meninigitidis*, *Providencia stuartii*, *Salmonella* spp., *Serratia* spp., *Shigella* spp. and *Stenotrophomonas maltophilia*.

Table I shows the percentage susceptibility for each drug calculated by combining all species but excluding those with inherent resistance to a particular drug, Table II shows antibiotic use at the different levels of care, and Table III shows the percentage of MRSA, ESBL-producing isolates and ampC-producing isolates identified together with the use of antibiotics known to select for these types of resistance.[1]

Three per cent ($N = 40$) of the total number of isolates were sensitive to all antibiotics tested and 6% ($N = 79$) were resistant to a single agent only. The remaining 1 151 isolates were multi-resistant.

Resistance rates could be correlated with the chronological development within antibiotic classes, for example, greater resistance to the earlier agents such as the penicillins and nalidixic acid and considerably less resistance to the newer cephalosporins and fluoroquinolones respectively.

A trend of highest sensitivity in district hospitals followed by regional and then tertiary hospitals was evident in 58% of the susceptibility test results, while 38% depicted the opposite trend, i.e. highest sensitivity in tertiary hospitals followed by regional and then district, and 6% showed no trend. The first trend was consistent with the referral system where health conditions become increasingly severe/complex requiring both greater antibiotic use and broader-spectrum agents at different hospital levels. However, this was only borne out in 42% of the antibiotics, specifically broader-spectrum drugs such as piperacillin, piperacillin-tazobactam, cefotaxime, cefoxitin, amikacin, nitrofurantoin and vancomycin, albeit the majority without reaching statistical significance (Table II). Further, although graphical representations of use and resistance depicted negative associations in some instances, they did not reach statistical significance.

Table I. Antimicrobial susceptibility (%) for each drug calculated by combining all species but excluding those with inherent resistance to a particular drug for different levels of hospital-based health care*

	Hospital level						
	District		Regional		Tertiary		
Antibiotic	*N*	%	*N*	%	*N*	%	*p*-value†
Penicillin G	118	18	185	20	34	12	0.5
Ampicillin	335	22	416	22	133	27	0.4
Amoxicillin-clavulanate	379	53	504	53	165	48	0.6
Piperacillin	284	46	386	54	129	45	0.07
Piperacillin-tazobactam	284	89	386	88	129	73	< 0.0001
Oxacillin	102	83	145	72	30	77	0.2
Cephalothin	379	60	504	57	165	42	< 0.0001
Cefuroxime	250	52	315	49	119	35	0.008
Cefotaxime	284	84	386	71	129	66	< 0.0001
Ceftazidime	284	98	386	91	129	82	< 0.0001
Cefepime	444	93	619	89	191	81	< 0.0001
Cefoxitin	315	78	430	67	145	66	0.002
Meropenem	315	100	430	99	145	98	0.03
Gentamicin	315	89	430	82	145	70	< 0.0001
Amikacin	417	97	575	91	175	76	< 0.0001
Chloramphenicol	444	63	619	64	191	56	< 0.0001
Naladixic acid	281	70	359	64	135	47	0.003
Ciprofloxacin	315	91	430	87	145	80	0.2
Nitrofurantoin	281	58	359	55	135	47	0.1
Trimethoprim-sulphamethoxazole	444	48	619	46	191	43	0.5
Erythromycin	118	65	185	66	34	59	< 0.001
Clindamycin	129	74	189	76	46	59	0.06
Vancomycin	129	100	189	100	46	100	NA

*Isolates were grouped and tested against antibiotics indicated for their treatment according to their inherent resistance profiles.
†Chi-square test.

Table II. Average antimicrobial use (DDD/1 000 patient-days) from different levels of hospital-based health care

Antibiotic	District	Regional	Tertiary	*p*-value
Penicillin G	371.17	430.44	565.364	0.7
Ampicillin	0.028	0.034	0.01	0.6
Amoxicillin-clavulanate	0.025	0.152	0.09	0.2
Piperacillin	0	0.001	0.001	0.3
Piperacillin-tazobactam	0	0.005	0.008	0.009 (T = R) > D $p < 0.05$
Cloxacillin	0.026	0.04	0.029	0.6
First cephalosporins (cefazolin, cephradine)	0.054	0.176	0.069	0.3 (R = T) $p = 0.6$ and T > D $p < 0.05$
Cefuroxime	0.015	0.39	0.046	0.054
Cefotaxime	0.006	0.012	0.01	0.5
Ceftazidime	0	0.001	0	0.7
Ceftriaxone	0.024	0.018	0.032	0.8
Cefepime	0	0	0	0
Cefoxitin	0	0.009	0.018	0.01 T > D $p < 0.05$
Meropenem	0	0	0.001	0.4
Gentamicin	0.088	0.001	0.001	0.02 D > R = T
Amikacin	0	0.006	0.009	0.03 T > D
Chloramphenicol	0.007	0.007	0.002	0.5
Naladixic acid	0.248	0.065	0.009	0.2
Ciprofloxacin	0.071	0.056	0.035	0.5
Nitrofurantoin	0.008	0.011	0.094	3E-04 T > (R = D)
Trimethoprim-sulphamethoxazole	1.299	2.052	0.642	0.3
Erythromycin	0.614	0.681	0.096	
Clindamycin	0	0.004	0.003	0.08
Vancomycin	0	0.002	0.003	0.2
Total use	2 978.3	2 764.98	1 091.88	

Analysis of variance (ANOVA) was used to test overall significance, which is reported if non-significant. Where significant, it is not reported. The Duncan multiple range test was used to test pairwise comparisons. Where multiple comparisons are significant, the most conservative *p*-value is reported.
DDD = daily divided dose.

Table III. Percentage MRSA, ESBL-producing isolates and ampC-producing isolates and use of antibiotics* selecting resistance

	Hospital level			
	District	Regional	Tertiary	*p*-value
MRSA	17	28	23	0.15¶
MRSA-selecting β-lactam use†	0.151	0.449	0.296	0.05‖ R > D
ESBL-producing organisms	1	3	9	0.001¶
ESBL-selecting β-lactam use‡	0.1	0.251	0.168	0.13‖
Gentamicin use	0.088	0.001	0.001	0.02‖ D > R = T
AmpC-producing organisms	22	33	34	< 0.002¶
Cefoxitin use	0	0.009	0.018	0.2‖
AmpC-selecting β-lactam use§	0.031	0.04	0.06	0.5‖

*Average daily divided dose/1 000-patient days.
†Cloxacillin, all cephalosporins and penicillin-inhibitor combinations.
‡All cephalosporins.
§All 1st, 2nd and 3rd generation cephalosporins.
¶Chi square/exact test.
‖Analysis of variance (ANOVA) was used to test overall significance which is reported if non-significant. Where significant, it is not reported. The Duncan multiple range test was used to test pairwise comparisons. Where multiple comparisons are significant, the most conservative p-value is reported.
MRSA = methicillin-resistant *Staphylococcous aureus*; ESBL = extended-spectrum β-lactamase.

The large SD values ranging from 0% to 55% emphasised susceptibility differences between hospitals within district, regional and tertiary levels.

When all isolates were combined in Table I, significantly lower levels of susceptibility were found in isolates from tertiary care hospitals for piperacillin-tazobactam ($p < 0.0001$) but not for piperacillin. There were also significantly lower levels of susceptibility for the different generations of cephalosporins ($p < 0.0001$ to $p = 0.008$). This was accompanied by a higher number of ESBL-producing *K. pneumoniae* isolates at this hospital level (Table I). However, when all ESBL-selecting β-lactams were combined no significant differences in use were found (Table III).

Resistance to cefoxitin was significantly higher in both regional and tertiary hospitals as compared with district hospitals ($p = 0.01$) (Table I). This was accompanied by a similar distribution of ampC-producing organisms but not with use of ampC-selecting drugs (Table III).

The remaining significant findings in difference in susceptibility (gentamicin, amikacin, meropenem and clindamycin) were all between tertiary and both the other levels of care, with higher resistance in the former (Table I). This corresponded with higher antibiotic use in the tertiary institutions for meropenem ($p = 0.4$) and amikacin ($p = 0.03$). However, use of clindamycin was similar at both tertiary and regional levels while use of gentamicin was highest at district level ($p = 0.02$) (Table II).

There was a difference in the use of MRSA-selecting antibiotics between district hospitals and both other levels of care. The percentage of MRSA among the *S. aureus* isolates followed this trend but this did not reach statistical significance (Table III).

Discussion

This study reports on resistance patterns among potentially clinically significant isolates of bacteria from hospitalised patients at different levels of health care and relates this to antibiotic selective pressure. A general trend of highest susceptibility in isolates from district hospitals followed by those from regional and then tertiary hospitals was evident and this is consistent with the referral system where health conditions become increasingly severe/complex requiring both greater antibiotic use and broader-spectrum agents at different hospital levels.

When use and prevalence of resistance were compared for individual antibiotics, differences in levels of resistance were found for 13 (57%) of the 23 antimicrobials tested (Table I). However, significant differences in amounts used were found with only 3 (13%) of these drugs (Table II). In only 1 of these (amikacin), resistance levels increased with use. Time-wise, resistance should follow increased use. This lack of correlation may be attributed to the fact that use data were collected in the same period as the resistance data. However, this was believed to be an unlikely explanation because the same antimicrobial policies have been in place for many years in both regional and tertiary care hospitals.

The three significant associations found were between piperacillin-tazobactam use and ESBL producers, between cefoxitin use and ampC producers, and between amikacin use and amikacin resistance. In tertiary hospitals, piperacillin-tazobactam is successfully used as first-line agent for the treatment of infections with ESBL-producing organisms.[11] Therefore, despite its association with the prevalence of ESBL producers, it is unlikely that this drug is the selective agent for these organisms. Despite the fact that in our environment ESBL production is associated with gentamicin resistance,[12] the association between use of this drug and ESBL prevalence was a negative one (Table III). Although this did not reach statistical significance, the higher use of the cephalosporins in regional and tertiary hospitals is therefore the most likely explanation for the higher prevalence of ESBL-producing organisms in these hospitals compared with the district hospitals.

Cefoxitin is used for surgical prophylaxis. The use pattern reflects the fact that most surgery for which prophylaxis is indicated takes place in the higher-level hospitals. This might explain the higher prevalence of ampC-carrying organisms (Table III) and cefoxitin resistance (Table I).

Because of the high prevalence of ESBL producers (Table III) also exhibiting gentamicin resistance in our environment, the first-line aminoglycoside in regional as well as tertiary hospitals is amikacin. This explains the high level of amikacin resistance (Table I) in these hospitals and the negative association between gentamicin use and ESBL producers (Table III).

Selection of resistance to one particular antibiotic is not the result of use of the drug in question only, but also use of all related drugs. Therefore, we looked at associations between the prevalence of resistant organisms and use of categories of selective antimicrobials (Table III). Here we found an association between β-lactam use and the prevalence of MRSA. Associations between ESBL-producing organisms, ampC carriers and the use of their respective selective drug categories were not found.

Like others,[5,13-15] we found that the association between drug use and resistance patterns is not straightforward. Factors such as infection control, hospital level, ward type, patient and disease profiles, invasive procedures and staffing have all been reported as confounders. More recently, the mechanisms by which antibiotics select resistance in bacteria (mutation versus acquisition of resistance genes) have also been quoted in this context.[13,14]

While this multicentre study clearly established the prevalence of high levels of resistance in certain hospitals, a limitation of the study was that the data could not be correlated with clinical outcome and did not inform potential strategies, partly because a multiplicity of factors impacts on antibiotic resistance in hospital settings. Resistance may emerge by selection pressure (overuse/indiscriminate antimicrobial use in developed versus underuse/misuse in developing countries) but is perpetuated by diverse risk factors and maintained within environments as a result of poor infection control. Population-specific drug pharmacokinetics and pharmacodynamics also play a role.

This study showed that associations between use of antimicrobials and resistance patterns in bacteria do exist but proof of a direct causal relationship is constrained by several confounding factors. Studies that take those confounders into account are needed.

On a clinical level, the study showed that resistance profiles among bacteria vary too much to allow a national antibiotic policy as proposed in the standard treatment guidelines. Rather; such guidelines should be directed to specific profiles found in different hospitals and at different levels of health care. Regular surveillance to adjust such guidelines is essential.

A way forward would be to institute a surveillance programme which should be disease-based, establishing sensitivity profiles of common causative organisms to inform the development of or amendment to standard treatment guidelines and essential drugs lists adopted within national drug policies in developing countries globally. The manner of antimicrobial use (overuse, underuse, inadequate dosing) associated with resistance must be established for appropriate intervention in terms of rational drug use, a reduction in use and dosing regimens based on population-specific pharmacokinetics and pharmacodynamics. Risk factors unique to South African communities (poverty, HIV and AIDS)

and hospitals (duration of hospitalisation, location within the hospital, intensive care unit stay, surgery, wounds, previous and current antimicrobial therapy, mechanical ventilation, urinary catherterisation, nasogastric intubation, central venous and peripheral catheters, previous hospitalisation, transfer from another unit or hospital, etc.) must be determined and due vigilance exercised in patients exhibiting classic risk factors for the acquisition of or colonisation with resistant pathogens. Hygiene and sanitation (in communities) and infection control (in hospitals) status must be determined and interventions initiated to prevent the spread of resistance. Pharmacokinetics and pharmacodynamics specific to diverse populations must be devised to optimise antimicrobial therapy.

South Africa has unique needs in the antimicrobial resistance arena, needs to be addressed in the context of severe financial, human-resource and technological challenges.

Detailed results on species distribution at the different levels of hospital-based care, percentage susceptibility per species and mean percentage susceptibility and SD within hospital levels are available on request from the corresponding author.

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