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Full Length Research Paper

Treatment guidelines and nosocomial infections: The South African experience

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Nationally-devised standard treatment guidelines (STGs) for nosocomial infections were evaluated in the context of antibiotic resistance within the public health care system in Kwazulu-Natal. A multi-centre surveillance study instituted in 3 hospitals at 3 progressive levels of health care (district, regional and tertiary) collected consecutive, non-repetitive isolates commonly implicated in nosocomial infections as cited by the STGs, viz., *Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter* spp. Isolates were subjected to susceptibility testing against antibiotics recommended in the treatment guidelines as empirical treatment for nosocomial infections using the Kirby Bauer disc diffusion method advocated by the CLSI. Percentage susceptibility across (1) bacterial species, (2) antibiotics and (3) hospital levels was compared. Susceptibility to antibiotics recommended in the treatment guidelines and hence potentially successful empiric therapy ranged from 5 to 95% with multi-resistance evident in all isolates. Statistically significant differences in overall susceptibility were observed (1) across bacterial species, (2) within 2 of the 3 bacterial species for different antibiotics and; (3) across hospital levels for 2 antibiotics with p values <0.001 for across bacterial species, (1), ranging from 0.003 to <0.001 for within 2 of the 3 bacterial species for different antibiotics (2) and ranging from 0.001 to <0.001 for across hospital levels for 2 antibiotics (3). This study showed that the success of empiric therapy as dictated by treatment guidelines would vary depending upon the bacterial species, the antibiotic used and the hospital, thus making a strong case for institution-specific guidelines based on evidence from well-executed surveillance.

Key words: Treatment guidelines, nosocomial infections, antibiotic resistance.

INTRODUCTION

The South African National Department of Health implemented standard treatment guidelines (STGs) and an essential drugs list (EDL) for common health problems, including all infections, encountered at primary care and hospital level. STGs and the EDL are critical aspects of the national health policy devised in the process of health care transformation in South Africa; addressing major health problems, initiating equity in health care delivery (availability and accessibility of essential drugs to all citizens), and, providing for rational prescribing and dispensing (National Department of Health, 1998).

Pharmacokinetic and pharmacodynamic data, drug interactions, adverse effects, routes of administration, concentrations at anatomical sites and cost are considered in the development of STGs and the EDL. However, the vacillating nature of antimicrobial susceptibility often nullifies such factors in the development of STGs for infections (Blondeau and Tillotson, 1999).

This study evaluated nationally-devised STGs for nosocomial infections in the context of antibiotic resistance within the public health care system in Kwazulu-Natal, South Africa.

MATERIALS AND METHODS

Setting

The study was conducted in 1 tertiary, 1 regional and 1district public hospital in the greater Durban metropole in Kwazulu-Natal.

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Table 1. Percentage susceptibility to antibiotics recommended as empiric therapy in Nosocomial *S. aureus* infections.

Antibiotic	Hospital level		
	Tertiary	Regional	District
Penicillin	5	10	25
Oxacillin	7	49	16
Clindamycin	86	82	82
Amikacin	84	90	93
Vancomycin	95	92	93

Table 2. Percentage susceptibility to antibiotics recommended as empiric therapy in nosocomial infections caused by aerobic Gram-negative bacteria.

Antibiotic	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.
For hospital-acquired *Pneumoniae*			
Piperacillin-tazobactam	55	77	19
cefepime	41	55	13
meropenem	93	54	14
For urinary tract infections			
Amikacin	69	81	16
Ciprofloxacin	49	89	27

Isolates

Passive surveillance elicited 105 *S. aureus* isolates from the tertiary hospital, 60 from the regional hospital and 49 from the district hospital. One hundred and sixteen (116) *K. pneumoniae*, 100 *Acinetobacter* spp. and 83 *P. aeruginosa* from the tertiary hospital formed the Gram-negative sample. Inadequate numbers of Gram-negative bacteria were recovered from the regional and district hospitals and they thus did not form part of the study. *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 served as controls.

Antibiotics

The anti-staphylococcal antibiotic test panel consisted of penicillin, oxacillin, clindamycin, amikacin, and vancomycin while the anti-Gram-negative antibiotic test panel consisted of piperacillin-tazobactam, cefepime, meropenem, ciprofloxacin and amikacin as recommended as by empiric therapy in the STGs and EDL of 2006 (National Department of Health, 2006).

Identification

Identification methods included standard in-house laboratory procedures[4] for Gram-positive isolates and the applicable API (bioMérieux sa, Lyon, France) systems for gram-negatives.

Susceptibility testing

Susceptibility testing was performed by means of the Kirby Bauer agar diffusion method following CLSI guidelines (CLSI, 2005). Discs were obtained from Mast Diagnostics, Merseyside, UK. 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).

Statistical methods

Categorical data were reported as percentage 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. Data was analysed in SAS V8 statistical software.

RESULTS AND DISCUSSION

Susceptibility to antibiotics recommended in the treatment guidelines and hence potentially successful empiric therapy ranged from 5 to 95% (Tables 1 and 2) with multi-resistance evident in all isolates. Tables 3 to 5 show statistically significant differences in overall susceptibility across bacterial species; (1), within 2 of the 3 bacterial species for different antibiotics (2) and; across hospital levels for 2 antibiotics (3) with p values <0.001 for across bacterial species (1), ranging from 0.003 to <0.001 for within 2 of the 3 bacterial species for different antibiotics (2) and ranging from 0.001 to <0.001 for across hospital levels for 2 antibiotics (3).

Table 3. Statistical analysis across bacterial species.

Antibiotic	Overall p value	Pairwise comparisons		
		K. pneumonia* vs. *P. aeruginosa	***K. pneumonia* vs. *Acinetobacter* spp.**	***P. aeruginosa* vs. *Acintebacter* spp.**
Cefepime	<0.001	0.08	<0.001	<0.001
Meropenem	<0.001	<0.001	<0.001	<0.001
Piperacillin- Tazobactam	<0.001	0.002	<0.001	<0.001
Amikacin	<0.001	0.07	<0.001	<0.001
Ciprofloxacin	<0.001	<0.001	<0.001	<0.001

Table 4. Statistical analysis across antibiotics.

Antibiotic	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter* spp.
Overall	<0.001	0.003	0.1
For hospital-acquired Pneumoniae			
Cefepime vs. Meropenem	<0.001	0.9	Not done as no overall significance
Cefepime vs. Piperacillin-tazobactam	0.04	0.004	
Meropenem vs. Piperacillin-tazobactam	<0.001	0.003	
For urinary tract infections			
Amikacin vs. Ciprofloxacin	0.003	0.2	Not done as no overall significance

Table 5. Statistical analysis across hospitals.

Antibiotic	Overall p value	Pairwise comparisons		
		Tertiary vs. Regional	**Tertiary vs. District**	**Regional vs. District**
Penicillin	0.001	0.3	<0.001	0.08
Oxacillin	<0.001	<0.001	0.06	0.001
Clindamycin	0.7	Not done as no overall significance		
Amikacin	0.17	Not done as no overall significance		
Vancomycin	0.2	Not done as no overall significance		

DISCUSSION

As in many other developing countries, South Africa has developed STGs for most diseases, including infections. Two of the most important factors influencing the inclusion of an antibiotic in an EDL are microbial aetiology of the disease and the incidence of antibiotic resistance (Blondeau and Tillotson, 1999). It is evident from this study that antibiotic resistance varies across bacterial species and antibiotics and within hospitals and thus impacts on empiric therapy as dictated in treatment guidelines.

The Hospital Level Standard Treatment Guidelines and Essential Drugs List (National Department of Health, 2006) specifically cites *K. pneumoniae, P. aeruginosa* and *Acinetobacter* spp. as causative aerobic Gram-negative nosocomial pathogens in hospital-acquired Pneumoniae (HAP) and urinary tract infections (UTIs) with the recommended treatment being piperacillin/tazobactam or cefepime or meropenem for HAP and amikacin or ciprofloxacin for nosocomial UTIs. *S. aureus* is considered a common causative nosocomial pathogen in intravascular line infections, surgical wound infections and HAP with the recommended treatment being cloxacillin or vancomycin (in the event of penicillin allergy or known high levels of cloxacillin resistance) for the first two infections and benzylpenicillin + amikacin for ward cases and vancomycin/clindamycin + ciprofloxacin (in penicillin allergy) for HAP.

Susceptibility results of the Gram-negative bacteria, collected at the single tertiary hospital, are used to illustrate the impact of bacterial species and antibiotic type while *S. aureus* susceptibility results are used to illustrate differences between hospitals at 3 levels ranging progressively from general medical services to highly specialised care.

Cefepime would effectively treat HAP caused by both

K. pneumoniae and *P. aeruginosa* (p=0.08) as amikacin would nosocomial UTIs (p=0.07). There are significant differences in susceptibility and thus successful empiric therapy shown by pairwise comparisons of bacterial species in Table 3. Similarly cefepime would work as well as meropenem against *P. aeruginosa* implicated in HAP (p=0.9) and as would amikacin and ciprofloxacin against *P. aeruginosa* in nosocomial UTIs (p=0.2).

There are again significant differences in susceptibility and thus successful empiric therapy shown by pairwise comparisons of antibiotics in Table 4. A trend of highest sensitivity in district hospitals followed by regional and then tertiary hospitals was evident for penicillin and amikacin consistent with the referral system where health conditions become increasingly severe/complex requiring both greater antibiotic use as well as broader spectrum agents at different hospital levels. The absence of similar trends for the other antibiotics could be attributed to differences in sample sizes as detailed in the methodology as well as factors such as differences in antibiotic use, infection control practices and patient transfers. The unusually high vancomycin resistance particularly in the district hospital requires further investigation.

Statistically significant differences in susceptibility shown in Tables 3 to 5 thus clearly demonstrate that the success of empiric therapy as dictated by treatment guidelines would vary depending upon the bacterial species, the antibiotic used for empiric treatment and the hospital-specific levels of resistance determined by the quantity of antibiotic use and infection control, thus making a strong case for evidence-based, institution-specific treatment guidelines based on regular surveillance. Microbial surveillance supports empirical treatment decisions and provides epidemiological data informing containment strategies including but not limited to infection control measures and antibiotic use policies (Masterton et al., 2007).

Adequate empiric therapy is particularly important for nosocomial infections because treatment is influenced by the microbial agent, patient susceptibility, environmental factors and bacterial resistance (WHO, 2002). However, antibiograms generated from routine susceptibility testing merely provide susceptibilities of a particular bacterial species to individual antibiotics, but do not indicate alternate antibiotics in the event of resistance to the entire test panel nor the impact of combination therapy (Beardsley et al., 2006). So while the South African treatment guidelines may be criticized for being formulated by “expert committees” and not necessarily on evidence from surveillance studies, any surveillance studies launched to provide the evidence to inform treatment guidelines in the future must allow provide information on alternate and combination therapy.

Masterton et al. (2007) in the context of formulating comprehensive pan-European guidelines for HAP and in an attempt to rationalize conflicting proposals, provide a useful resource and curb guideline proliferation, strongly recommended that due consideration be given to the principles of guideline development to ensure rigorous, broadly applicable, easily updated output as the evidence base increases. The group advocated that a pan-European guideline, similar to the South African treatment guidelines which are applicable nationally, should be evidence-based, provide recommendations on core aspects of HAP (nosocomial infections) common to all healthcare settings and provide general treatment guidelines suitable for local adaptation. Because of a limited evidence base, the group recommended a formalized evidence-grading system to ensure consistency in the evidence-assessment process, encouraged a systematic review approach with a clear statement that expert opinion should be included only in the absence of quality data and should be delineated as such. Expert opinion is thus relatively low on the evidence grading and assessment system and is borne out in this study noting that South African guidelines were compiled after extensive consultation with “numerous individuals and groups, including professional societies, expert committees, medical schools and secondary and tertiary hospitals” (National Department of Health, 2006).

It is thus imperative that South Africa utilise the evidence-based approach to the development of treatment guidelines from well-executed and informative surveillance.

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