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Assessing the Effectiveness of Empiric Aantibiotic Treatments: The Use of an Antibiogram Based Methodology in the Case of Selected Public Hospitals in Lesotho

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ABSTRACT

Background: Antibiotics prescribed in the presumptuous treatment of infections may be ineffective if causative pathogens acquire resistance to prescribed antibiotics. In the absence of patient follow ups for treatment outcome assessments, healthcare providers may be unaware of the effectiveness of antibiotic treatments they provide. In the empiric treatment of infections particularly, such situations may compromise appropriate selection of antibiotics. The study aimed at assessing the effectiveness of antibiotics prescribed in the empiric treatment of infections using a methodology based on information derived from antibiograms.

Method: Culture sensitivity test results and relevant data on antibiotic treatment among inpatients from selected hospitals were used to construct an antibiogram and also determine pathogen associations with infections and antibiotics most frequently prescribed in their empiric treatment. Parameters describing levels of antibiotic activities against pathogens associated with given infections were defined and used to evaluate the effectiveness of prescribed antibiotics. Clinical validity of results was assessed by comparing results of a simultaneous treatment outcome evaluation of antibiotic treatments of selected infections carried out.

Results: The methodology was used to successfully evaluate the effectiveness of commonly prescribed antibiotics. Ampicillin and co-trimoxazole, two of the antibiotics most prescribed in the empiric treatment of infections, were predicted to be grossly ineffective in treating staphylococcal and Gram-negative bacilli (GNB) infections for which they were observed to be prescribed.

Conclusion: Polymicrobial causes of infections attributable mainly to gram-positive cocci and gram-negative bacilli were established as an etiological feature of most infections. Multiple antibiotic treatments were shown, in effect, to be more effective than single use of the agents in treating most infections.

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Introduction

Presumptuous antibiotic prescribing is a common means of treating infections in medical practice both in community and even in hospital practice settings where opportunities for diagnostic precision exists (1). In clinical environments like those found in many developing countries, where functional microbiology laboratories may be unavailable or where systems of disseminating results of laboratory investigations may be deficient (2), empiric antibiotic prescribing may indeed be the only option of treating infections. To be effective, antibiotics selected in such treatments must be appropriate for bacterial pathogens suspected to be the causative agents of the treated infection (3). This in principle requires the healthcare provider to have adequate knowledge of the most likely infecting microorganisms and their local susceptibilities to antimicrobial agents (4). In situations where care providers lack such knowledge, this mode of treating infections could result in inappropriate choices and hence injudicious use of antibiotics. This may lead to poor treatment outcomes prevailing unnoticed, particularly in clinical settings where patient follow ups are not easily done. Therefore, it is good practice to evaluate the effectiveness of antibiotics routinely against pathogen antibiotic sensitivities, especially in clinical environments where empiric use of antibiotics is a mainstay. Such evaluations can provide healthcare providers with a means of more reliably predicting outcomes of antibiotic treatments.

We report this study as a methodological research in which a novel approach was used to assess the effectiveness of antibiotics when prescribed empirically in treating infections within a defined clinical environment. This study's objective was to demonstrate the use of an assessment tool that uses antibiogram-derived information to evaluate antibiotic effectiveness in the empiric treatment of infections. The methodology differs from traditional methods of drug effectiveness studies which characteristically are expensive, complex in design and may require years of investment (5). It is cheap and simple in design and conduct and is considered useful in assessing the effectiveness of empiric antibiotic treatments particularly in resource limited environments.

Materials and Methods

The research is a drug utilisation cross-sectional study designed in case series format. Relevant data on antibiotic treatments were collected from case notes of all patients in both inpatient and outpatient departments prospectively from 15th June to 15th July 2009 in five study site hospitals in Lesotho. The hospitals included the Queen Elizabeth II referral hospital and the Motebang, Berea, Maluti and Scott hospitals. Retrospective data on culture sensitivity test (CST) results dating from January 1, 2003 to the end of prescription data collection in July 2009 were similarly collected from microbiology laboratories of study site hospitals and analysed. All laboratories used disc diffusion methods in evaluating microorganisms' susceptibility to antibiotics.

Data analysis was done using Statistical Analysis System (SAS) version 9. A total of 307 inpatient and 865 outpatient prescriptions were analysed to determine patterns and rates of prescribing antibiotics in the empiric treatment of infections. A total of 5007 CST result records from inpatient settings were analysed (Table 1). We used the results of this analysis to ascertain both the types of bacteria isolates associated with given infections and the percentage frequencies of isolations of these bacteria. Based on their frequencies of isolation, we also established pathogens' strengths of associations with infections.

Percentage activities (PAs) of prescribed antibiotics against given pathogens were determined as equivalent to pathogens' sensitivities to the given antibiotics. Accordingly, we calculated the PA of a given antibiotic against a specified bacterial isolate as the number of times such isolate was found sensitive to the antibiotic divided by the total number of times it was tested against the given antibiotic. This was then multiplied by 100.

The percentage overall activity (POA) of a given antibiotic is a characteristic property of the antibiotic that determines its chances of eradicating all of the pathogens that possibly could be causing the infection. The equation for its determination has been previously published (6). We determined it for prescribed antibiotics who's PAs were determined for all pathogens identified as commonly associated with given infections.

Culture sensitivity tests were not routinely carried out for certain infections. For such infections, local data on both pathogen antibiotic sensitivities and incidences of isolating pathogens associated with these infections were not available for determining POAs. We used antibiotics' PAs instead of their POAs in determining the chances of prescribed antibiotics being effective in treating such infections. We created and defined for this purpose four levels of antibacterial activities and used these as parameters in determining the effectiveness of prescribed antibiotics (Table 2). For infections for which antibiotics' POAs were determined, we used these as parameters in determining the comparative effectiveness of prescribed antibiotics' in their treatment.

We validated the use of POAs as parameters in evaluating antibiotics' effectiveness by comparing them with patient recovery status (PRS) in a subgroup of patients (n = 169) in whom antibiotics were prescribed for infections identified as absolutely caused by bacterial pathogens. PRS was expressed as the percentage of patients who improved on specified antibiotic treatments. Patients on antibiotic treatment were considered "improved" when nursing notes indicated that the patient was discharged "feeling better" or "feeling well". "Improved" was also

Table 1. Counts (n) and percentage frequencies (n %) of bacterial isolates from specimens taken from patients with diagnosis of various infections. Percent frequencies are calculated per column.

Bacterial isolates	Frequencies of bacterial isolates according to specimen											
	Ascitic fluid		Cerebrospinal fluid		Pleural Fluid		Ear swab		Eye swab		Pus swab	
	n.	n%	n.	n%	n.	n%	n.	n%	n.	n%	n.	n%
α-Haemolytic streptococci (*S. pneumoniae*)	2	11.8	37	47	5	21.7	5	1.6	1	14	37	1.5
β-Haemolytic streptococci (*S. pyogenes*)	0	0	0	0	1	4.4	1	0.3	1	14	82	3.3
Non-haemolytic streptococci (Enterococci)	0	0	2	2.6	2	8.7	12	3.8	1	14	75	3
Neisseria spp	0	0	5	6.4	0	0	0	0	1	14	10	0.4
Peptococcus spp	0	0	0	0	0	0	0	0	0	0	4	0.2
Staphylococcus aureus	3	17.6	4	5.1	6	26.1	128	41	1	14	938	37.7
Staphylococcus epidermidis	1	5.9	14	18	1	4.4	8	2.5	2	29	57	2.3
Staphylococcus saprophyticus	0	0	0	0	0	0	0	0	0	0	0	0
Acinetobacter spp	0	0	0	0	0	0	0	0	0	0	11	0.4
Bacteroides spp	0	0	3	3.8	0	0	0	0	0	0	3	0.1
Corynebacterium spp	0	0	0	0	0	0	2	0.6	0	0	1	0
Escherichia coli	6	35.3	4	5.1	3	13	20	6.3	0	0	411	16.5
Haemophilus influenza	0	0	4	5.1	1	4.4	5	1.6	0	0	2	0.1
Haemophilus parainfluenzae	0	0	0	0	0	0	0	0	0	0	0	0
Klebsiella spp	3	17.6	1	1.3	2	8.7	12	3.8	0	0	225	9.1
Pseudomonas spp	1	5.9	4	5.1	0	0	54	17	0	0	249	10.0
Proteus spp	1	5.9	0	0	0	0	69	22	0	0	376	15.1
Salmonella spp	0	0	0	0	2	8.7	0	0	0	0	1	0
Shigella spp	0	0	0	0	0	0	0	0	0	0	2	0.1
TOTAL	17	100	78	100	23	100	316	100	7	100	2485	100
α-Haemolytic streptococci (*S. pneumoniae*)	9	22.5	1	11	9	20	1	0.1	1	4.76	2	0.8
β-Haemolytic streptococci (*S. pyogenes*)	9	22.5	0	0	4	8.9	0	0	0	0	7	2.8
Non-haemolytic streptococci	12	30	1	11	4	8.9	40	2.3	0	0	7	2.8
Neisseria spp	0	0	0	0	0	0	0	0	0	0	4	1.6
Peptococcus spp	0	0	0	0	0	0	40	2.3	0	0	1	0.4
Staphylococcus aureus	7	17.5	2	22	15	33	1	0.1	12	57.1	157	62
Staphylococcus epidermidis	0	0	1	11	2	4.4	0	0	1	4.76	4	1.6
Staphylococcus saprophyticus	0	0	0	0	0	0	53	3.1	0	0	0	0
Acinetobacter spp	0	0	0	0	0	0	17	1	0	0	0	0
Bacteroides spp	0	0	0	0	0	0	4	0.2	0	0	0	0
Corynebacterium spp	0	0	0	0	0	0	0	0	2	9.52	0	0
Escherichia coli	0	0	0	0	0	0	1262	74	2	9.52	36	14
Haemophilus influenza	0	0	0	0	1	2.2	0	0	0	0	0	0
Haemophilus parainfluenzae	0	0	0	0	1	2.2	0	0	0	0	0	0
Klebsiella spp	1	2.5	1	11	7	16	236	14	1	4.76	18	7.1
Pseudomonas spp	1	2.5	1	11	1	2.2	23	1.3	2	9.52	1	0.4
Proteus spp	1	2.5	2	22	1	2.2	71	4.1	0	0	12	4.7
Salmonella spp	0	0	0	0	0	0	0	0	0	0	1	0.4
Shigella spp	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	40	100	9	100	45	100	1713	100	21	100	253	100

Table 2. Definition of antibiotic evaluation categories.

Level of effectiveness evaluation	Definition
1	Chances of 80% and above of being effective in the empiric treatment of infection
2	Chances of 50% and above but below 80% of being effective in the empiric treatment of infection
3	Between 25% to 50% chances of being effective in the empiric treatment of infection
4	Below 25% chances of being effective in the empiric treatment of infection

used to describe PRS when a patient was monitored and positive response to antibiotic treatment was established as abatement of indicated monitoring parameter such as fever, pus production and bacteria induced inflammatory pains. Patients were considered as "not improved" when they were monitored and their responses to antibiotic treatments were established as non-abatement of indicated monitoring parameters. "Not improved" was also used to describe PRS when notes in the patient chart indicated that they were referred to another hospital due to worsening clinical conditions.

Rationale of data analysis and evaluation

We considered only the antibacterial activity characteristics on the basis of their being most fundamental in determining the effectiveness of the agents. We did not consider other factors like the pharmacodynamic and pharmacokinetic properties of the agents as these, for example, were key factors considered in their formulation and dosage regimen design. Local CST data were not available for determining pathogens implicated in the aetiologies of some infections. For such infections, we used organisms documented in the literature as their causative agents as reference pathogens in our evaluations to determine the effectiveness of antibiotics prescribed for their empiric treatment of infection.

Ethical Considerations

Approval for the conduct of this study was received from the Ethics Committee of the Lesotho Ministry of Health and the Research and Ethics Committee of North-West University of South Africa (Permission Number 06K17), where the principal researcher compiled the study report. Patient anonymity and hence their confidentiality in the entire process of data collection and data analysis was preserved by the use of codes instead of patients' names in the identification of patient records.

Results

Bacterial pathogen associations with infections

Pathogen associations with infections at study site hospitals based on local CST data are shown in Table 3. Also shown in this table are literature-documented pathogen associations with infections for which local data were not available. Gram-positive cocci (GPC), gram-negative bacilli (GNB), and other gram negative bacteria were implicated in all infections diagnosed and treated at study sites. However, some pathogens were more often causative agents of certain infections. *Staphylococcus aureus* emerged as a dominant causative pathogen of most infections among inpatients, including lower respiratory tract infections (LRTI) with or without pleural effusions, skin and soft tissue infections (SSI) and urogenital tract infections. *Neisseria gonorrhoea* was not strongly associated with genitourinary tract infections (GUTI) manifesting with discharges among inpatients. *Escherichia coli* and *Klebsiella* spp. were the dominant GNB associated with urinary tract infections (UTI). *Streptococcus pneumoniae* and *Staphylococcus epidermidis* were more strongly associated with bacterial meningitis as compared to GNB which were moderately associated with this infection.

GPC (staphylococci and streptococci) and GNB were implicated to equal extents as causative agents of bacteraemia. Our literature search for the purpose of establishing pathogen associations with infections for which CST results data were not available showed gastrointestinal infections (GI) to be associated with GNB and anaerobic bacteria (7,8). GNB and *Staphylococcus aureus* similarly were found to be associated with bone infections as causative agents (9).

Patterns of antibiotic prescribing in the treatment of diagnosed infections

Antibiotics most prescribed for diagnosed infections are shown in the right-hand column of Table 3. Generally, multiple antibiotics were prescribed for the empiric treatment of infections regardless of the type of infection. These included ampicillin, penicillin, co-trimoxazole, chloramphenicol, gentamicin, cefotaxime and metronidazole. A few antibiotics including erythromycin, cloxacillin, ciprofloxacin and nitrofurantoin were prescribed only for particular infections.

Except for gastrointestinal infections, where it was the third most prescribed, ampicillin was the most prescribed in the empiric treatment, including infections of respiratory and genitourinary tracts, ear and pyrexia of unknown origin (PUO).

Table 3. Bacterial pathogen associations and antibiotics most commonly prescribed in the empiric treatment of infections among inpatients.

Infection type / Source of isolates	Bacterial pathogen associations and strengths of such associations with infections*														Most commonly prescribed antibiotics in order of relative frequencies for given infections
	Gram positive cocci (GPC)						Gram negative baccili (GNB) and other gram negative bacteria								
	Staphylococcus aureus	*Staphlococcus epidemidis*	*Staphylococcus saprophyticcus*	*Streptococcus pneumoniae*	*Streptococcus pyognes.*	*Non-haemolytic streptococci (Enterococcus)*	*Escherichia coli*	*Klebsiella* spp	*Proteus* spp	*Pseudomonas* spp	*Haemophylus influenzae*	*Haemophylus parainfluenzae*	*Neiserria* spp	*Corynebacterium* spp	*Anaerobic bacteria*	
Respiratory tract infections (Sputum/ pleural fluid specimens)	++++	+		++++		+++	+++	+++		+	++	++				Ampicillin, cotrimoxazole, Penicillin, Gentamicin/ metronidazole
Ear infections	++++			+	+	++	++	++	+++	+++				+		Ampicillin cotrimoxazole, Penicillin
Throat infections	++++			++++	++++	++++		+	+	+						Penicillin, Erythromycin
Skin and soft tissue infections (Pus swab specimen)	++++			+	+	+	+++	+++	+++	+++						Cloxacillin, Ampicillin Metronidazole, Gentamicin
Urinary tract infections (Urine specimens)			+	+	+	++	++++	+++	++	++						Nitrofurantoin, Ciprofloxacin, Ceftriaxone
Genitourinary tract infections (High vaginal and penile swab specimens)	++++	++		++		++	++	++	++	++				++	+	Ampicillin Metronidazole, Gentamicin
Meningitis/Central nervous system infections (Cerebrospinal fluid specimens)		+++		++++		+	++			++	++		++			Ampicillin, Penicillin, Chloramphenicol, Metronidazole
Bacteraemia/Blood infections (Blood specimens)	+++	+++		+++		+++		+++		+++						Ampicillin, Gentamicin, Metronidazole,
Infections for which local CST data was not available	**Associated pathogens as derived from literature**															
Gastrointestinal infections	*Escherichia coli*, *Klebsiella*, *Proteus* spp, anaerobic bacteria, *Salmonella, Shigella* spp most commonly associated(7,8,9)															Metronidazole, Cotrimoxazole, Ampicillin, Cefotaxime
Osteomyelitis	*S. aureus* and gram-negative bacilli most commonly implicated(10)															Metronidazole, Ampicillin, Gentamicin
Pyrexia of unknown origin	*Staphylococcus aureus* and GNB in focal infections associated with neutropenia, HACEK group of bacteria (*Haemophillus aphrophylus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*) if endocarditis is suspected as aetiology, *Bartonella* spp., *Legionella* spp., Coxiella burnetti, *Chlamydia psittaci(*11)															Ampicillin, Cotrimoxazole

*Strengths of associations: Determined from relative frequencies of isolation from specimens.

*Interpretation of symbols of association: ++++ = Very strong association; +++ = Strong association; ++ = Moderate association, + = Weak association

Co-trimoxazole ran second to ampicillin in treating respiratory tract and ear infections and PUO. The agent was also the second most prescribed after metronidazole for gastrointestinal infections. Cloxacillin was the most prescribed antibiotic for skin and soft tissue infections. Other antibiotics, though prescribed at lower rates, were prescribed mainly for specific infections among inpatient and outpatient settings. Erythromycin was prescribed mainly for respiratory tract infections among outpatients. Gentamicin was prescribed mainly within inpatient settings for infections of the respiratory tract, skin and soft tissue, bone and blood and also for genitourinary tract infections among both inpatients and outpatients.

Cefotaxime was prescribed mainly for respiratory tract and skin and soft tissue infections among inpatients and ciprofloxacin largely for genitourinary tract infections among both inpatients and outpatients and also for skin and soft tissue infections among inpatients. Nitrofurantoin was prescribed only for UTI among outpatients.

Effectiveness evaluations of prescribed antibiotics among inpatients

PAs of antibiotics and their interpretations in respect to the effectiveness of monotherapies of antibiotics when used in the empiric treatment of infections are listed in Table 4. Antibiotics' POAs as used to determine monotherapies of antibiotics that would be most effective in treating infections with polymicrobial causes are similarly listed in Table 5.

Ampicillin monotherapy had 90% chances of being effective in treating LRTI and central nervous system (CNS) infections and 81% chances of being similarly effective in treating throat infections in hospitalised patients if *Streptococcus pneumoniae* and *Streptococcus pyogenes* were sole aetiologies of these infections respectively. [Effectiveness assessment level (EAL) in streptococcal infections = 1; Table 4]. The antibiotic, however, would be largely ineffective in treating staphylococcal and GNB components in polymicrobial causes of the infections that include these pathogens. It would also be ineffective in the empiric treatment of infections of the ear, skin and soft tissue and the genitourinary tract in patients in whom *Staphylococcus aureus* and GNB were implicating pathogens [$EAL_{(staphylococci)} = 3$, $EAL_{(GNB)} = 4$; Table 4].

Ampicillin was also observed as the most prescribed antibiotic in the empiric treatment of bacteraemia. Its monotherapy of the infection would be attended with low treatment failures on account of its low PAs against staphylococci and GNB including *Klebsiella* and *Pseudomonas* spp. These pathogens and *Streptococcus pneumonia* were strongly associated with bacteraemia (Table 3). In events of haematogenous seeding of blood coming from sources known to be infected with *Streptococcus pneumonia*, ampicillin monotherapy in the treatment of the infection would be appreciably successful [$EAL_{(Streptococus\ pneumonia)} = 1$; Table 4]. Prescribed for streptococcal throat infections, ampicillin would be more effective [$EAL_{(Streptococcus\ pyogenes)} = 1$] than penicillin and erythromycin in treating these infections among inpatients [$EAL_{(Streptococcus\ pyogenes)} = 2$] (Table 3). *C*o-trimoxazole monotherapy in the empiric treatment of LRTI, SSI and ear, throat, GI and GUT infections were predictive of high treatment failures [$EAL_{(staphylococci)} = 3$; $EAL_{(GNB)} = 4$, Table 4].

Among antibiotics tested against both GPC and GNB including chloramphenicol, the third generation cephalosporin (TGC), cefotaxime, had the highest POA and was considered most appropriate in monotherapy of LRTIs, SSI and CNS infections among inpatients (Table 5). With similar but higher effectiveness assessment levels the TGCs cefotaxime and ceftriaxone prescribed for GUTI had chances of above 80% in treating the infection successfully [$EAL_{(GNB)} = 1$; Table 4]. Empiric therapy of cloxacillin in SSI among inpatients had above 50% but less than 80% chances of treating *Staphylococcus aureus* component of aetiological agents of the infection [$EAL_{(staphylococci)} = 2$; Table 3]. The antibiotic was not tested against GNB but these pathogens were found to have strong associations with SSI among inpatients (Table 3). Its POA value for comparison with the effectiveness of monotherapies of other antibiotics in the treatment of SSI was undeterminable.

Gentamicin as prescribed in the empiric treatment of LRTI, SSI , GUTI and bacteraemia among inpatients had above 50% but less than 80% chances of successfully treating GNB component of bacteria pathogens causing these infections [$EAL_{(GNB)} = 2$; Table 3]. The exclusive uses of ciprofloxacin and nitrofurantoin in the empiric treatment of GUTI had chances of above 80% in treating the GNB component of the infection successfully [$EAL_{(GNB)} = 1$]. Gentamicin and ciprofloxacin similarly had high chances of effectively treating pseudomonas infections [$EAL_{(Pseudomonas)} = 1$; Table 4]

Unavailability of local CST results precluded the effectiveness assessment of metronidazole as used in the treatment of possible anaerobic infections of the respiratory and gastrointestinal tracts, skin and soft tissues, bone and blood (Table 3).

Blood infections were associated with GPC, GNB and *Pseudomonas* Spp. (Table 1). As the most prescribed antibiotic in the empiric treatment of the infection, ampicillin was predicted to have treatment failures on account of its low PAs against staphylococci and GNB except where haematologic seeding of blood comes from a source known to be infected with *Streptococcus pneumoniae*. Based on its PA of 71% - 79% against GNB generally, monthotherapy of gentamicin in infections of the bacterial grouping may have to be in definitive rather than empiric treatments of septicaemia.

Table 4. Antibiogram depictions of antibiotic effectiveness assessment levels

Major bacterial isolates from specimens	Major associated infections for which antibiotic was most prescribed	Antibacterial activity descriptors and values of effectiveness levels		
		Commonly prescribed Antibiotic	Pathogen sensitivity(%)[Antibiotic Percentage activity (PA)]	Effectiveness assessment level (EAL)
Streptococcus pneumoniae	Respiratory tract (RTI) and ear infections, meningitis and bacteraemia	Ampicillin	90	1
		Penicillin	78	2
		Erythromycin	77	
		Cotrimoxazole	66	2
		Cefotaxime (TGC)	75	2
Streptococcus pyogenes	RTI, throat, skin and soft tissue infections (SSI)	Ampicillin	81	1
		Penicillin	61	2
		Erythromycin	61	2
		Cotrimoxazole	21	4
		Cloxacillin	80	1
		Cefotaxime (TGC)	82	1
Non-haemolytic streptococci (Enterococcus)	Throat, RTI, SSI, urinary tract infections (UTI), meningitis and bacteraemia	Ampicillin	71	2
		Penicillin	48	3
		Erythromycin	59	2
		Cloxacillin	50	2
		Cefotaxime (TGC)	91	1
Staphylococcus aureus	RTI, ear and throat infections, SSI, genito-urinary tract (GUTI) and bone infections bacteraemia,	Ampicillin	39	3
		Cotrimoxazole	29	4
		Penicillin	24	4
		Cloxacillin	70	2
		Cefotaxime (TGC)	73	2
Staphylococcus epidermidis	SSI, central nervous system infections (CNS) infections	Ampicilin	49	3
		Cotrimoxazole	50	2
		Penicillin	31	3
		Cloxacillin	50	2
		Chloramphenicol	55	2
		Cefotaxime (TGC)	69	2
Escherichia coli	RTI,SSI, UTI/GUTI, CNS, gastrointestinal tract (GIT) and bone infections	Ampicillin	16	4
		Cotrimoxazole	35	4
		Gentamicin	78	2
		Cefotaxime (TGC)	88	1
		Ciprofloxacin	78	2
		Chloramphenicol	57	2
Klebsiella spp	RTI,SSI, UTI/GUTI, CNS, gastrointestinal tract (GIT) and bone infections	Ampicillin	18	4
		Cotrimoxazole	32	3
		Gentamicin	71	2
		Cefotaxime (TGC)	49	3
		Ciprofloxacin	74	2
		Chloramphenicol	53	2
Proteus spp	RTI,SSI, UTI/GUTI, CNS, gastrointestinal tract (GIT) and bone infections	Ampicillin	28	3
		Cotrimoxazole	24	3
		Gentamicin	79	2
		Cefotaxime (TGC)	91	1
		Ciprofloxacin	90	1
		Chloramphenicol	48	2
Pseudomonas spp	UTI/GUTI, RTI, SSI CNS infections and bacteraemia	Ampicillin	16	4
		Gentamicin	92	1
		Ciprofloxacin	90	1
		Chloramphenicol	39	3

Differences between POAs and patient recovery status (PRS) for ampicillin, cotrimoxazole and TGC as used in treating LRTI were not statistically significant (p-values >0.05 determined for the comparative parameters for all antibiotics) (Table 6). No statistically significant differences between POAs and PRSs of ampicillin, cotrimoxazole, penicillin and erythromycin as used in treating throat infections were similarly demonstrated. Differences in POAs and PRSs of TGCs and cloxacillin as used in treating SSIs were also statistically insignificant (p-value >0.05 for either antibiotic) (Table 6). Clinical outcomes of the multiple use of gentamicin and beta-lactam antibiotics were generally higher than the POAs of the respective antibiotics with which it was prescribed (Table 6). Generally, comparison of antibiotics POAs and PRS established a positive correlation between patient recovery status and antibiotics' POAs. We interpreted this as a validation of the authenticity of the use of prescribed antibiotics' activity characteristics in evaluating the effectiveness of antibiotic treatments. Unavailability of data limited us to treatment outcome assessment of lower respiratory tract infections (LRTI), throat and skin and soft tissue infections (SSI) only infections (Table 6).

Discussion

The antibacterial activity of an antibiotic is fundamental to its effective use in treating an infection. Formulary antibiotic choices or their doses presumably take into account the pharmacodynamic and pharmacokinetic properties of the antibiotics. However, the antibacterial activities of antibiotics change according to changing sensitivity patterns of bacterial pathogens in the clinical environment. It is appropriate on this basis to use antibiotics' activities as a parameter in evaluating their therapeutic effectiveness in a clinical environment in which they are prescribed regularly.

Major infections for which antibiotics were prescribed in the study were associated with both gram-positive cocci (staphylococci, streptococci and enterococci mainly) and gram-negative bacteria (*Enterobacteraceae* mainly), often as mixed aetiological agents (Table 3). Ampicillin, generally considered a broad spectrum antibiotic, was largely prescribed in the empiric treatment of most of these infections. Infections of the respiratory and gastrointestinal tracts, skin and soft tissues, the ear, blood, the CNS and also pyrexia of unknown origin (PUO) were typical infections for which the antibiotic was prescribed (Table 3). With the exception of *Streptococcus pneumoniae* and *Streptococcus pyogenes* which were reasonably susceptible to ampicillin, the antibiotic demonstrated activities of below 40% against most of the pathogens implicated in these infections. Prescribed second after ampicillin, cotrimoxazole similarly appeared to be an antibiotic of choice used in treating infections of the ear and the respiratory and gastrointestinal tracts. Like ampicillin, it demonstrated very low activities against pathogens most commonly associated with these infections. Evaluations of the effectiveness of the two antibiotics when used as single agents in the empiric treatment of these infections were largely predictive of high treatment failures. High prescribing rates and the resultant overuse of the antibiotics may account for the development of the high levels of resistance shown to them by most organisms (12-14). It is recommended on this basis to curtail the rampant use of these two antibiotics to reverse observed pathogen resistance trends (15). The empiric prescribing of ampicillin in this aspect could be restricted to the use of the antibiotic in the treatment of pneumococcal respiratory tract infections or in treating streptococcal throat infections in preference to penicillin and erythromycin. The resistance of *Streptococcus pneumoniae* and *Streptococcus pyogenes* to ampicillin was below the recommended cut-off of 20% for empiric antibiotic prescribing (16).

The prescribing of the semisynthetic penicillinase-resistant penicillin, cloxacillin, presumably targeted *Staphylococcus aureus* as the major pathogen implicated in SSI. The antibiotic had an activity of 70% against this pathogen which was below the recommended 80% permitting the empiric use of antibiotics in treating infections (16). For this reason and also for the reason that GNB were strongly associated with SSI among inpatients, prescribing cloxacillin in an empiric mono-antibiotic therapy of the infection among this patient group was not considered a good treatment option.

Ciprofloxacin, and cefotaxime demonstrated high PAs of 80% - 91% against GNB, indicating high possibilities of achieving satisfactory treatment success rates in empiric monotherapies of infections of these pathogens with the antibiotics. Among antibiotics that had been tested against both GPC and GNB, cefotaxime had the highest POA against possible pathogens that caused LRTI, SSI and CNS. The antibiotic was by these evaluations considered the most effective in the empiric treatment of these infections among the patient groups studied. Cefotaxime, gentamicin and ciprofloxacin showed activity levels of 49%, 71% and 74% against *Klebsiella* Spp. among the *Enterobacteraceae* respectively (Table 4). These activity levels are below the permitted levels for empiric antibiotic use (16). On the basis of implications of the pathogens as major aetiological agents in most GNB infections, we recommend empiric prescribing of antibiotics for these infections among inpatients to be preceded by requests for culture sensitivity tests.

Differences between POAs and PRSs of some antibiotics used in treating selected infections were all statistically insignificant. We therefore conclude that the use of these antibiotic activity parameters were clinically relevant.

Diagnosed infections in inpatient settings were typically observed to be caused by gram-positive

Table 5. Effectiveness evaluations of commonly prescribed antibiotics in the empiric treatment of infections: Percentage overall activity considerations.

Antibiotic	Antibacterial activity descriptors and effectiveness evaluations		
	Infection	Percentage overall activity (POA) (%)	Effectiveness assessment level (EAL)
Ampicillin	LRTI	51 – 54	2
	SSI	34	3
	Ear Inf	34	3
	Throat Inf	71	2
	CNS	69	2
	GUTI	20	4
Cotrimoxazole	LRTI	41 – 45	3
	Ear Inf	38	3
	Throat Inf	34	3
Erythromycin	LRTI	Undeterminable	-
	Throat Inf	65	2
Penicillin	LRTI	Undeterminable	-
	Throat inf	53	2
Cloxacillin	SSI	Undeterminable	-
Chloramphenicol	LRTI	66 – 69	2
	CNS	77	2
	SSI	57	2
Cefotaxime	LRTI	75	2
	SSI	78	2
	CNS	78	2

Table 6. A comparative assessment of the effectiveness of commonly prescribed antibiotics using antibacterial activity descriptors and patient recovery status of patients treated for selected infections.

Most commonly Single or Multiple prescribed antibiotics in treating selected infections	Percentage overall activities (POA) and Patient recovery status (PRS) (%Improved) for Lower respiratory tract infections (LRTI), Throat and Skin and soft tissue infections (SSI).								
	LRTI			Throat infections			SSI		
	POA	PRS	Difference † between POA and PRS p-values	POA	PRS	Difference † between POA and PRS p-values	POA	PRS	Difference † between POA and PRS p-values
Ampicillin	53.3	56.3	0.87	71	72	0.96	-	-	-
Cotrimoxazole	43.5	43.0	0.98	34	29	0.78	-	-	-
TGC	75	100	0.22	-	-	-	78	75	0.86
Erythromycin	-	-	-	65	66.7	0.93	-	-	-
Penicillin	-	-	-	53	54	0.96	-	-	-
*Cloxacillin	-	-	-	-	-	-	70	83.3	0.43
Cloxacillin + Ampicillin	-	-	-	-	-	-	-	85	-
Ampicillin + Gentamicin	-	80	-	-	-	-	-	-	-
Penicillin + Gentamicin	-	78	-	-	-	-	-	-	-

* Percentage activity (PA) of antibiotic against *S. aureus* as most commonly associated pathogen in SSI used in the situation of undeterminable percentage overall activity (POA)
† p-value from Z-test for two proportions

cocci, *Enterobacteraceae* and other bacteria types. Until specimens are cultured for identification of actual aetiological agents, infections within inpatient settings should be considered as being caused by multiple pathogens of varied bacterial classifications. Although single antibiotic prescribing is considered best practice (13), in our setting multiple antibiotic therapy had higher rates of improved treatment outcomes.

Limitations of the study

The use of retrospective CST results data limited us mostly to the analysis of a CST results data set with information on inpatients only. This compromised data interpretation to include effectiveness assessments of antibiotics in outpatient settings. It did also appear that specimens were sent to laboratories after treatment failures of patients to respond to initial courses of antibiotics. This may obscure the true picture of pathogen associations with infections and also frequencies of pathogens' isolations from specimens sent to laboratories for CSTs. In a survey we conducted parallel to this study, more than 70% of health care providers admitted that they did request CSTs in practice only after patients' non-response to initial antibiotic treatments (19). Microbiology laboratories in most cases also reported CST results for species of organisms rather than for specific isolates in most cases. This made it impossible in some cases to associate reported antibiotic sensitivity patterns to specific organisms and is thought to compromise adequate data interpretation. Site laboratories also tested given pathogenic isolates against specific antibiotics making it impossible to determine POAs of all antibiotics for infections for which they were prescribed. The limitation compromised our ability to evaluate and compare the effectiveness of monotherapies of all antibiotics prescribed for infections as diagnosed. The use of PAs of such antibiotics, instead of POAs, against characteristic pathogens frequently associated with the infections, however, allowed for relevant inferences to be made on the expected effectiveness of those antibiotics in treating infections for which they were prescribed. Notes in patients' charts and CST results did not indicate whether infections were hospital or community acquired. This limited our ability to report the number of hospital acquired infections separately in our results interpretations.

Due to possible changes in the sensitivities of bacterial pathogens to antibacterial agents, the results may have to be revised based on current pathogen antibiotic sensitivity patterns before any adoption in clinical practice.

Recommendations

We recommend periodic future updates of the results of this study using new information from revised antibiograms. Such results if adopted in practice have the potential of reducing the likelihood of adverse treatment outcomes while curtailing the development of antibiotic resistance. Our results documented mixed infections as an aetiological feature of most infections. It also showed multiple antibiotic treatments to have higher positive treatment outcomes in comparison with single antibiotic treatment. On the basis of this we recommend judiciously prescribed antibiotic combinations in the empiric treatment of most infections within the described clinical environment for the study.

Conclusion

A methodology based on bacterial sensitivity patterns to prescribed antibiotics has been used successfully in evaluating antibacterial agents for their expected effectiveness as prescribed in a circumscribed clinical environment defined by selected hospitals in Lesotho. Generally we established polymicrobial causes of infections attributable mainly to gram-positive cocci and gram-negative bacilli and showed that appropriate multiple use of antibiotics would be more effective than the single use of these antibiotics in treating most infections.

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