Tropical Journal of Pharmaceutical Research December 2013; 12 (6): 1029-1034
**ISSN:** 1596-5996 (print); 1596-9827 (electronic)


Available online at http://www.tjpr.org
**http://dx.doi.org/10.4314/tjpr.v12i6.24**

**Original Research Article**

# Making Antibiotic Choices: Formula Derivation and Usage in the Rational Selection of Antibiotics in the Empirical Treatment of Infections

**Matthias Adorka[1], Martie Lubbe[2], Jan Serfontein[2], Kirk Allen[3] and Honore Mitonga Kabwebwe[4]**

*[1]School of Pharmacy, FOHS, University of Namibia. P/B 13301, Windhoek, Namibia. [2]Medicine Usage in South Africa, School of Pharmacy, North-West University, Potchefstroom, 2520, South Africa [3]Faculty of Health & Medicine, Lancaster University, Lancaster, England, [4]Department of Community Medicine, School of Medicine, University of Namibia, Windhoek, Namibia.*

**For correspondence: **Email:** madorka@yahoo.com; madorka@unam.na; **Tel:** +264 817761424*

*Received: 4 September 2013* *Revised accepted: 16 November 2013*

## Abstract

***Purpose:*** *To develop mathematical formulae to aid the selection of antibiotics most appropriate in the empirical treatment of infections.*
***Methods:*** *Formulae quantifying the characteristics of antibiotics with regard to their cost and activity against associated bacterial isolates of given infections were derived from probability laws. Data from records of culture sensitivity test results were compiled and analysed to ascertain bacterial pathogen associations with infections and their sensitivities to prescribed antibiotics. Applicability of derived formulae was demonstrated in the rational selection of antibiotics most appropriate in the empirical treatment of urinary tract infections (UTIs) in selected hospitals in Lesotho.*
***Results:*** *Escherichia. coli, followed by Klebsiella spp, Proteus spp, non-haemolytic Streptococci, Streptococcus pyogenes and then, Pseudomonas spp were identified as the most common uropathogens at the hospitals studied. Two mathematical formulae were derived and used in quantifying activity and cost characteristics of prescribed antibiotics. Cefotaxime, followed by ciprofloxacin - were considered most appropriate for use in treating UTIs empirically among inpatients of the hospitals.*
***Conclusion:*** *Quantifying and using procedurally antibacterial activities and cost characteristics of antibiotics provides a suitable means of making antibiotic choices in the empirical treatment of infections.*

***Keywords:*** *Antibiotics, Derived formulae, Rational selection, Empiric treatment, Urinary tract infection, Lesotho .*

**Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts**

## INTRODUCTION

Empiric antibiotic treatment of infections, though commonly done in medical practice, presents formidable challenges to prescribers [1,]. In developing countries where laboratory assisted information is least used as an aid to infection diagnosis and appropriate prescribing of antimicrobials, this may remain a major means of treating infections [2]. Making antibiotic choices for empiric treatments of infections, however, can be complex and difficult. It requires logical reasoning in which prescribers' use of their knowledge of relevant therapeutic and cost properties of all antibiotics legible for prescribing becomes important [1,3].

To be seen as appropriately prescribed, antibiotics need to be selected on comparative basis to enable the selection of an agent or agents that is/are most cost-effective in treating an infection in question. Considerations in such instances need to be given essentially to factors contributing to the clinical efficacy as well as the safety of the selected agent(s). Identification and hence appropriate targeting of bacterial pathogens most likely to be implicated in the infection being treated is crucially important. Knowledge about the antibiotic's spectrum of activity, its adverse effect profiles, pharmacokinetic disposition and dosage likewise are important factors to be considered in the choice of therapy [4].

In situations where correct lines of reasoning are applied, antibiotics are most likely to be selected and prescribed appropriately. The reverse logically will be true in events of inappropriate prescribing of the agents when flawed lines of reasoning are used in making such choices [5].
Dosage regimens of antibiotics recommended in treatment guidelines or as individualised in patients with specific prevailing clinical conditions are designed based on the pharmacodynamic and pharmacokinetic properties of the agents. It is reasonable on this account to assume that the major determinant of what choice of antibiotic one prescribes in treating a given infection would be the antibacterial activities and costs of the agents from which such choices are made. On this basis and on the assumption that selected antibiotics would be used in their recommended doses, it is practically realistic to base the selection of antibiotics on antibacterial activity and cost properties of the agents. As a further feasible option it is also possible to quantify such properties as numeric values to enable comparisons of the agents on a linear scale as decisions are made on their choices. This study developed and demonstrated the practical use of formulae in selecting antibiotics most appropriate in the empiric treatment of infections in clinical environments comprising five hospitals in the southern African state of Lesotho.

## EXPERIMENTAL

We derived and used formulae based on probabilities of pathogens' sensitivities to antibiotics, their incidences of isolation from specimens taken from sites of infections as well as costs of antibiotic treatments in a procedure formulated for appropriate selection of antibiotics in the empiric treatment of infections. In the derivations of the formulae we considered in principle that:

infections at a given anatomic body site can be caused by any one, some or all of the bacterial pathogens commonly associated with infections at the site; the chances of a given pathogen being the cause of an infection are equal to the pathogen's incidence of isolation from specimens taken from the site of the given infection; and that the chances of a prescribed antibiotic terminating the growth and hence the process of infection of a given pathogen are equivalent to the chances of the pathogen being sensitive to the antibiotic.
Based on the above considerations, we postulated that the chances of a pathogen, e.g. 'pathogen A' being the causative agent of an infection and the chances of it being sensitive to a prescribed antibiotic at the same time can be determined as the product of two probabilities according to the laws of probability [6,7]; these are the probability of 'A' being isolated from the infection **($P_{(iA)}$)** and the probability of 'A' being sensitive to the prescribed antibiotic (**$P_{(sA)}$**). By interpretation the product of these two probabilities is the probability or the chances of the prescribed antibiotic being active against pathogen A. Mathematically this can be expressed as $P_{(iA)} \cap P_{(sA)}$.

We introduced, defined and derived mathematical expressions for quantifying relevant terms that characterised the activity and cost properties of antibiotics. These included "overall activity (OA)" and "percentage overall activity (POA)" of a prescribed antibiotic and also "antibiotic treatment success to failure ratio (ATSFR)" and "antibiotic selection factor (ASF)".
Antibiotic treatment success ratio (ATSR) and antibiotic treatment failure ratio (ATFR) were other terms we introduced and from which we determined ATSFR. They are the respective probabilities of using a given antibiotic to successfully or unsuccessfully treat an infection for which common isolates and their sensitivity patterns to the given antibiotic are known. These are directly proportional to the antibiotic's percentage overall activity in the case of ATSR or its percentage overall resistance (POR) in the case of ATFR. Mathematically ATSR = C*POA and ATFR = C*POR. The proportionality constant "C" in the two formulae is presumed to be related to characteristics inherent to the antibiotic. These, like the disposition kinetics of the antibiotic, particularly its penetration of infected tissue, may equally influence the activity of the antibiotic against infecting pathogens. If determined, "C" can serve as a useful numeric factor in deciding whether the antibiotic can or cannot be used in treating certain infections.

Overall activity (OA) by our definition is the probability of a prescribed antibiotic being active

against all possible causative pathogens of a given infection. It is equal to the sum total of the products of the probabilities of the individual pathogens being isolated from the infection and the probabilities of their being sensitive to a prescribed antibiotic. In its derivation we used a method similar to that used by Blondeau and Tillotson in a study in which they proposed the use of percentage overall activity as a basis for making rational choices of antibiotics.[9] Designating pathogens commonly associated with a given infection as A, B, C, ….N, we expressed the value of OA mathematically as in Eq 1.

$OA = P_{(iA)} \cap P_{(sA)} + P_{(iB)} \cap P_{(sB)} + P_{(iC)} \cap P_{(sC)} \ldots\ldots + P_{(iN)} \cap P_{(sN)}$ …… (1)

Percentage overall activity (POA) of an antibiotic is an expression of OA as a percentage of the sum total of the incidences of isolation of pathogens associated with the infection, as shown in Eq 2.

$POA = \{(OA)/( P_{(iA)} + P_{(iB)} + P_{(iC)} \ldots\ldots + P_{(iN)})\}100$ …….. (2)

where $P_{(iA)}+P_{(iB)}+P_{(iC)} \ldots + P_{(iN)}$ is the sum total of the incidences of isolation of pathogens associated with the infection. It is a weighted average of pathogen sensitivities relative to their probabilities of isolation and is a characteristic property of the antibiotic that determines its chances of eradicating any or all of the pathogens which could possibly be a causative agent of the infection.

The term ATSFR refers to the ratio of an antibiotic's treatment success rate to its treatment failure rate. It is a numeric factor that characterizes the effectiveness of an antibiotic in terms of its chances of being successfully used to treat a given infection as per chance of its failure to treat that infection. It is calculated from the relationship ATSFR = ATSR/ATFR = POA/POR = POA/(100 – POA), where POA is expressed as a percentage as defined above. The higher the ATSFR of an antibiotic, the more effective it will be in treating an infection in question.

Antibiotic selection factor (ASF) is a measure of the extent to which the cost of an antibiotic limits its selection for prescribing irrespective of its ATSFR. It is a preferred parameter to be used in the selection process when consideration is to be given to antibiotic costs. It is derived from Eqs. 3 and 4, respectively, in separate instances when choices are to be made among oral antibiotic formulations on one hand and among parenteral formulations on the other.

*Oral formulations: ASF = ATSFR / Cost of antibiotic per course of treatment ……. (3)*

*Parenteral formulations: ASF = ATSFR / Daily cost of antibiotic treatment …….. (4)*

We considered that parenteral preparations often may not be used for the full course of antibiotic therapy and therefore decided to use daily cost of antibiotic treatment instead of cost of antibiotic per course of treatment in determining ASF for parenteral antibiotic formulations. Antibiotics with the highest ATSFR or ASF among a group of antibiotics considered for use in treating a given infection are selected in preference to those with lower ATSRF or ASF.

We compiled retrospectively over a five year period data from records of culture sensitivity test results obtained from microbiology laboratories of five hospitals in Lesotho. This included the now defunct Queen Elizabeth II referral hospital and the Motebang, Berea, Maluti and Scott hospitals. Specimens tested for microbial culture were collected from sites of various infections among inpatients. Five thousand and seven (5007) data records were analysed to determine pathogen associations with various infections, their incidences of isolation as well as their sensitivity patterns to formulary antibiotics. We determined the ATSFR and ASF of various antibiotics in the exemplary case of UTI (1713 cases) and demonstrated how these values can be used in making antibiotic choices in the empiric treatment of this infection among inpatients of our study site hospitals.

**Ethical permission**

Ethical permissions were granted by the Lesotho Ministry of Health and Social Welfare and also the ethics committee of North-West University (ref no. 06K17) where the principal researcher was a PhD student, for the conduct of this research.

## RESULTS

Bacterial isolates commonly isolated from urine specimens which are hence considered most common causative agents of UTI among inpatients of study site hospitals were found, and in order of their frequencies of isolation, to be *Escherichia coli*, *Klebsiella* spp, *Proteus* spp, Non-haemolytic streptococci, *Streptococcus pyogenes* and *Pseudomonas* spp. Frequencies of isolation of these pathogens, their sensitivities to commonly prescribed antibiotics and also the POAs of such commonly prescribed antibiotics as determined are also as shown in Table 1.

**Table 1:** Percent overall activity determinations of antibiotics against major pathogens associated with urinary tract Infections among inpatients (specimen: urine)

| Pathogen | FI | %FI | $P_{(i)}$ | Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Ampicillin | | Co-trimoxazole | | Tetracycline | |
| | | | | $P_{(s)}$ | $P_{(i)} \cap P_{(s)}$ | $P_{(s)}$ | $P_{(i)} \cap P_{(s)}$ | $P_{(s)}$ | $P_{(i)} \cap P_{(s)}$ |
| Non-Haem strep | 40 | 2.4 | 0.024 | 0.71 | 0.017 | 0.32 | 0.008 | 0.51 | 0.01 |
| *Streptococcus. pyogenes* | 40 | 2.4 | 0.024 | 0.81 | 0.019 | 0.21 | 0.005 | 0.56 | 0.013 |
| *Escherichia coli* | 1262 | 75.5 | 0.755 | 0.16 | 0.121 | 0.35 | 0.260 | 0.32 | 0.24 |
| *Klebsiella* spp | 236 | 14.1 | 0.141 | 0.18 | 0.025 | 0.32 | 0.045 | 0.37 | 0.05 |
| *Proteus* spp | 71 | 4.2 | 0.042 | 0.28 | 0.012 | 0.24 | 0.010 | 0.19 | 0.03 |
| *Pseudomonas spp* | 23 | 1.4 | 0.014 | 0.16 | 0.002 | 0.19 | 0.003 | 0.31 | 0.004 |
| **OA** | | | | | **0.196** | | **0.32** | | **0.35** |
| **POA** | | | | | **19.6** | | **32.0** | | **35.0** |

| Pathogen | FI | %FI | $P_{(i)}$ | Chloramphenicol | | Ciprofloxacin | | TGC (Cefotaxin) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $P_{(s)}$ | $P_{(i)} \cap P_{(s)}$ | $P_{(s)}$ | $P_{(i)} \cap P_{(s)}$ | $P_{(s)}$ | $P_{(i)} \cap P_{(s)}$ |
| Non-Haem strep | 40 | 2.4 | 0.024 | 0.74 | 0.01 | 1.00 | 0.02 | 0.91 | 0.02 |
| *S. pyogenes)* | 40 | 2.4 | 0.024 | 0.42 | 0.01 | 0.80 | 0.02 | 0.75 | 0.02 |
| *Escherichia coli* | 1262 | 75.5 | 0.755 | 0.57 | 0.43 | 0.78 | 0.59 | 0.88 | 0.66 |
| *Klebsiella* spp | 236 | 14.1 | 0.141 | 0.53 | 0.07 | 0.74 | 0.10 | 0.49 | 0.07 |
| *Proteus* spp | 71 | 4.2 | 0.042 | 0.48 | 0.07 | 0.90 | 0.04 | 0.76 | 0.03 |
| *Pseudomonas spp* | 23 | 1.4 | 0.014 | 0.39 | 0.005 | 0.90 | 0.13 | 0.91 | 0.13 |
| **OA** | | | | | **0.595** | | **0.90** | | **0.93** |
| **POA** | | | | | **59.5** | | **90.0** | | **93.0** |

***ABBREVIATIONS:*** *FI (Frequency of isolation); %FI (Percentage Frequency of isolation); $P_{(i)}$ (Probability of pathogen isolation); $P_{(s)}$ (Probability of pathogen sensitivity to antibiotic); %S (Pathogen sensitivity to antibiotic); OA (Overall activity); POA (Percentage overall activity)*

**Table 2:** Antibiotic selection in the empiric treatment of urinary tract infections based on antibiotic activity and cost considerations

| Antibiotic selection determining factors | | | | | | Selected antibiotics | |
|---|---|---|---|---|---|---|---|
| **Antibiotics** | **POA** | **POR** | **ATSFR** | **Antibiotic cost per day (PF) or per COT (OF)** | **ASF** | **ATSFR ranking** | **ASF ranking** |
| Cefotaxime Inj. | 93 | 7 | 13.3 | 17.80 | 0.75 | 1 | 2 |
| Ciprofloxacin | 90 | 10 | 9 | 8.50 | 1.1 | 2 | 1 |
| Chloramphenicol | 60 | 40 | 1.5 | 4.48 | 0.33 | 3 | 3 |
| Tetracycline | 35 | 65 | 0.5 | 1.96 | 0.26 | 4 | 4 |

***Abreviations:*** *ASF (Antibiotic selection factor); ATSFR (Antibiotic treatment success to failure ratio); POA (Percentage overall activity); POR (Percentage overall resistance); PF (Parenteral formulation) COT (Course of treatment); OF (Oral formulation): Antibiotic cost in ZAR ( South African Rand).*

ATSFR and ASF values of the prescribed antibiotics as further determined from calculated POAs are recorded in Table 2. Based on their ATSFR values (Table 2), cefotaxime, followed by ciprofloxacin, were most appropriate in the empiric treatment of UTI in the patient group considered for this study. The POAs of ampicillin, co-trimoxazole, tetracycline and chloramphenicol (Table 1) were comparatively lower than those of cefotaxime and ciprofloxacin and disqualified the use of these antibiotics in the empiric treatment of UTI in the patient group. In terms of their ASF values (Table 2), ciprofloxacin among the oral antibiotic formulations was considered most appropriate for the empiric treatment of UTI among the patient group studied.

## DISCUSSION

### Methods development

Mathematical steps used in developing formulae for use in selecting antibiotics for the empiric treatment of infections were as outlined in the methodology. Apart from a study by Blondeau and Tillotson in which a formula-based methodology antibiotic selection was proposed [8], our search of the literature provided no information on any other study in which formulae were developed for use in procedures of antibiotic selection for the empiric treatment of infections. In effect, no comparisons of results for this study were made with results of similar studies to authenticate this developed process of antibiotic selection. Cost of antibiotics as used in the formula was treated as a linear function. This may be argued as having a negative effect of unduly diminishing the value of ASF, the quantified characteristic of the antibiotic with a cost component. Such arguments notwithstanding, costs of antibiotics can be considered as the same in situations where antibiotics from which selections are made are relatively cheap. In such instances, other factors may count most in the selection process. In clinical environments where cheaper traditional antibiotics are dominantly used, this may actually be the case. In such clinical environments as exemplified by hospitals in Lesotho, considerations of other factors, like POAs or ATSFRs as determined in this study, may assume prominence over costs in antibiotic selection processes. Costs of courses of antibiotic treatment most frequently used in Lesotho, as determined from costs of antibiotics at the time of data collection lied between ZAR1.20 – ZAR11.20 (South African rands) (approximately US$0.16 – US$1.50 ).

### Points of note on the practical use of derived formulae in making antibiotic choices

For the practical use of POAs or ATSFRs and ASFs in the rational selection of antibiotics, the following need to be taken into consideration as decisions are made in the choice of an antibiotic. An antibiotic with the highest ATSFR or ASF should be selected for prescribing in favour of those with lower values of the selection factors. An antibiotic's ATSFR primarily determines its effectiveness. For this reason antibiotics may be compared on the basis of their ASF values in a second step of the selection process after they have been selected on the basis of their ATSFR values. Based solely on the ASF, it is possible for extremely cheap antibiotics to score relatively well even if they are not very effective.

The final decision on which antibiotic to prescribe in preference to others must equally consider the therapeutic uses of the agents. These include, for example, their side-effects and toxicities and patients allergies to them. Further, the drugs' physicochemical and pharmacokinetic properties, including their clearances and the extents of binding to proteins may also have to be taken into consideration. Antibiotics' physicochemical properties and the extents of their binding to proteins may affect their ability to penetrate tissues and concentrate at sites of infections [2]. The clearance of the antibiotic determines its duration of action. The World Health Organization in this aspect emphasised that prescribers should select the best possible antibiotics that have optimal durations of actions to prevent the emergence of resistant strains of infecting pathogens [5]. Other factors like concomitant disease states may also have to be considered in the selection process. Older patients with hearing deficits, for example, are poor candidates for potentially ototoxic aminoglycoside therapy and so also are patients with a pre-existing seizure to whom imipenem therapy may not have to be given if a less toxic therapy can be used [3].

On the same note, antibiotics with certain known characteristics that preclude their use in certain infections may also not be considered in the selection process for first choice prescribing even if their ASF or ATSRF values are higher than those of other antibiotics from which the selection is made. Ciprofloxacin can be cited as a classic example in this case. Even if the antibiotic demonstrates higher ATSRF and ASF values than other antibiotics, it may not be selected as a first choice antibiotic in treating lower respiration tract infections in which *Streptococcus pneumoniae* may be a causative agent. The antibiotic is noted to have moderate activity only against gram-positive cocci and is precluded in the empiric treatment of pneumococcal pneumonia [9]. ATSFR and ASF values by these notations may be taken only as guiding documentations on the characteristics of antibiotics which may help in antibiotic selection.

Parenteral formulations are more expensive in terms of monetary costs than oral preparations and they would generally have lower ASFs than oral preparations. This is exemplified in the case of cefotaxime injection (Table 1). In antibiotic selection, both types of formulations can be

compared only on the basis of their ASTFRs and not their ASF values.

**Study limitations and recommendations**

Laboratories had the practice of testing selected antibiotics against certain types of bacterial isolates only. This was a limitation of the study since data for the practical demonstration of the use of the formulae were collected retrospectively. As a result, we were unable to calculate POA values for other commonly prescribed antibiotics. Antibiotics like the aminoglycosides (gentamicin and amikacin), nitrofurantoin and nalidixic acid which were also observed to be prescribed for urinary tract infections were for example tested against gram-negative bacilli (GNB) only. They were not tested against gram-positive cocci isolates like non-haemolytic streptococci, and *Streptococcus pyogenes* which were also identified as associated causative agents of UTI in the patient group studied. In effect, we could not calculate ASTFR and ASF values for these antibiotics to enable their comparisons with antibiotics from which the selection was made in illustrating the practical use of the derived formulae. Retrospective data collection also limited the ability of the study to identify and associate precise members of certain species of bacterial pathogens with infections from which they have been isolated. Such pathogens like *Proteus* and *Klebsellia* were identified just by their species names as recorded by laboratory staff.

In spite of these limitations, we consider our derived formulae authentic. We, however, recommend further studies to authenticate their clinical effectiveness before recommending their use in clinical practice.

## CONCLUSION

Quantification of properties of antibiotics as measurable entities in respect to their therapeutic efficacies and costs has been successfully done in this study using formulae derived for the purpose. The use of these formulae was demonstrated and was found to be a reliable means of selecting antibiotics appropriately in the empiric treatment of infections. In given clinical environments where the formulae are used in procedures of selecting antibiotics, it is recommended that periodic revisions of calculated antibiotic selection parameters are carried out to ensure therapeutic effectiveness of selected antibiotics. For such revisions, it is necessary to make regular updates of lists and frequencies of isolation of pathogens associated with infections and their antibiotic sensitivities as compiled for the clinical environment in question.

**ACKNOWLEDGEMENT**

The authors are thankful to Prof H Derendorf and Prof PA Gulip of the University of Florida for their valuable comments on procedures for formula derivation.

## REFERENCES

1. *Chambers HF. Antimicrobial agents: General considerations. In: Hardman JG, Limbird LE, editors. The Pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill; 2001; pp 1143-1169.*
2. *Archibald LK, Reiller LB. Clinical microbiology in developing countries. Emerg infect Dis 2001; 7(2): 302-304.*
3. *Zhanel GG. Influence of pharmacokinetic and pharmacodynamic principles on antibiotic selection. Curr Infect Dis Rep 2001; 3:29 -34.*
4. *Guglielmo BJ. Principles of infectious diseases. In: Koda-Kimble MA., Young LY., Alldredge BK, Corelli RL, Guglielmo BJ, Kradjan WA, William BR, Eds. Applied therapeutics: The clinical use of drugs. 9th edn. Philadelphia: Wolters Kluwer Health/Lippincott & Wilkins; 2008; pp 56-1 – 56-25.*
5. *Yu VL, Stoehr GP, Starling RC. Empiric antibiotic selection by physicians: Evaluation of reasoning strategies. Am J Med Sci 1991; 301(3):165-172.*
6. *Turner LK, Knighton D. Advanced mathematics. Essex: Longman Group Ltd; 1989.*
7. *Utts JM, Heckard RF. Mind on Statistics. Duxbury: Thompson Brookes/Cole; 2007; p 770.*
8. *Blondeau JM, Tillotson GS. Formula to help select rational antimicrobial therapy (FRAT): its application to community and hospital acquired urinary tract infections. Int J Antimicrob Agents 1999; 12: 145-150.*
9. *British Medical Association and Royal Pharmaceutical Society of Great Britain. Quinolones: British National Formulary. London 2008; p 320.*