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Original Article

Is adherence to national guidelines for parenteral empiric antibiotic therapy effective? Experience from a Sri Lankan center

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Abstract

Introduction: Guidelines for the selection of empirical antibiotics have been developed to improve patient outcomes and reduce unnecessary antibiotic use. We assessed the extent of adherence to the national guidelines for the selection of parenteral empirical antibiotics for three selected infections at a tertiary care center.

Methodology: A prospective cross-sectional study was conducted in medical and surgical wards of a tertiary care hospital in Sri Lanka. Adult patients with a positive culture for a lower respiratory tract infection (LRTI), skin and soft tissue infection (SSTI), or urinary tract infection (UTI) and who were prescribed parenteral empirical antibiotic therapy by the attending physician were included. Bacteria were identified and antibiotic susceptibility was determined by standard microbiological methods. Adherence to the guidelines was defined as prescribing the empiric antibiotic concordant with the national guidelines on the empirical use of antibiotics.

Results: A total of 160 bacterial isolates were obtained from 158 patients with positive cultures, the majority were from UTIs (n = 56). The selection of empirical antibiotics was concordant with the national guidelines in 92.4% of patients and 29.5% of the bacterial isolates obtained from these patients were resistant to the prescribed empiric antibiotic. Only 47.5% (76/160) of the bacterial isolates were sensitive to the empiric antibiotic and therefore can be considered an appropriate antibiotic prescription.

Conclusions: Empirical antibiotic guidelines should be updated based on the latest surveillance data and information on prevailing bacterial spectra. Antibiotic prescribing patterns and guideline concordance should be periodically evaluated to ensure whether antimicrobial stewardship programs are moving in the right direction.

Key words: Antibiotics; empirical therapy; guidelines; antimicrobial resistance (AMR).

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Introduction

Bacterial infections have become a global health problem with around 700,000 deaths reported annually worldwide [1]. In Sri Lanka, zoonotic and other bacterial diseases were the second leading cause of hospital deaths in 2019 [2]. Changing epidemiology and antimicrobial resistance contribute to the ever-increasing mortality in bacterial diseases and it is estimated that by 2050, ten million lives a year would be lost due to the rise of drug-resistant infections [1].

Timely initiation of appropriate antibiotic therapy plays an important role in improving the outcomes of patients with infections. Definitive identification of effective antibiotics against causative bacteria is done by microbiological cultures and antibiotic sensitivity tests. As microbiological results do not become available for 24 to 72 hours, initial therapy for infection is empiric and guided by clinical presentation and *in-vitro* antibiotic sensitivity patterns according to local epidemiology [3]. Empirical therapy is defined as the initial antibiotic regimen starting within 24 hours of admission [4]. Many international professional societies (e.g., Infectious Diseases Society of America, and the European Society of Clinical Microbiology and Infectious Diseases) have developed guidelines for the selection of empiric antibiotics. Such guidelines have helped physicians to maintain the balance between optimizing empirical therapy for individual patients while consistently improving outcomes, and reducing unnecessary antimicrobial use which contributes to antimicrobial resistance [5]. Direct application of these international guidelines at the national level is likely to be less effective as the local antimicrobial sensitivity and resistance patterns may differ [6]. Therefore, it is important to develop and periodically evaluate national guidelines locally as antibiotic sensitivity patterns change over time [7]. Studies done in several countries have shown significant improvements in patient outcomes when the compliance of clinicians with antibiotic guidelines is high [6,8-10]. Assessment of the extent of physicians' adherence to the national guidelines is also important to evaluate whether national antibiotic stewardship efforts are moving in the right direction [11]. The objectives of the present study were to assess the extent of physicians' adherence to the national guidelines for the selection of parenteral empirical antibiotics for three selected infections, to determine whether the national guidelines reflect the current bacterial susceptibility patterns of three selected infections, and to determine the appropriateness of the selected parenteral empirical antibiotics for the three selected infections.

Methodology

This prospective cross-sectional study was conducted in medical and surgical wards of a tertiary care hospital in Sri Lanka between August 2018 and March 2019. The study hospital is the second largest hospital in the country with a bed strength of 1110.

Ethical approval for the study was obtained from the Ethics Review Committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka (Ref. No: 63/17).

The study included microbiologically significant positive cultures obtained from adult in-ward patients who were diagnosed to have a lower respiratory tract infection (LRTI), skin and soft tissue infection (SSTI), or urinary tract infection (UTI) by the attending physician.

Inclusion and exclusion criteria

Bacterial isolates from adult patients presenting with the three selected infections and who were prescribed parenteral empirical antibiotic therapy by the attending physician were included in the study. Repeated cultures from the same patient were excluded. As prolonged antibiotic exposure might influence the spectrum of isolated bacteria due to selective pressure [12], bacterial isolates obtained from patients who were on parenteral antibiotics for more than 48 hours prior to specimen collection for culture were excluded.

Empirical antibiotic regimen and data collection

Data regarding antibiotic regimens (choice of empirical antibiotic, duration) were extracted from in-patient clinical records. Patient demographic data (age, gender, and duration of hospital stay) was also collected.

Microbiological investigations

Bacterial isolates obtained from positive cultures performed in the microbiology laboratory of the hospital were subcultured onto suitable media for further testing. All culture media (Blood agar base, MacConkey agar, and Mueller-Hinton agar) were purchased from Oxoid Limited, UK. Microorganisms were identified by Gram staining followed by standard biochemical methods [13]. Bacteria in the family *Enterobacteriaceae* and genus *Acinetobacter* were identified up to the species level by API® 20E and 20NE test kits (bioMérieux, USA), respectively. Isolates were tested for antibiotic susceptibility (ABST) by the disc diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) 2018 guidelines [14]. Antibiotic discs were purchased from Mast Group Ltd., UK (MASTDISCS® AST). Extended-spectrum β-lactamase (ESBL) production was tested by the disc diffusion method on Mueller–Hinton Agar according to the CLSI guidelines and confirmed by the combination disc method [14]. A 30μg cefoxitin disc was used in the ABST to detect methicillin resistance in *Staphylococcus aureus.*

Adherence to the guidelines was defined as prescribing the empiric antibiotic concordant with the National guidelines on the Empirical Use of Antibiotics published by the Sri Lanka College of Microbiologists (SLCM) [15].

Empirical therapy was considered appropriate/adequate or inappropriate/inadequate based on the *in-vitro* susceptibilities of the subsequently isolated pathogens. Empirical therapy was deemed appropriate if the isolated pathogen(s) was sensitive *in-vitro* to at least one of the antibiotics prescribed empirically. Therapy was deemed inappropriate if the pathogen(s) was resistant *in-vitro* to all of the empirical antibiotics or when the empirical antibiotic did not have the spectrum of activity against the causative bacteria according to The Sanford Guide [16].

Statistical analysis

IBM SPSS statistics version 25 was used for data analysis. Descriptive statistics were reported as percentages. Pairwise prop. test with Holm-Bonferroni correction was used to determine the significance of the difference between multiple proportions.

Results

A total of 160 significant bacterial isolates were obtained from 158 cultures. The majority of these positive cultures were from the patients with UTI (n =

Table 1. Proportions (%) of bacteria in each infection type.

	LRTI	SSTI	UTI
Escherichia coli	12.2 (6/49)	7.3 (4/55)	62.5 (35/56)
Pseudomonas spp.	20.4 (10/49)	38.2 (21/55)	–
Staphylococcus aureus	6.1 (3/49)	16.4 (9/55)	1.8 (1/56)
Acinetobacter spp.	14.3 (7/49)	3.6 (2/55)	–
Klebsiella pneumoniae	26.5 (13/49)	12.7 (7/55)	19.6 (11/56)
Proteus mirabilis	–	10.9 (6/55)	–
Moraxella spp.	6.1 (3/49)	–	–
Enterococcus spp	–	–	5.4 (3/56)
Others	14.3 (7/49)	10.9 (6/55)	10.7 (6/56)

LRTI: Lower respiratory tract infections; SSTI: skin and soft tissue infections; UTI: urinary tract infections.

56) while SSTI and LRTI accounted for 53 and 49 positive cultures respectively.

The spectrum of isolated bacteria

The majority of the bacterial isolates (86.3%, 138/160) were Gram-negative in all three types of infections. *Escherichia coli* was the most frequent (28.1%; 45/160) species among all isolates. *Klebsiella pneumoniae* was the most frequently isolated pathogen from LRTI (26.5%) whereas *Escherichia coli* (62.5%) and *Pseudomonas* spp. (38.2%) predominated in UTI and SSTI respectively. Table 1 shows the distribution of pathogenic bacteria in each infection type. Bacteria in the family *Enterobacteriaceae* (coliforms) accounted for 58.8% (94/160) of the isolates.

Antibiotic susceptibility patterns

Antibiotic susceptibility rates of the most frequently isolated bacterial pathogens are shown in Table 2. Highest susceptibility of the *Enterobacteriaceae* isolated from all three groups of infections was observed for amikacin while the lowest susceptibility was observed for amoxicillin-clavulanic acid. The rate of extended-spectrum β-lactamase (ESBL) production among *Enterobacteriaceae* isolates from UTIs was 30.4% (n = 17). ESBL positivity rate was 7.3% (n = 4) and 4.1% (n = 2) in SSTIs and LRTIs respectively. Carbapenem resistance in *Enterobacteriaceae* was found to be 8.5% (8/94).

All *Pseudomonas* isolates demonstrated a > 50% susceptibility rate for all the tested antibiotics. The highest susceptibility of the *Pseudomonas* spp. was observed for imipenem (96.8%) and piperacillin-tazobactam (96.8%) while the lowest susceptibility was for ticarcillin-clavulanic acid (67.7%). Of the *S. aureus* isolates, 11/13 were methicillin-resistant (MRSA)

Empirical antibiotics prescribed

The most frequently prescribed antibiotic for SSTI was amoxicillin-clavulanic acid (24.5%, 13/53) while it was ceftriaxone (34.7%, 17/49) for LRTI and ciprofloxacin (39.3%, 22/56) for UTIs. Amoxicillin-clavulanic acid (21.5%, 34/158) and ciprofloxacin (20.8%, 33/158) were the most commonly prescribed

Table 2. Susceptibility rates (%) of common bacterial pathogens in each infection category.

	Enterobacteriaceae				***Pseudomonas* spp.**			***S. aureus***	
	LRTI (n = 23)	**SSTI (n = 23)**	**UTI (n = 48)**	**Overall (n = 94)**	**LRTI (n = 10)**	**SSTI (n = 21)**	**Overall (n = 31)**	**LRTI (n = 3)**	**SSTI (n = 9)**
Gentamicin	73.9	78.3	75	75.5	100	71.4	80.6	**	**
Ciprofloxacin	52.2	65.2	43.8	51.1	90	66.7	74.2	00	44.4
Amikacin	100	87.0	97.9	95.7	100	90.5	93.5	**	**
Imipenem	**	**	**	**	100	95.2	96.8	**	**
Meropenem	91.3	82.6	93.8	90.4	100	90.5	87.1	**	**
Aztreonam	73.9	56.5	56.3	60.6	80	81.0	80.6	**	**
Ceftriaxone	73.9	47.8	50	55.5	**	**	**	**	**
Amoxicillin-clavulanic	39.1	30.4	39.6	37.2	**	**	**	**	**
Cefuroxime	60.9	47.8	47.9	51.1	**	**	**	**	**
Piperacillin-tazobactam	82.6	73.9	72.9	75.5	100	95.2	96.8	**	**
Ceftazidime	**	**	54.2	**	100	85.7	90.3	**	**
Ticarcillin-clavulanic	**	**	**	**	60	71.4	67.7	**	**
Nitrofurantoin	**	**	68.8	**	**	**	**	**	**
Cloxacillin	**	**	**	**	**	**	**	00	11.1
Clindamycin	**	**	**	**	**	**	**	00	55.6
Erythromycin	**	**	**	**	**	**	**	00	33.3
Linezolid	**	**	**	**	**	**	**	**	100

LRTI: Lower respiratory tract infections; SSTI: skin and soft tissue infections; UTI: urinary tract infections; **not tested.

antibiotics among all patients in the three selected infection groups. A combination of two or more antibiotics was administered to 8.1% (12/158) of the study population. The majority (75%, 9/12) of the combination antibiotic prescriptions were for SSTIs. None of the patients with UTIs were given a combination of antibiotics.

The selection of empirical antibiotics was concordant with the national guidelines in 92.4% (146/158) of patients. The rate of adherence to the guideline was lowest for SSTI (86.7%, 46/53) and highest for UTI (94.6%, 53/56). Resistance to the prescribed empirical antibiotic was observed in 29.5% (43/146) of the bacterial isolates obtained from patients who received guideline-concordant (GC) therapy and 21.4% (3/14) in bacteria isolated from patients who received non-guideline concordant (non-GC) antibiotics. However, this difference is not statistically significant ($p = 0.52$). Figure 1 shows the susceptibility of isolated bacteria against the prescribed empirical antibiotic.

Only 47.5% (76/160) of the bacterial isolates were sensitive to the empirical antibiotic and therefore can be considered an appropriate antibiotic prescription. Resistance was observed in 28.8% (46/160) isolates while the prescribed empirical antibiotic did not have the spectrum of activity against the bacteria in 15.1% (24/160) isolates. The proportion of patients that received appropriate empirical therapy varied between the selected infection types (LRTI = 49%, SSTI = 43.7%, and UTI = 50%). This difference was not statistically significant ($p > 0.05$).

Antibiotic prescription according to WHO AWaRe classification [17]

Of the total antibiotics prescribed, only 32.9% were from the "Access" category while the rest were from the "Watch" group with an Access: Watch ratio of 0.49. Antibiotics in the "Reserve" group were not prescribed. Use of Access category antibiotics was 46.7% for SSTI, 23.07% for LRTI, and 26.7% for UTI (Figure 2). According to the recommendations of the national guideline for LRTI, all the parenteral antibiotics except amoxicillin-clavulanic acid belong to the "Watch" category. For UTIs, the guideline recommends parenteral antibiotics from the "Access" category (amoxicillin-clavulanic acid, gentamicin, amikacin) as primary therapy agents while antibiotics from the "Watch" category are recommended for alternative therapy. Parenteral antibiotics from both "Access" and "Watch" categories are recommended for SSTI.

Discussion

Guidelines for empirical antibiotics are intended to improve the outcome of infectious diseases through early and appropriate antimicrobial therapy while minimizing the emergence of antimicrobial resistance (AMR). Better adherence to antibiotic guidelines has been shown to improve patient outcomes in terms of the length of hospitalization and mortality [8,10,18]. Our study has found a high rate of compliance with the current national guidelines on empirical antibiotic therapy. However, nearly 30% of the bacteria isolated from patients who received guideline-concordant therapy, were resistant to the given antibiotic. This reduces the favorable outcomes expected by implementing antibiotic guidelines.

The majority of the isolated bacteria in this study belong to the family *Enterobacteriaceae* (coliforms). Similar findings were observed in several studies done in Sri Lanka on urinary tract infections and lower respiratory tract infections [19-21]. In a study conducted in the same study setting in 2009, *E. coli* was identified as the main causative bacteria for UTIs and the ESBL production rate among urinary coliforms was 33% [21]. This is comparable to our findings in 2019.

Figure 1. Susceptibility of isolated bacteria against the prescribed empirical antibiotic.

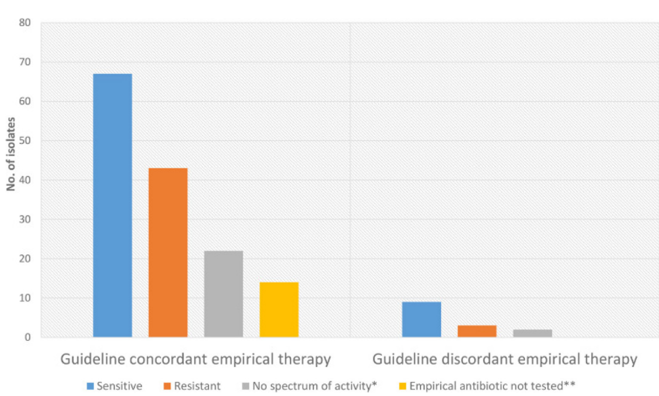
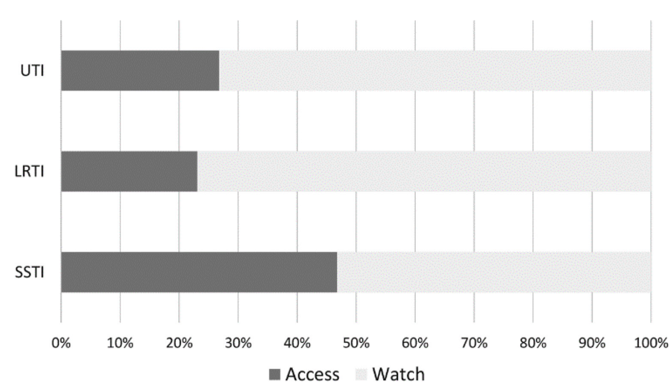


Figure 2. Use of antibiotics from "Access" and "Watch" categories.



However, in comparison with 2009 data, antibiotic-resistant rates among urinary coliforms in our study have increased considerably except for gentamicin and amikacin. Another Sri Lankan study conducted in 2009/2010 at a tertiary care center has observed higher antibioitc resistance rates among urinary coliforms isolated from adult in-patients [19]. Those rates were higher than that of our findings for most of the tested antibiotics. Ciprofloxacin was the most commonly prescribed empirical antibiotic for UTIs in that study [19] which is similar to our findings.

In the current study, *K. pneumoniae* was the predominant bacteria isolated from patients with LRTIs followed by *P. aeruginosa*. Amarasinghe *et al* [20] reported a higher prevalence of *P. aeruginosa* among patients with LRTI at Colombo Central Chest Clinic. A survey conducted in five Sri Lankan public hospitals revealed that 53% of patients with SSTI received inappropriate antibiotic therapy while 32.6% of antibiotic prescriptions were discordant with the national guidelines [22]. We observed a higher concordance with the guidelines for SSTI.

In 2017, the national consumption of “Watch” group antibiotics in the public sector was nearly 25% [23]. Our observed usage of “Watch” group antibiotics was 67.1%. This difference could be because we only considered the prescription of parenteral antibiotics in our study. Amoxicillin-clavulanic acid is the recommended “Access” antibiotic for the selected infections and the observed sensitivity was low (37.2%). The increased use of “Watch” antibiotics could be because the prescribers have noticed these poor responses to “Access” antibiotics. However, this could lead to indiscriminate use of “Watch” antibiotics and the development of resistance to those antibiotics as well. “Reserve” group antibiotics were not prescribed for the selected infections. This is an important and favorable finding as “Reserve” antibiotics are considered the last resort of treatment and should only be used when all other antibiotics have failed or cannot be used due to contraindications.

Antibiotic resistance has become a major public health problem all over the world for which inappropriate antibiotic prescription is an important contributing factor, especially in developing countries [24,25]. Adequate consideration must be given to the prevailing resistance patterns when developing antibiotic guidelines to prevent the use of less effective antibiotics as well as the overuse of “Watch” and “Reserve” antibiotics. According to the literature two-thirds of the guidelines do not provide meaningful information on antibiotic-resistant patterns which has contributed to the inappropriate use of antibiotics despite the availability of such guidelines [26]. Researchers have used different methodologies to assess the appropriateness of antibiotic therapy. We used the *in-vitro* susceptibilities of the isolated bacteria to determine the appropriateness. This method is identified as one of the least subjective and most clinically important assessments of appropriate therapy because it identifies patients at high risk of treatment failure [27].

According to our findings, 43.9% (n = 70) of the patients had received inappropriate antibiotic therapy despite the higher rate of adherence (92.4%) to guidelines. Appropriateness rates were not statistically significant ($p = 0.18$) for guideline-concordant and non-guideline-concordant therapy. The high rate of inappropriate therapy in our study is a cause for concern as similar studies from other countries have observed lower inadequacy/inappropriate rates with guideline adherence [28,29].

The Sri Lanka College of Microbiologists, in collaboration with several other healthcare professional bodies, published the national guidelines on the empirical and prophylactic use of antibiotics in 2016 [12]. This guideline recommends empiric antibiotic regimens for common bacterial infections. Although this guideline has been in practice for approximately five years, little is known about adherence to these recommendations by clinicians. Also, the current guideline does not reflect the changes that have occurred to antibiotic sensitivity with time. The effectiveness of antibiotic guidelines has been shown to decline over time due to the emergence and expansion of antibiotic resistance [30]. We observed high resistance to the antibiotics recommended in the guidelines for the selected infections which has led to inappropriate therapy. Therefore, timely revisions of guidelines are important to maintain the effectiveness and acceptance of the guidelines.

Conclusions

Antibiotic-sensitivity patterns and bacterial spectra of infections change over time. Based on our findings we recommend empirical antibiotic guidelines be updated in accordance with the latest surveillance data and information on prevailing bacterial spectra. The presence of varying antibiotic-resistant rates across different treatment facilities in a country is a challenge to the uniform implementation of national guidelines. Modifying the national guidelines according to the local sensitivity patterns would help to improve patient outcomes in such instances. The effectiveness of the guidelines should be periodically evaluated to optimize the prescribing patterns. Proper documentation in health care settings is important to evaluate the guidelines and antibiotic stewardship programs.

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