First Point-Prevalence Study of Inpatient Antimicrobial Use in Five Public Hospitals in Southern Sri Lanka

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Department of Global Health in the Graduate School
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ABSTRACT

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Abstract

Objectives

Inappropriate antimicrobial use is associated with adverse drug effects and antimicrobial resistance. Understanding prescribing practices is important for optimizing antimicrobial use. We investigated the prevalence, types, and indications for antimicrobial use among inpatients in Sri Lanka.

Methods

A point-prevalence study was conducted among inpatients at one tertiary, one secondary, and three primary-level public hospitals in Southern Province, Sri Lanka. From June-August 2017, all patients in medical, surgical, pediatric, and intensive care wards were included. Charts were assessed for systemic antibiotic, antifungal, and antiviral use in 1-day point-prevalence studies. Demographics, clinical characteristics, and antimicrobial use data were recorded from charts. Hospital and patient characteristics associated with antimicrobial therapy were assessed using the Chi-square test and Kruskall-Wallis tests. Potentially inappropriate combinations of antimicrobial use were defined as the receipt of two beta-lactam antibiotics or two antibiotics with activity against anaerobes, *Pseudomonas aeruginosa,* or methicillin-resistant *Staphylococcus aureus* (MRSA).

Results

A total of 1,709 patients were included (69.6% tertiary, 21.7% secondary, and 8.7% primary). Patients were in medical (55.2%), surgical (27.2%), pediatric (12.9%), and intensive care wards (4.7%). Overall, 54.7% (95% CI, 52.3%-57.1%) of patients were receiving antimicrobials. Antimicrobial use prevalence was similar across hospital type (p= 0.439), but varied by ward type: 43.1% in medical, 68.0% in surgical, 61.1% in pediatric, and 97.6% in intensive care wards (p<0.001). Commonly used antimicrobials were amoxicillin/clavulanate (33.8%), third-generation cephalosporins (23.6%), metronidazole (16.6%), narrow and extended-spectrum penicillins (15.8%), clarithromycin (12.3%), second-generation cephalosporins (10.7%), and carbapenems (10.4%). Common antimicrobial indications were lower respiratory infections (20.7%), urinary tract infections (9.7%), soft tissue infections (9.4%), , and surgical prophylaxis (7.8%). Of patients receiving antimicrobials, potential inappropriate combinations were seen in 17.1%: 9.2% double anaerobic coverage, 7.6% double beta-lactam coverage, 1.5% double *P. aeruginosa* coverage, and 0.3% MRSA coverage.

Conclusions

We report the first point-prevalence study of antimicrobial use in public hospitals in southern Sri Lanka. Over half of inpatients were receiving

antimicrobials. High and potentially inappropriate antimicrobial use should be addressed by future antimicrobial stewardship efforts.

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1 Introduction

Antimicrobial resistance is a global public health crisis and is largely driven by antimicrobial use.[1] Both the appropriate and inappropriate use of antimicrobials drives resistance; studies indicate that roughly 30 percent of antimicrobials used in US hospitals are unnecessary or prescribed incorrectly.[2] In low- or middle-income countries (LMICs), the problem of antimicrobial overuse appears to be worse. LMICs have a higher burden of infectious diseases and non-prescription antibiotic use is also common.[3]

Hospital antimicrobial stewardship programs (ASPs), which optimize the use of antimicrobials, have been developed to improve the safety and quality of clinical care and potentially decrease antimicrobial resistance.[4] In the US, the Joint Commission now mandates that all acute care centers have ASPs.[4] In resource-limited settings, ASPs are limited and actions they should target are not agreed upon. To identify appropriate antimicrobial stewardship interventions, understanding the prevalence and pattern of local antimicrobial use is vital. For many LMICs, point-prevalence studies, which can be conducted in a relatively short period of time and with limited resources, may be an initial feasible step for identifying patterns of antimicrobial use and potential interventions for reducing inappropriate use.[1]

In Sri Lanka, a LMIC, ASPs are not widely implemented in public hospitals.[5] Limited available data indicate that antimicrobial overuse may be widespread.[5] A

recent study in Sri Lanka showed that 99% of children admitted with lower respiratory tract infections to a tertiary-care hospital were given antibiotics, with many patients receiving broad-spectrum therapy or intravenous antibiotics that may have been unnecessary.[6] Among outpatients with influenza-like illness in the largest tertiary care hospital in southern Sri Lanka, 81.4% received antibiotic prescriptions despite 47.3% patients being positive for influenza.[7] A study conducted at the National Hospital of Sri Lanka showed that almost all the coliforms obtained from the study samples were resistant to third-generation cephalosporins, suggesting high antecedent antibiotic use.[8] Significantly, no point-prevalence studies of antimicrobial use have been published from the inpatient or outpatient settings in Sri Lanka.

The objective of this study was to identify the prevalence and patterns of antimicrobial use among patients admitted to public hospitals of varying levels of care in the Southern Province, Sri Lanka. Indications for antimicrobial use and potential inappropriate combinations of antimicrobials were also identified.

2 Material and methods

2.1 Study design and setting

A point-prevalence study of antimicrobial use was conducted using one-day cross-sectional studies among inpatients at five public hospitals in the Southern Province, Sri Lanka from June 14, 2017 to August 10, 2017. Five public hospitals belonging to three levels of the health system were chosen to represent the province: one tertiary-level hospital (Teaching Hospital Karapitiya, 1745 beds), one secondary-level hospital (Base Hospital Balapitiya, 365 beds), and three primary-level hospitals (Primary Hospital Rathgama, 26 beds; Primary Hospital Baddegama, 104 beds; and Primary Hospital Hikkaduwa, 60 beds).[9] Medical, surgical, pediatric, and intensive care units were surveyed in the secondary and tertiary-level hospitals. Medical, surgical, and pediatric units were surveyed in the primary-level hospitals, which do not contain intensive care units. The one-day point-prevalence studies were repeated twice for the tertiary and secondary-level hospitals and four times for the three primary-level hospitals to ensure adequate sample size and precision of measurement in antimicrobial use. To reduce the chances of a patient being captured twice in the survey, a minimum of one week was allotted before the point-prevalence study was repeated on a ward.

2.2 Study population and data collection

Trained, MBBS-qualified research assistants visited the pre-specified wards at 8am on the days of the point-prevalence studies. All patients who were hospitalized on the ward at the time of the survey were included. Patients' medical records were used to

collect sociodemographic information as well as clinical data including chronic medical conditions, antimicrobial allergies, admission diagnoses, antimicrobials actively prescribed at the time of the survey, and indications for antimicrobial use. Antimicrobial agents that were captured included antibiotics, antifungals, and antivirals prescribed by either the intravenous or oral route.

The questionnaire was piloted at the tertiary-level hospital to evaluate the feasibility of collecting data from the medical record. Informed consent was waived as all information was collected solely from the medical record and there was no direct contact with patients. Ethical approval for this study was obtained by the Ruhuna University Ethical Review Committee and the Duke University Institutional Review Board. The directors of each hospital and the Regional Director of Health Services in Galle, Sri Lanka also approved this study.

2.3 Data Analysis

Data were entered into a Research Electronic Data Capture (REDCap) database and statistical analyses were performed using R version 3.4.1.[10] The overall prevalence of antimicrobial use was defined as the number of patients receiving at least one antimicrobial agent at the time of the survey divided by the total number of patients captured in the study. If the admission diagnosis was not listed in the medical record, the first documented clinical diagnosis was recorded. If neither an admission diagnosis nor a clinical diagnosis was listed, the presenting symptoms were recorded. Both chronic medical conditions and admission diagnoses were grouped based on

International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes.[11] The mid-P exact method was used to generate confidence intervals for antimicrobial use. Demographic and clinical characteristics associated with antimicrobial use were assessed using the Chi-square test for categorical variables and the Kruskall-Wallis test for continuous variables. A two-tailed p-value of <0.05 was considered to be statistically significant in this study. Potentially inappropriate antimicrobial use was defined as concurrent therapy with two or more antimicrobials that were beta-lactam antibiotics or concurrent therapy with two or more antimicrobials that had a spectrum of activity against *Pseudomonas aeruginosa*, anaerobes, or methicillin-resistant *Staphylococcus aureus* (MRSA).

3 Results

3.1 Study Population

A total of 1,709 patients were included in the point-prevalence study: 1,190 (69.6%) from the tertiary-level hospital, 371 (21.7%) from the secondary-level hospital, and 148 (8.7%) from the primary-level hospitals. Of total patients enrolled in the study, 943 (55.2%) were in medical wards, 465 (27.2%) were in surgical wards, 221 (12.9%) were in pediatric wards, and 80 (4.7%) were in intensive care units (Table 1).

Table 1: Prevalence of antimicrobial use, by hospital[a] and type of ward[b], Southern Province, Sri Lanka, 2017

Hospital/ Ward Characteristic	Total Patients		Prevalence of Antimicrobial Use		P values
	No.	% of total	No.	% in hospital/ward	
Tertiary level hospital					
Teaching Hospital Karapitiya	1,190	69.6	657	55.2	
Secondary level hospital					
Base Hospital Balapitiya	371	21.7	193	52.0	
Primary level hospitals					
Government Hospital Rathgama	24	1.4	4	16.7	0.439
Government Hospital Baddegama	78	4.6	53	67.9	
Government Hospital Hikkaduwa	46	2.7	28	60.9	
All primary level hospitals	148	8.7	85	57.4	
Overall	**1,709**	**100.0**	**935**	**54.7**	
Medical Wards	943	55.2	406	43.1	
Surgical Wards	465	27.2	316	68.0	
Pediatric Wards	221	12.9	135	61.1	<0.001
Intensive Care Units	80	4.7	78	97.5	
Overall	**1,709**	**100.0**	**935**	**54.7**	

[a] The level of care of hospitals is defined by the Ministry of Health and the Provincial Ministries of Health in Sri Lanka.
[b] Mixed medical/ surgical wards and primary care units in primary level hospitals are classified as medical wards.

The majority (55.6%) of patients were male and median age was 42.2 years (IQR 21-63 years). The most common admission diagnoses included dengue fever (311, 18.2%),

acute lower respiratory tract infection (126, 7.4%), cellulitis (98, 5.7%), and fever of unclear origin (97, 5.7%) (Table 2). Many patients (689, 40.3%) had chronic medical conditions, including cardiovascular disease (346, 20.2% of all patients), endocrine disorders (283, 16.6%), and pulmonary disease (144, 8.4%). Only 25 patients (1.5%) had a reported antimicrobial allergy. Median hospitalization duration at the time of the survey was 5.9 days (IQR 2-6 days; Table 2).

Table 2: Demographic and clinical characteristics among patients enrolled in a point-prevalence survey of antimicrobial use, Southern Province, Sri Lanka, 2017

Characteristic	Total Patients (N = 1,709)		Patients on Antimicrobials (N = 935)		Patients Not on Antimicrobials (N = 774)		P Values
	No. or median	% or IQR[m]	No. or median	% or IQR	No. or median	% or IQR	
Age, years	42.2	21.0-63.0	43.1	20.0-64.0	41.1	22.0-60.7	0.053
Age Categories							
Age < 12	249	14.6	152	16.3	97	12.5	0.268
Age 12-18	110	6.4	57	6.1	53	6.8	
Age 19-45	509	29.8	272	29.1	237	30.6	
Age 46-64	454	26.6	252	27.0	202	26.1	
Age > 65	343	20.1	182	19.5	161	20.8	
Gender							
Male	950	55.6	530	55.8	420	44.2	0.332
Hospitalization Duration[a], days	5.9	2.0-6.0	7.0	3.0-8.0	4.5	2.0-4.0	<0.001
Antimicrobial Allergy							
Available	25	1.5	20	2.1	5	0.6	0.019
Chronic Medical Conditions[b]							
Total patients with chronic medical conditions	689	40.3	428	45.8	261	33.7	<0.001
Cardiovascular disease[c]	346	20.2	196	21.0	150	19.4	0.479
Neurologic disease[d]	40	2.3	20	2.1	20	2.6	0.647
Psychiatric disease[e]	9	0.5	6	0.6	3	0.4	0.703
Renal/Genitourinary disease[f]	51	3.0	35	3.7	16	2.1	0.061

Endocrine disease[g]	283	16.6	180	19.2	103	13.3	0.001
Pulmonary disease[h]	144	8.4	102	10.9	42	5.4	<0.001
Gastrointestinal disease[i]	33	1.9	19	2.0	14	1.8	0.884
Hematologic disease[j]	15	0.9	8	0.9	7	0.9	1.000
Rheumatologic disease[k]/ arthritis	19	1.1	10	1.1	9	1.2	1.000
Malignancy	19	1.1	14	1.5	5	0.6	0.153
Other	58	3.4	41	4.4	17	2.2	0.019
Admission Diagnosis[l]							
Dengue fever	311	18.2	43	4.6	268	34.6	<0.001
Acute lower respiratory infection	126	7.4	125	13.4	1	0.1	<0.001
Cellulitis and acute lymphangitis	98	5.7	96	10.3	2	0.3	<0.001
Fever of unknown origin	97	5.7	53	5.7	44	5.7	1.000
Disorders of the urinary system	62	3.6	61	6.5	1	0.1	<0.001
Acute myocardial infarction	42	2.5	11	1.2	31	4.0	<0.001
Infectious gastroenteritis and colitis	38	2.2	18	1.9	20	2.6	0.450
Asthma	35	2.0	26	2.8	9	1.2	0.029
Pain in throat and chest	31	1.8	5	0.5	26	3.4	<0.001
Sepsis	27	1.6	27	2.9	0	0	<0.001
Nausea and vomiting	25	1.5	13	1.4	12	1.5	0.943
Open wound of ankle, foot and toes	24	1.4	21	2.2	3	0.4	0.002
Fracture of lower leg	22	1.3	18	1.9	4	0.5	0.018
Disorders of vestibular function	21	1.2	5	0.5	16	2.1	0.008

[a] At time of enrollment.
[b] One patient may have more than one chronic medical condition.
[c] Cardiovascular disease includes hypertension, ischemic heart disease, dyslipidemia, valvular heart disease, arrhythmia, and congenital heart disease.
[d] Neurologic disease includes epilepsy, seizures, cerebrovascular accident, transient ischemic attack, intellectual/developmental disability, and migraine.
[e] Psychiatric disease includes bipolar affective disorder, schizophrenia, depression, and psychiatric illness.
[f] Renal/Genitourinary disease includes chronic kidney disease, end-stage renal failure, renal/bladder calculi, benign prostatic hyperplasia, and recurrent urinary tract infection.
[g] Endocrine disease includes diabetes mellitus and hypothyroidism.
[h] Pulmonary disease includes asthma, chronic obstructive pulmonary disease, bronchiectasis, and tuberculosis.
[i] Gastrointestinal disease includes gastroesophageal reflux disease, gastritis, and chronic liver disease.
[j] Hematologic disease includes anemia, thrombocytopenia and beta thalassemia.
[k] Rheumatologic disease includes psoriasis, dermatomyositis, ulcerative colitis, vitiligo, and systemic lupus erythematosus.
[l] Only diagnoses attributed to 20 patients or more are listed.
[m] The interquartile range corresponds to 25th - 75th percentile.

3.2 Prevalence of Antimicrobial Use

Among 1,709 patients enrolled in the study, 54.7% (95% CI, 52.3%-57.1%) were receiving at least one antimicrobial agent at the time of the study (Table 1). Prevalence of antimicrobial use did not vary significantly across hospitals of different levels of care: 55.2% in the tertiary-level hospital, 52.0% in the secondary-level hospital, and 57.4% in the primary-level hospitals (p=0.439). However, prevalence of antimicrobial use did vary significantly across different types of wards: 43.1% in medical wards, 68.0% surgical wards, 61.1% in pediatric wards, and 97.6% in intensive care units (p<0.001).

Demographic and clinical characteristics were associated with antimicrobial use. Patients receiving antimicrobial therapy were older than patients not receiving antimicrobials (median age 43.1 years versus 41.1 years, p<0.001) and had a longer duration of hospitalization (median 7.0 days versus 4.5 days, p<0.001). In addition, patients receiving antimicrobial therapy were more likely to have chronic medical conditions than patients not receiving antimicrobials 62.1% versus 49.8, p<0.001). Patients with admission diagnoses of dengue fever, acute myocardial infarction, pain in throat and chest, and disorders of vestibular function were less likely to receive antimicrobials (p<0.05), while patients with admission diagnoses of acute lower respiratory tract infection, cellulitis, disorders of the urinary system, asthma, sepsis, and open wounds and fractures of the lower extremities were more likely to receive antimicrobials (p<0.05; Table 2).

3.3 Antimicrobials Prescribed

Among 935 patients who were prescribed antimicrobial drugs, the most commonly prescribed antimicrobial was amoxicillin/clavulanic acid (316, 33.8% of patients receiving antimicrobials; Figure 1). Third-generation cephalosporins (221, 23.6%) were next most common, followed by narrow and extended-spectrum penicillins (148,15.8%). Other commonly prescribed antimicrobial drugs included metronidazole (155, 16.6%), clarithromycin (115, 12.3%), second-generation cephalosporins (100, 10.7%), carbapenems (97, 10.4%), fluoroquinolones (92, 9.8%), and first-generation cephalosporins (11, 1.2%). Of 935 patients receiving antimicrobial therapy, 451 (48.2%) were receiving more than one antimicrobial agent: 338 (36.1%) were receiving two antimicrobial agents, 93 (9.9%) were receiving three antimicrobial agents, and 18 (1.9%) were receiving four or more antimicrobial agents.

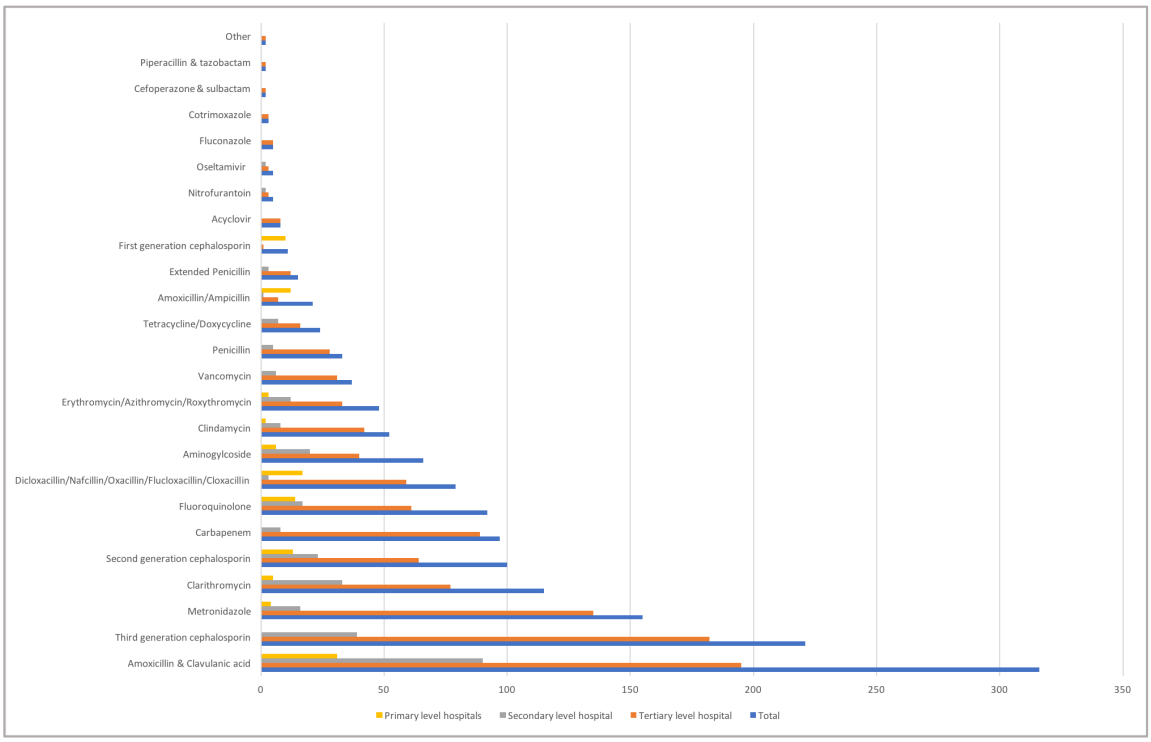

Figure 1: Antimicrobial agents used at different hospitals, southern Sri Lanka, 2017

Commonly used antimicrobials varied by hospital level of care. In the tertiary-level hospital, amoxicillin/clavulanic acid (195, 29.7% of patients receiving antimicrobials in the tertiary-level hospital), third-generation cephalosporins (182, 27.7%), and metronidazole (135, 20.5%) were the three most commonly used antimicrobials. In the secondary-level hospital, amoxicillin/clavulanic acid (90, 46.6% of patients receiving antimicrobials in the secondary-level hospital), third-generation cephalosporins (39, 20.2%), and clarithromycin (33, 17.1%) were the most commonly used while in the primary-level hospitals, amoxicillin/clavulanic acid (31, 36.5% of patients receiving antimicrobials in the primary-level hospitals), extended-spectrum penicillins (17, 20.0%), and fluoroquinolones (14, 16.5%) were the most commonly used (Figure 1).

Antimicrobials that were used most commonly also varied by ward type. Among 406 patients receiving antimicrobial therapy in medical wards, amoxicillin/clavulanic acid (136, 33.5% of patients receiving antimicrobials in medical wards) and third-generation cephalosporins (117, 28.8%) were the most frequently used antimicrobials. Among 316 patients receiving antimicrobial therapy in surgical wards, amoxicillin/clavulanic acid (137, 43.4%) and metronidazole (87, 27.5%) were the most frequently used antimicrobials. Among 135 patients receiving antimicrobial therapy in pediatric wards, clarithromycin (43, 31.8%) and third generation cephalosporins (40, 29.6%) were the most frequently used antimicrobials. Among 78 patients receiving antimicrobial therapy in intensive care units, metronidazole (30, 38.5%) and third generation cephalosporins (25, 32.0%) were the most frequently used antimicrobials.

3.4 Indications for antimicrobial use and potentially inappropriate antimicrobial use

Among 935 patients on antimicrobial therapy, 779 (83.3%) had one or more indication for antimicrobial use: 350 patients (44.9%) had indications explicitly written in medical charts, 54.94% did not have indications that were explicitly written and were inferred by research assistants based on the clinical record, and 0.1% did not have indications that were written or could be inferred. Overall, the most common indications for antimicrobial use included lower respiratory tract infection/pneumonia (194, 20.7% of patients receiving antimicrobials), cellulitis/abscess/soft tissue infection (181, 19.4%),

urinary tract infection/pyelonephritis(91, 9.7%), and surgical prophylaxis (73, 7.8%) (Table 3).

Table 3: Indications for antimicrobial use, organized by type of ward, southern Sri Lanka, 2017

Characteristic	Total Patients on Antimicrobials (N = 935)		Medical Wards (N = 406)		Surgical Wards (N = 316)		Pediatric Wards (N = 135)		Intensive Care Units (N = 78)		P Values
	No.	%	No.	%	No.	%	No.	%	No.	%	
Indication for Antimicrobials Listed											
Yes	779	**83.3**	330	**81.3**	260	**82.3**	117	**86.7**	72	**92.3**	**0.076**
Per chart	350	**37.4**	136	**33.5**	127	**40.2**	65	**48.1**	22	**28.2**	**0.004**
Inferred	428	**45.8**	194	**47.8**	132	**41.8**	52	**38.5**	50	**64.1**	**0.001**
Number of Indications											
1	750	**80.2**	318	**78.3**	251	**79.4**	117	**86.7**	64	**82.1**	**0.206**
2	25	**2.7**	11	**2.7**	7	**2.2**	0	**0**	7	**9.0**	**0.001**
>= 3	2	**0.2**	1	**0.2**	0	**0**	0	**0**	1	**1.3**	**0.161**
Number of Antimicrobial Agents											
1	485	**51.9**	226	**55.7**	141	**44.6**	94	**69.6**	24	**30.8**	
2	338	**36.1**	147	**36.2**	130	**41.1**	34	**25.2**	27	**34.6**	
3	93	**9.9**	28	**6.9**	41	**13.0**	7	**5.2**	17	**21.8**	**<0.001**
4	16	**1.7**	5	**1.2**	3	**0.9**	0	**0**	8	**10.3**	
5	2	**0.2**	0	**0**	0	**0**	0	**0**	2	**2.6**	
Indications[a,b]											
Lower respiratory infection/Pneumonia	194	**20.7**	121	**29.8**	3	**0.9**	56	**41.5**	14	**17.9**	**<0.001**
Cellulitis/Abscess/Soft tissue infection	181	**19.4**	51	**12.6**	125	**39.5**	2	**1.5**	3	**3.8**	**<0.001**
Urinary tract infection/Pyelonephritis	91	**9.7**	54	**13.3**	25	**7.9**	11	**8.1**	1	**1.3**	**0.003**
Surgical prophylaxis	73	**7.8**	1	**0.2**	54	**17.1**	1	**0.7**	17	**21.8**	**<0.001**
Upper respiratory infection	40	**4.3**	22	**5.4**	0	**0**	18	**13.3**	0	**0**	**<0.001**
Primary bacteremia	34	**3.6**	10	**2.5**	1	**0.3**	5	**3.7**	18	**23.1**	**<0.001**
Meningitis/Encephalitis	23	**2.5**	13	**3.2**	0	**0**	5	**3.7**	5	**6.4**	**0.002**
Infected wound	21	**2.2**	3	**0.7**	18	**5.7**	0	**0**	0	**0**	**<0.001**
Leptospirosis	18	**1.9**	14	**3.4**	1	**0.3**	0	**0**	3	**3.8**	**0.004**
Fractures	18	**1.9**	2	**0.5**	14	**4.4**	0	**0**	2	**2.6**	**<0.001**
Fever of unclear etiology	10	**1.1**	2	**0.5**	0	**0**	5	**3.7**	3	**3.8**	**<0.001**
Secondary bacteremia	10	**1.1**	5	**1.2**	1	**0.3**	0	**0**	4	**5.1**	**0.002**
Culture Result[c]											
None ordered/ available	798	**85.3**	356	**87.7**	281	**88.9**	120	**88.9**	41	**52.6**	**<0.001**
Positive	57	**6.1**	20	**4.9**	14	**4.4**	4	**3.0**	19	**24.3**	**<0.001**
Potentially Inappropriate Antimicrobial Use											
Double anaerobic coverage	86	**9.2**	14	**3.4**	53	**16.8**	1	**0.7**	18	**23.1**	**<0.001**
Double beta-lactam combination	71	**7.6**	31	**7.6**	27	**8.5**	6	**4.4**	7	**9.0**	**<0.001**

Double Pseudomonas coverage	14	**1.5**	3	**0.7**	5	**1.6**	0	**0**	6	**7.7**	**<0.001**
Double MRSA coverage[d]	3	**0.3**	0	**0**	2	**0.6**	0	**0**	1	**1.3**	**<0.001**

[a] Patients may have more than one indication thus the total percentage of patients in patients with indications is not 100%.
[b] Indications that have less than 10 patients are listed in the text.
[c] Culture result relevant to the indication for antimicrobials.
[d] MRSA = methicillin-resistant *Staphylococcus aureus*

Indication for antimicrobials varied by ward type. Among 406 patients receiving antimicrobial therapy in medical wards, lower respiratory infection/pneumonia (120, 29.6% of patients on antimicrobials) and urinary tract infection/pyelonephritis (52, 12.8%) were the most common indications. Among 316 patients receiving antimicrobial therapy in surgical wards, cellulitis (124, 39.2%) and surgical prophylaxis (54, 17.1%) were the most common indications. Among 135 patients receiving antimicrobial therapy in pediatric wards, lower respiratory tract infection/pneumonia (56, 41.5%) and upper respiratory tract infection (18, 13.3%) were the most common indications. Among 78 patients receiving antimicrobial therapy in intensive care units, primary bacteremia (18, 23.1%) and surgical prophylaxis (17, 21.8%) were the most common indications.

The most commonly used antimicrobial drugs for lower respiratory infection/pneumonia were amoxicillin/clavulanic acid (76, 39.8% of total patients diagnosed with lower respiratory infection/pneumonia), clarithromycin (75, 39.3%), and third-generation cephalosporins (62, 32.5%). The most commonly used antimicrobial drugs for cellulitis/abscess/soft tissue infection were amoxicillin/clavulanic acid (73, 40.6% of total patients diagnosed with cellulitis/abscess/soft tissue infection), extended-spectrum penicillins (45, 25.0%), and metronidazole (40, 22.2%). The most commonly used antimicrobial drugs for urinary tract infection/pyelonephritis were amoxicillin/clavulanic acid (30, 34.9% of total patients diagnosed with urinary tract

infection/pyelonephritis), fluoroquinolones (27, 31.4%), and third-generation cephalosporins (20, 23.2%). The most commonly used antimicrobial drugs for surgical prophylaxis were amoxicillin/clavulanic acid (32, 43.8% of total patients diagnosed with surgical prophylaxis), metronidazole (24, 32.9%), and second-generation cephalosporins (23, 31.5%). The most commonly used antimicrobial drugs for upper respiratory infection were amoxicillin/clavulanic acid (18, 45% of total patients diagnosed with upper respiratory infection), clarithromycin (7, 17.5%), and second-generation cephalosporins (4, 10.0%) (Table 4).

Table 4: The most common antimicrobials for the top 5 indications

Indications	Antimicrobials	N	%	Total Patients
Lower respiratory infection/pneumonia	Amoxicillin & clavulanic acid	76	39.8	191
	Clarithromycin	75	39.3	
	Third-generation cephalosporins	62	32.5	
	Carbapenems	22	11.5	
	Second-generation cephalosporins	15	7.8	
Cellulitis/abscess/soft tissue infection	Amoxicillin & clavulanic acid	73	40.6	180
	Extended-spectrum penicillins	45	25.0	
	Metronidazole	40	22.2	
	Clindamycin	40	22.2	
	Third-generation cephalosporins	25	13.9	
Urinary tract infection/pyelonephritis	Amoxicillin & clavulanic acid	30	34.9	86
	Fluoroquinolone	27	31.4	
	Third-generation cephalosporins	20	23.2	
	Carbapenems	13	15.1	
	Clarithromycin	6	7.0	
Surgical prophylaxis	Amoxicillin & clavulanic acid	32	43.8	73
	Metronidazole	24	32.9	
	Second-generation cephalosporin	23	31.5	
	Aminogylcoside	9	12.3	
	Carbapenems	8	11.0	
Upper respiratory infection	Amoxicillin & clavulanic acid	18	45.0	40
	Clarithromycin	7	17.5	
	Second-generation cephalosporins	4	10.0	

First-generation cephalosporins	4	10.0
Erythromycin/azithromycin/roxythromycin	3	7.5

The most commonly used antimicrobial drugs by intravenous were third-generation cephalosporins (217, 21.7% of total antimicrobial drugs by intravenous), amoxicillin/clavulanic acid (208, 20.8%), and metronidazole (129, 12.9%). The most commonly used antimicrobial drugs by oral were amoxicillin/clavulanic acid (108, 21.2% of total antimicrobial drugs by oral), clarithromycin (105, 20.7%), and fluoroquinolones (55, 10.8%) (Figure 2).

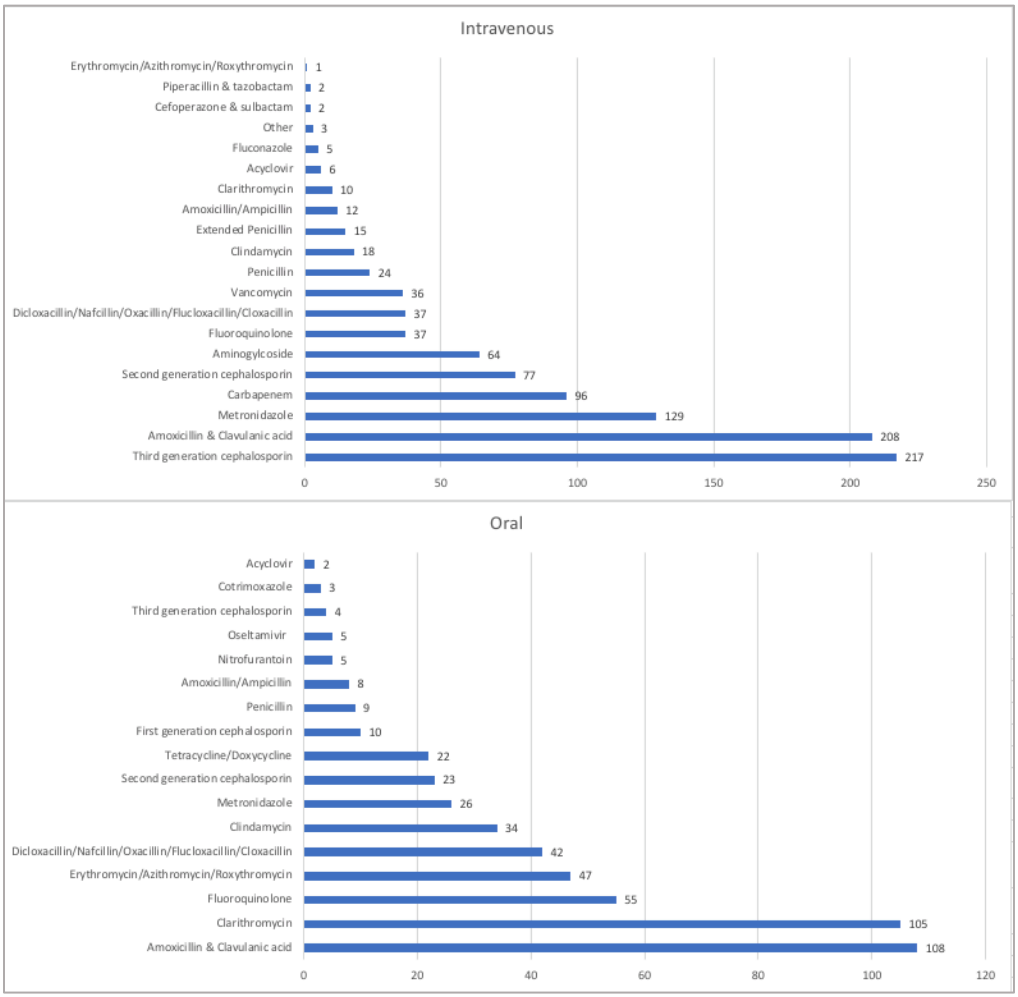

Figure 2: Antimicrobial agents grouped by intravenous and oral medications, southern Sri Lanka, 2017

Among 935 patients receiving antimicrobial therapy, only 135 (14.4%) had a culture result relevant to the indication for antimicrobial therapy at the time of the survey. Of 935 patients, 160 patients (17.1%) were receiving potentially inappropriate antimicrobial therapy: 86 patients (9.2%) were receiving double beta-lactam therapy, 71 patients (7.6%) were receiving double anaerobic coverage, 14 patients (1.5%) were receiving double *P. aeruginosa* coverage, and 3 patients (0.3%) were receiving double MRSA coverage (Table 3).

4 Discussion

Antimicrobial resistance is a growing global problem. Antimicrobial point-prevalence surveys have been widely used to evaluate antimicrobial use globally and to identify targets for improving use and decreasing antimicrobial resistance [1-5, 12-18, 19-23] We report the first point-prevalence study of antimicrobial use in public hospitals in Sri Lanka. Over 50% of patients were on antimicrobials at the time of the survey. Prevalence of antimicrobial use did not differ by level of care of hospitals, but did vary by type of ward. Receipt of multiple antimicrobials and broad-spectrum antimicrobial therapy was common; amoxicillin/clavulanic acid was the most commonly used antimicrobial drug for all the major indications, including for indications such as cellulitis and surgical prophylaxis for which it may not be necessary. A significant percentage of patients were also receiving potentially inappropriate combinations of antimicrobial therapy.

In our study, prevalence of antimicrobial use was approximately 50%. This prevalence in general is greater than that reported from higher-income settings. At a Canadian tertiary care hospital, the prevalence of antimicrobial agents in acute care units and long-term care was 31% and 4%, respectively, in 2012.[12] In 226 hospitals from 41 countries from Europe, Africa, Asia, Australia, Latin America, and North America, a web-based point-prevalence survey identified the prevalence of antimicrobial use in inpatient children and neonates as 36.7% among 17,693 admissions.[13] In nine nursing homes in the US, the prevalence of antimicrobial use was 11.1% among 1,272 eligible residents and 32% of antimicrobials were given for urinary tract infections.[14] However,

in 183 US acute care hospitals, the prevalence of antimicrobial use was 49.9% among 11,282 patients in 2011.[9]

Point-prevalence studies of antimicrobial use in low- or middle-income countries are less common but generally indicate that antimicrobial use is higher. In a point-prevalence survey conducted in India, 50% of 1,834 adult hospitalized patients were receiving antimicrobials on survey days.[16] In 13 Chinese hospitals, a point-prevalence survey showed that 56% of 12,409 inpatients were receiving antibiotic therapy and the most commonly used antibiotics were beta-lactam antibiotics.[17] Another point-prevalence study performed in Vietnamese hospitals found that 67.4% of 7,571 inpatients were receiving antibiotic therapy on the day of the study and that the most commonly prescribed antibiotic agents were cephalosporins, penicillins, and aminoglycosides. Of patients receiving antibiotics, 30.8% in the Vietnamese study had an inappropriate indication for prescription.[18] According to a global point-prevalence survey of antimicrobial consumption and resistance of 223 hospitals in 2015, the prevalence of antimicrobial use was 42.1% in West & Central Asia and 33.3% in East & South Asia.[24] The prevalence of antimicrobial use in our study in Sri Lanka was similar to other areas in Asia. The potential high usage of antimicrobial agents needs to be addressed in future studies and interventions. We found that antimicrobial use was highest in surgical wards and intensive care units, with almost all patients in the latter receiving antimicrobial therapy. The results in our study correlate with those from other studies focusing on surgical units and intensive care units.[15, 21-22]

As would be expected, the indications for antibiotic use varied by ward type, with respiratory tract infections and urinary tract infections being the most common indications in medical wards, and cellulitis and surgical prophylactic therapy being most common indications in surgical wards. Of patients receiving antimicrobial therapy, almost 40% did not have a clear indication documented in the medical chart, with the indication being inferred by the research assistants. Prior studies have shown that documenting an indication for antimicrobials reduces inappropriate therapy, and documenting an indication in the medical record is now a basic metric monitored by antimicrobial stewardship teams.[25-26] Approximately 15% of patients in our study did not have a clear indication for antimicrobial therapy either documented or that could be inferred, and may represent another subset of patients that could be targeted in antimicrobial stewardship activities.

Amoxicillin & clavulanic acid was the most common used antimicrobial agent in our study followed by third-generation cephalosporins and metronidazole. These findings are consistent with results from prior studies in China, Vietnam, and Japan that show that broad-spectrum antimicrobial use is common in the inpatient setting.[17-18,23] Studies from Sri Lanka show that antimicrobial resistance is a growing problem, especially among gram-negative organisms, with up to 40% of isolates showing multidrug-resistant phenotypes from both community and hospital sources.[27-28] Thus the use of broad-spectrum agents in the inpatient setting may be warranted, but likely in turn drives further selection pressure and bacterial resistance. Approximately 10% of

patients surveyed in our study were receiving carbapenems, which are often considered the last line of therapy against multidrug-resistant gram-negative organisms. The need for carbapenem therapy in these patients represents another area for future study, with further restriction of this class of drugs being a potential antimicrobial stewardship action in the future.

Potential inappropriate antimicrobial use was seen in this study. Of 311 patients with dengue fever, almost 15% were on antimicrobial therapy on survey day, which may represent uncertainty in diagnosis or concern for the presence of bacterial co-infection. Amoxicillin & clavulanic acid was the most commonly used drug for all major indications, including lower respiratory infections, urinary tract infections, surgical prophylaxis, and cellulitis/ abscess/ soft tissue infections. While such broad-spectrum therapy is recommended by the Sri Lanka College of Microbiologists for use in many indications, it would likely not be necessary for the majority of patients for surgical prophylaxis, cellulitis/abscess/soft tissue infections, and upper respiratory infections, and represents possible overuse of a broad-spectrum agent.[29] In addition, 17.1% of patients were receiving dual therapy with agents of overlapping spectrum. While some combinations of antimicrobials may be necessary for empirically treating resistant infections or providing synergy, unnecessary overlap in bacterial coverage could increase bacterial mutations and further drive the problem of antimicrobial resistance.

Some limitations must be noted. Medical charts may contain limited information, especially for patients who were admitted on the day of survey. The admission

diagnosis and indications for antimicrobials might not be completed initially, which could cause bias. However, we recruited a large sample size to ensure significant power on data analysis. We did not capture antimicrobial use in all hospitals in the Southern Province; however, comparing the prevalence of antimicrobial use between hospital types and ward levels is expected to provide a reasonable representation of antimicrobial use among inpatients at public hospitals in southern Sri Lanka. Some patients may have been included in the study twice if they were captured on two point-prevalence surveys. However, we allotted a minimum of one week before repeating point-prevalence surveys on a ward to minimize the chance of patient duplication. Finally, we did not formally assess appropriateness of antimicrobial use based on indication, since the study was cross-sectional and not longitudinal in nature. Potentially inappropriate combinations of antimicrobials were identified based on spectrum of activity; combination use may have been warranted in some of these patients.

5 Conclusions

The prevalence of antimicrobial use among hospitalized patients in public hospitals in southern Sri Lanka was 54.7%. Opportunities for improving antimicrobial use were identified and need to be addressed by future antimicrobial stewardship efforts.

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