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Appropriateness of Empirical Antibiotic Use and Concordence with the WHO AWaRe Classification in Hospitalized Patients

Deepthi Gangula[1], Sheetal Kshirsagar[2], Satyanarayana SV Padi[3], Nadeem Ahmed[4]

[1,2]Pharm D, Department of Pharmacy Practice, Care College of Pharmacy, Kakatiya University, Hanamkonda, Telangana, India
[3]Professor and HOD, Ph.D., Department of Pharmacy Practice, Care College of Pharmacy, Kakatiya University, Hanamkonda, Telangana, India
[4]MBBS MDHM, Administrator and Head of Quality and Operations, Apollo Reach NSR Hospitals, Warangal, Telangana, India

Abstract

Background: Antibiotic prescription trends analysis is essential for monitoring the sensitivity and resistance patterns of microorganisms discovered, regularly generating and updating antibiograms, and providing the context for antibiotic usage and prevalence. Specifically, consistent prescription patterns and antibiotic therapy practices with the WHO AWaRe (Access, Watch, and Reserve) classification of antibiotics and the national or WHO essential medicine list would enhance the prudent use of antibiotics, prevent the emergence and spread of antimicrobial resistance, and preserve antibiotic efficacy for future requirements.

Objective: This study aimed to analyze selection of antibiotics for empirical use and definitive therapy and to evaluate rational use of antibiotics according to the WHO-AWaRe (Access, Watch, and Reserve) categories in hospitalized patients.

Methodology: An observational and cross-sectional study was conducted in a 300 bedded multispecialty tertiary care hospital from October 2022 to March 2023 for a period of six months. Evaluation of demographic data based on antimicrobial susceptibility reports, pathogen characteristics, and infection site; evaluation of antibiotics administered before and after AST reports; and classification of antibiotics using WHO AWaRe metrics from the WHO essential medicines list. Descriptive statistics were applied for the data collected using Microsoft Excel. Results are expressed as total count, frequency, and percentages.

Results: Antimicrobial susceptibility results from 162 patients were gathered from the laboratory. Of these 138 (85.18%) patients had positive results for Gram-negative bacteria and 24 (14.81%) for Gram-positive bacteria. The mean (SD) age of patients was 55 ± 28 years; predominantly male patients 92 (56.79%). 107 (66%) patients were hospitalized for 1-5 days. Monotherapy was given in 17 (10.5%) patients, Most of the patients were admitted into the general medicine 94 (58.02%), Bacteria were mainly isolated from urine (65 isolates, 40.1%), and a total of 36 organisms were isolated. The proportions of appropriate empirical therapy use were 84.05% for Gram-negative bacteria. A total of 706 antibiotics were prescribed out of which 334 are prescribed before AST and 372 are prescribed after AST. More prescribed empirical antibiotics were from the ‘Watch’ group (55.69%), followed by the ‘Access’ group (25.75%). ‘Reserve’ category (8.38%) and ‘not-recommended’ category (10.18%) antibiotics were also prescribed. A greater number of prescribed definitive antibiotics were from the ‘Watch’ group (48.11%). ‘Access’ group antibiotics should be preferable to the ‘Watch’ group. ‘Reserve’ antibiotics are always used as the last option when “Access” and “Watch” group antibiotics don’t work.

Conclusion: The high use of empirical antibiotics especially from the ‘Watch’ category is a disturbing trend as observed in our study. . Increasing the use of ‘Access' antibiotics while limiting the use of ‘Watch' and ‘Reserve' antibiotics at the same time is the highest priority for preserving effectiveness of important antibiotics and minimizing the danger of AMR. Conducting such studies and analysis of such data periodically would pave the way for promotion of rational use of antimicrobials and help restrict the emergence of resistant strains of bacteria.

Keywords: Antimicrobial Resistance (AMR), Antimicrobial stewardship (AMS), Antimicrobial chemotherapy, AWaRe (Access, Watch, and Reserve) classification.

1. Introduction

Antimicrobial resistance (AMR), especially that involving multidrug-resistant organisms (MDROs), also known as ‘superbugs’, is recognized as a global threat to human health. According to globally, the extensive and inappropriate use of antibiotics in primary care and hospital settings is a major contributing factor to the spread of AMR, especially in developing nations like India (Glinz et al., 2021) [1]. Antimicrobial stewardship (AMS) programs aim to optimize antimicrobial treatments and avoid overuse of antimicrobials (Zimmerman et al., 2022) [2]. Gram-positive and gram-negative bacteria that exhibit multidrug resistance are challenging to treat and may not respond to conventional therapies. Lacks of successful prevention measures, shortage of effective therapies, and lack of new antibiotics, require the development of novel treatment options and alternative antimicrobial therapies (Frieri et al., 2017) [3]. It has been estimated that 10 million people worldwide could die annually from infections that no longer respond to antibiotics, with the economic cost of this reaching USD 100 trillion annually if no concrete global action is undertaken by 2050 (Skender et al., 2021) [4]. Delaying appropriate empiric therapy in sepsis and septic shock greatly increases morbidity and mortality, especially when first-dose antimicrobials are given improperly or more than three hours after diagnosis. (Strich et al., 2020) [5]. Inappropriate empiric antimicrobial therapy was significantly more common in the gram-negative bacteria group than in gram-positive bacteria group (Luo et al., 2023) [6].

The initial antibiotic regimen initiated within 24 hours of admission was characterized as empirical antibiotic therapy (Sánchez et al., 2023) [7]. Antibiotics are given prior to the receipt of blood culture and antibiotic susceptibility test results. Before a culture's results, empiric antibiotics are used to treat any suspected bacteria (Calhoun et al., 2023) [8]. The selection of empiric antimicrobial therapy is influenced by a variety of factors including the patient's history, clinical status, and area epidemiologic considerations (Rhodes et al., 2017) [9]. A diagnosis of an infectious disease is made by identifying the site of infection, identifying the host (such as immunocompromised, diabetic, or elderly), and, if practical, establishing a microbiological diagnosis (Van Seventer et al., 2017) [10]. Antimicrobial susceptibility testing is carried out in accordance with standards published by the Clinical and

Laboratory Standards Institute (CLSI) and EUCAST, and it assesses an organism's capacity to develop in the presence of a certain medication in vitro. Minimum inhibitory concentration (MIC) data are presented as the lowest concentration of an antibiotic that prevents a microorganism's apparent growth and is classified by the laboratory as "susceptible," "resistant," or "intermediate," in accordance with CLSI (British Society for Antimicrobial Chemotherapy 2018; Gajic et al., 2022) [11,12].

The antibiotic treatment was administered after receiving the results of the blood culture and antibiotic susceptibility test (Cheng et al., 2019) [13]. Once culture and susceptibility data are available, an antibiotic with a narrow spectrum is chosen for treatment continuation (Gajic et al., 2022) [12]. The antibiogram is a critical resource for institutions tracking antimicrobial resistance developments and guiding empirical antibiotic therapy (Simner et al., 2022) [14]. Drug-level monitoring is needed to ensure antibiotic efficacy and avoid side effects (Calhoun et al., 2023) [8]. Irrational antibiotic use can be detected from ICU audits and feedback evaluation. Antibiotic stewardship programs depend on antibiotic education, and teaching guidelines and clinical pathways will greatly improve antimicrobial prescribing behavior (Bajpai et al., 2018) [15]. Patients with suspected severe infections need broad-spectrum antibiotics to reduce infection, complications, and undertreatment (Evans et al., 2021) [16].

The World Health Organisation (WHO) has created a standardized instrument, WHO Core Prescription Indicators, for assessing drug utilization as well as evaluating drug misuse (Nikki et al., 2019) [17]. Antibiotic stewardship policies that optimize antibiotic usage and reduce antimicrobial resistance can be tracked, targets can be set, and antibiotic consumption can be monitored with the use of the Access, Watch, Reserve (AWaRe) program. (WHO, 2021) [18]. Hence, Tackling AMR is a global burden and increases the cost of treatment. It is highly essential to analyze and monitor the selection of antibiotics for empirical use and definitive therapy according to the antimicrobial sensitivity reports, promoting awareness of using therapeutic guidelines, and rationalizing the use of antibiotics according to WHO-AWaRe (Access, Watch, Reserve) categories would decrease economic burden in low and middle–income developing countries (Klein et al., 2018; 2021) [19,20].

2. METHODS

Study design

An observational and cross-sectional study was conducted in a 300 bedded multispecialty tertiary care hospital in Hanamkonda, Telangana state from October 2022 to March 2023 for a period of six months. Data is collected by reviewing study participants' case sheets, patient discharge prescriptions, antimicrobial susceptibility reports as well as lab and diagnostic data.

Study population

Adults (above the age of 18) who had positive first blood culture results during their hospital stay and who were treated with at least one new systemic antibiotic within the first two days following blood sample collection were considered patients. The initial blood sample collection that yielded positive results for each patient throughout the hospital stay was identified as the index culture.

Inclusion criteria

Hospitalized patients receive antibiotics regardless of gender, or age. Patients who had positive results from first sample cultures during the hospitalization (The index culture was defined as the first sample collection that was found to have positive results per case during the hospitalization.). Patients who received treatment with at least 1 new systemic antimicrobial agent within the initial 48 hours of the sample collection. Patients or family members who signed the relevant hospital informed consent

Exclusion criteria

Out-patients, patients with polymicrobial infections, patients who refused to share treatment details, patients or family members who have not signed the relevant hospital informed consent, the patients' reports with insufficient information

Assessment of data

Assessment of demographic data based on antimicrobial susceptibility reports, characteristics of pathogens, and site of infection

The pathogen profile was constructed as a categorical variable with 2 levels according to the type of organism: gram-positive (GP) isolates and gram-negative (GN) isolates and assessed for frequency of bacterial isolates studied for antimicrobial sensitivity. Patient demographic data were categorized based on gender (male or female), age between 15 and 105 years with 15 years intervals, duration of hospitalization from 1 to 25 days with 5 days intervals, and antibiotics received during hospitalization (from 1 to 8). The patient data was also assessed for department of medical specialty in which treatment received, type of specimen collected for AST report, and associated co-morbidities.

Antibiotic susceptibility and appropriate initial empirical therapy

Appropriate empirical therapy was defined as the initiation of at least 1 new empirical antimicrobial agent to which the pathogen isolated from culture was susceptible either on the day of or the day after the sample was collected (Ohumuna et al., 2023) [21]. A resistant or intermediate microbial profile was considered non-susceptible to early empirical treatment. We used interpretation tables created by Rhee et al., 2020 in situations when susceptibilities to particular antimicrobial drugs given to patients were not listed in susceptibility data [22]. Because susceptibility was generally not reported for other GN isolates and anaerobic pathogens, those organisms were not included in the analysis. The data was carefully evaluated for the number of patients infected with pathogens and proportions of appropriate empirical antimicrobial therapy by a pathogen. Further, the data was systematically examined for appropriate and inappropriate antibiotics used in empirical therapy based on antimicrobial sensitivity reports.

Assessment of antibiotics given before and after AST reports and classification of antibiotic category based on the WHO AWaRe metrics

All the antibiotics prescribed and their frequency of prescription before (empirical antibiotic therapy) and after AST (definitive antibiotic therapy) were also classified into 'Access', 'Watch', 'Reserve', and 'Not recommended' categories based on the AWaRe metrics of the WHO essential medicines list (WHO, 2021) [18].

Statistical analysis

Using Microsoft Excel, descriptive statistics were applied to the gathered data. The overall count, frequency, and percentages of the results are presented. Results are expressed as total count, frequency, and percentages.

3. RESULTS

Table 3.1a: Characteristics of patients of the study

Characteristics	Patient No. (%)			
	GP isolates (n = 24)		GN isolates (n = 138)	
	Inappropriate therapy (n=1)	Appropriate therapy (n=23)	Inappropriate therapy (n=22)	Appropriate therapy (n=116)

Gender				
Male	1 (4.1)	11 (45.8)	10 (7.2)	70 (50.7)
Female	-	12 (50)	12 (8.6)	46 (33.3)
Age (Years)				
15-30	-	3 (12.5)	3 (2.1)	12 (8.69)
30-45	-	5 (20.83)	-	16 (11.59)
45-60	-	8 (33.3)	4 (2.89)	40 (28.98)
60-75	1 (4.1)	6 (25)	10 (7.24)	39 (28.26)
75-90	-	1 (4.1)	5 (3.62)	8 (5.79)
90-105	-	-	-	1 (0.72)
Duration of hospitalization				
1 to 5	1 (4.1)	19 (79.1)	11 (7.97)	76 (55.07)
5 to 10	-	3 (12.5)	10 (7.24)	24 (17.39)
10 to 15	-	-	1 (0.72)	9 (6.52)
15 to 20	-	-	-	7 (5.07)
20 to 25	-	1 (4.16)	-	-
Antibiotics received during hospitalization				
One antibiotics	-	4 (16.66)	4 (2.89)	9 (6.52)
Two antibiotics	1 (4.1)	11 (45.83)	9 (6.52)	37 (26.81)
Three antibiotics	-	5 (20.83)	4 (2.89)	31 (22.46)
Four antibiotics	-	1 (4.16)	2 (1.44)	19 (13.76)
Five antibiotics	-	1 (4.16)	2 (1.44)	12 (8.69)
Six antibiotics	-	-	-	3 (2.17)
Seven antibiotics	-	-	-	3 (2.17)
Eight antibiotics	-	1 (4.16)	-	3 (2.17)

Table 3.1a shows demographic characteristics of patients in which 2593 patients were admitted into the multispecialty tertiary care hospital for six months from October 2022 to March 2023 and received antimicrobial agents met study eligibility criteria, a total of 162 patient antimicrobial susceptibility reports were collected from laboratory. Overall, 85.18% of patients had positive results for Gram-negative bacteria, 14.81% had positive results for Gram-positive bacteria. Overall, mean (SD) age of the patients in the total sample was 55 ± 28 years; 56.79% were male and the remaining was female. Besides this, in-hospital mortality rate was 0.3%. The duration of hospitalization of the 162 patients was recorded. One hundred and seven patients (66%) were hospitalized for a period ranging from 1-5 days.

Monotherapy was given in 17 (10.5%) patients; 120 (74.07%) patients received 2-4 antibiotics and 25 (15.43%) patients received more than five antibiotics during their stay in the hospital.

Table 3.1b: Characteristics of patients of the study

Characteristics	Patient No. (%)			
	GP isolates (n=24)		GN isolates (N=138)	
	Inappropriate therapy (n=1)	Appropriate therapy (n=23)	Inappropriate therapy (n=22)	Appropriate therapy (n=116)
Departments				
General Medicine	-	13 (54.16)	16 (11.59)	65 (47.1)
Pulmonology	1 (4.16)	6 (25)	3 (2.17)	13 (9.4)
General Surgery	-	2 (8.33)	-	11 (7.9)
Nephrology	-	1 (4.16)	2 (1.44)	8 (5.7)
Cardiology	-	-	-	6 (4.3)
Urology	-	-	1 (0.72)	4 (2.8)
Neurosurgery	-	-	-	3 (2.1)
Neurology	-	1 (4.1)	-	2 (1.4)
Orthopedics	-	-	-	3 (2.1)
Plastic Surgery	-	-	-	1 (0.7)
Specimen type				
Urine	-	10 (41.66)	11 (7.97)	44 (31.88)
Blood	-	3 (12.5)	2 (1.44)	25 (18.11)
Sputum	-	6 (25)	3 (2.17)	14 (10.14)
Pus	-	1 (4.16)	3 (2.17)	12 (8.69)
Endotrachial secretion	-	-	3 (2.17)	8 (5.79)
Bronchial wash	1 (4.1)	3 (12.5)	-	3 (2.17)
Stool	-	-	-	7 (5.07)
Tissue	-	-	-	2 (1.44)
Pleural fluid	-	-	-	1 (0.72)

Table 3.1b reveals the clinical characteristics of patients who were admitted into the general medicine 94 (58.02%), pulmonology 23 (14.1%), general surgery 13 (8.02%), nephrology 11 (6.79%), cardiology 6 (3.70) and other departments 15 (9.25). Bacteria were mainly isolated from urine (65 isolates, 40.1%), blood (30 isolates, 18.5%), sputum (23 isolates, 14.1%), pus (16 isolates, 9.8%), endotracheal secretion (11 isolates, 6.7%), bronchial wash (7 isolate, 4.3%), stool (7 isolates, 4.3%), tissue (2 isolates, 1.2%), pleural fluid (1 isolate, 0.6%).

Table 3.1c: Characteristics of patients of the study

Characteristics	Patient No. (%)			
	GP isolates (n=24)		GN isolates (N=138)	
	Inappropriate therapy (n=1)	Appropriate therapy (n=23)	Inappropriate therapy (n=22)	Appropriate therapy (n=116)
Co-morbidities				
DM	-	5	10	57
Hypertension	1	11	14	73
Hypotension	-	1	-	-
Hypothyroidism	-	3	1	10
Parkinsonism disease	-	-	-	2
Rheumatoid arthritis	-	-	-	1
CKD	-	3	3	8
CAD	-	-	1	12
Axonal motor sensory neuropathy	-	-	-	1
Asthma	1	3	-	3
CHF	-	-	-	1
Renal caliculi	-	-	-	2
Seizures	-	-	2	2
Vertebroplasty	-	-	-	1
Multiple myeloma	-	-	-	2
COPD	-	-	-	2
Hip fracture	-	-	-	1
Alcoholic	-	-	-	5
Smoker	-	-	-	1
No co-morbidities	-	7	4	27

Table 3.1c highlights that diabetes mellitus (n=73), hypertension (n=99), hypothyroidism (n=15) were the most common co-morbidities in this study.

Figure 3.1: Number of patients infected with pathogens and proportions of appropriate empirical antimicrobial therapy by pathogen.

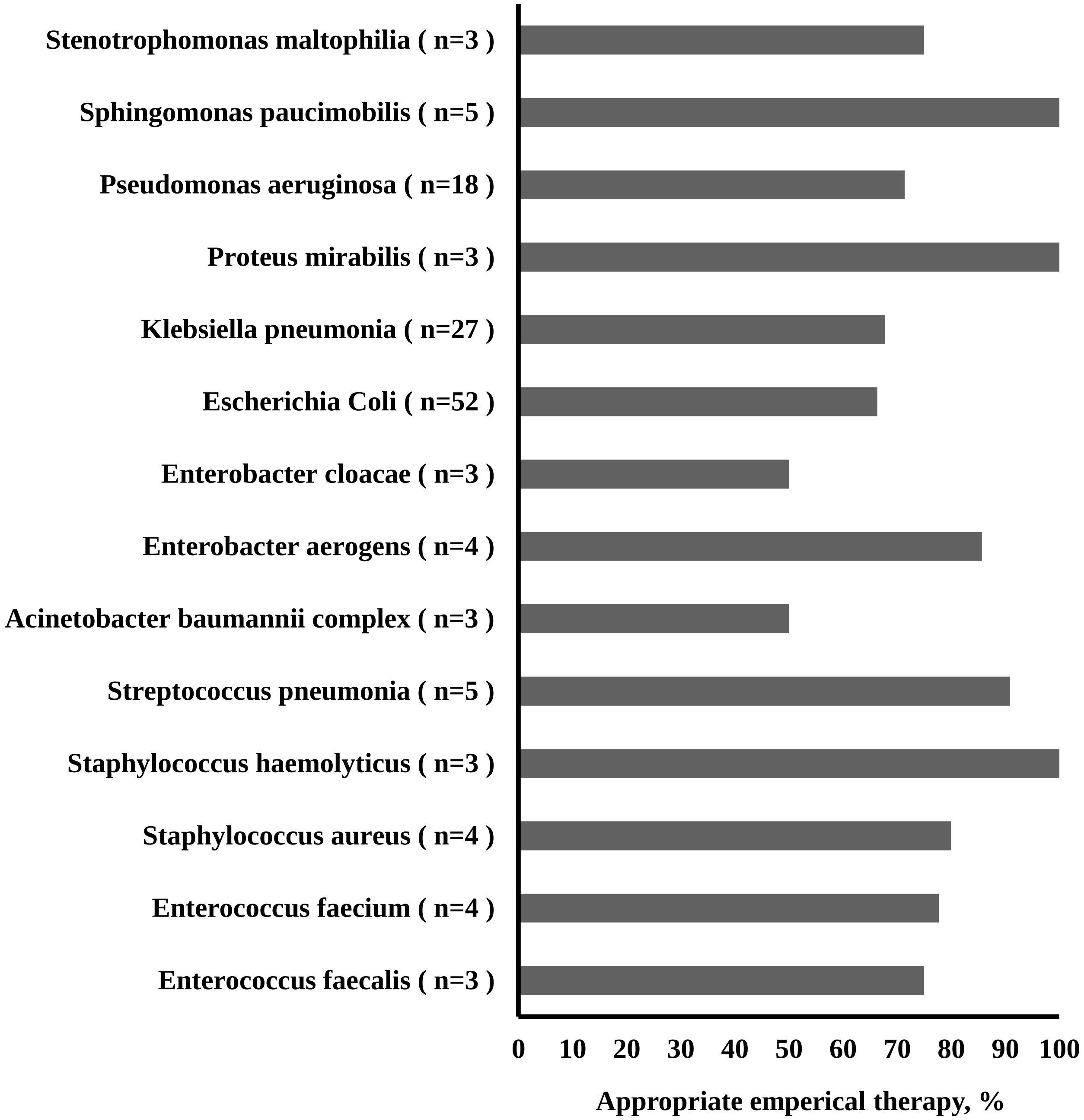

Figure 3.1 reveals the distribution of pathogens in patients, among 138 Gram-negative bacteria, E.coli (n=52) was the most common pathogen, followed by Klebsiella pneumonia (n=27), Pseudomonas aeruginosa (n=18), Sphingomonas paucimobilis (n=5). Other organisms were less frequently represented.

Table 3.1a reveals the proportions of appropriate empirical therapy use were 84.05% for Gram-negative bacteria, 95.83% for Gram-positive bacteria (Table 6.1a). The proportions of appropriate empirical antimicrobial therapy varied by pathogen, ranging from 50% for patients infected with Acinectobacter to 100% Sphingomonas paucimobilis. Acinetobacter species and Enterobacter cloacae had the lowest proportion of appropriate empirical therapy (50%) among gram-negative bacteria.

Figure 3.2: Frequency of bacterial isolates studied for antimicrobial sensitivity

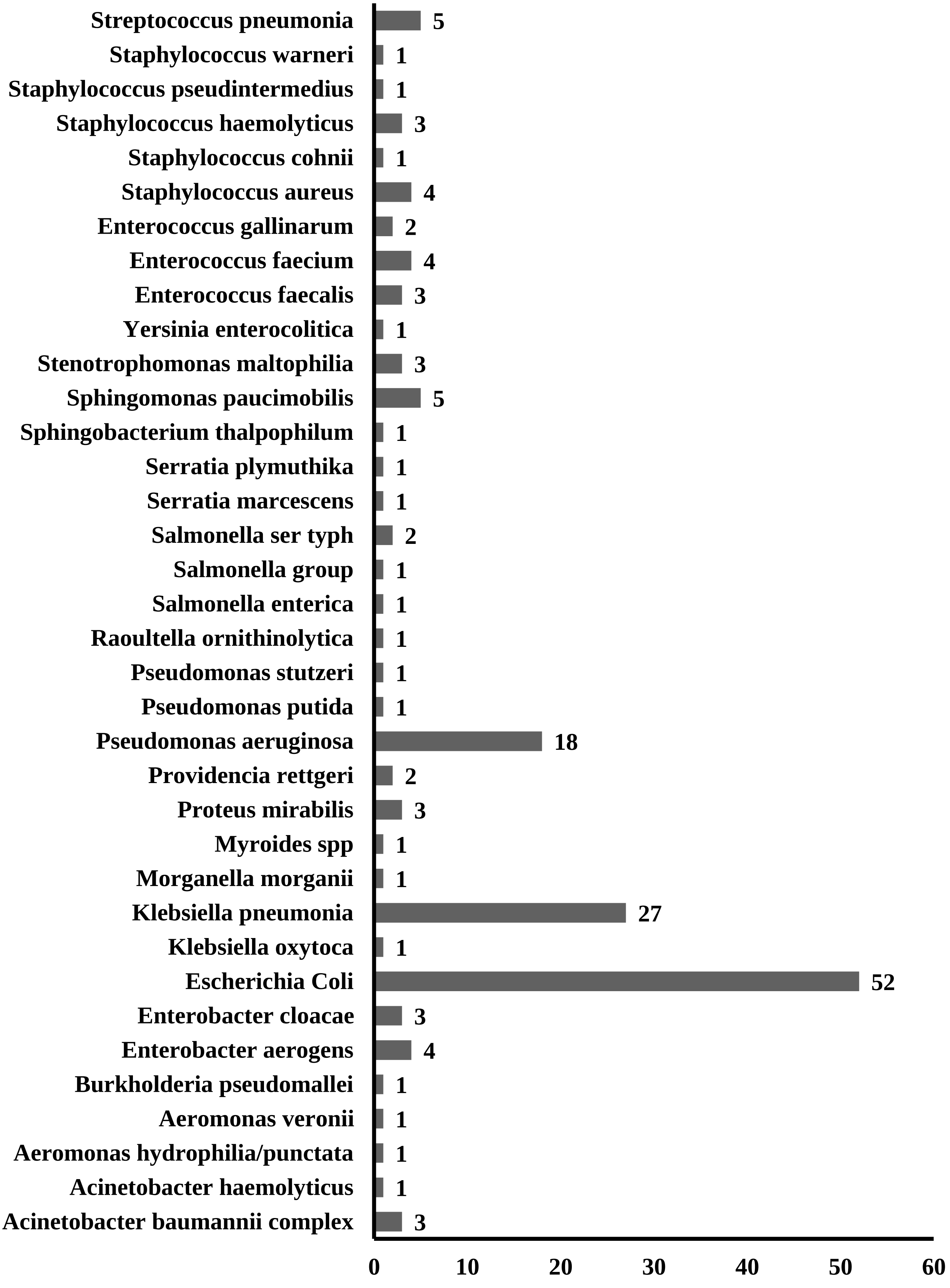

Figure 3.2 illustrates that a total of 36 organisms were isolated. The predominant organisms isolated were E. coli (n=52), Klebsiella pneumonia (n=27), Pseudomonas aeruginosa (n=18), Streptococcus pneumonia (n=5), Sphingomonas paucimobilis (n=5).

Table 3.2: Appropriate and inappropriate antibiotics used in empirical therapy based on antimicrobial sensitivity reports (n = 334)

Antibiotic	Inappropriate, n (%)	Appropriate, n (%)
Amikacin	5 (62.5)	3 (37.5)
Amoxicillin/clavulanic acid	-	3 (100)
Cefepime	2 (40)	3 (60)
Cefoperazone/sulbactum	18 (52.9)	16 (47)
Ceftazidime	2 (33.3)	4 (66.6)
Ceftazide/avibactum	-	1 (100)
Ceftriaxone	11 (31.4)	24 (68.5)
Ciprofloxacin	-	1 (100)
Clindamycin	3 (100)	-
Colistin	-	3 (100)
Doxycycline	6 (16.6)	30 (83.3)
Fosfomycin	-	4 (100)
Levofloxacin	6 (21.4)	22 (78.5)
Linezolid	3 (20)	12 (80)
Meropenem	4 (5.6)	67 (94.3)
Metronidazole	13 (44.8)	16 (55.1)
Minocycline	-	1 (100)
Piperacillin/tazobactum	6 (30)	14 (70)
Polymyxin-B	1 (100)	-
Teicoplanin	-	2 (100)
Tetracycline	1 (100)	
Tigecycline	-	3 (100)
Tobramycin	1 (100)	-
Vancomycin	1 (25)	3 (75)
Azithromycin	-	6 (100)
Ornidazole	2 (20)	8 (80)
Oflaxacin	1 (16.6)	5 (83.3)
Cefpodoxime	1 (50)	1 (50)
Rifaximin	2 (100)	

Clarithromycin	1 (100)	

Table 3.2 reveals a total of 706 antibiotics were prescribed out of which 334 are prescribed before AST and 372 are prescribed after AST. The total number of encounters prescribed with at least one antibiotic was 17 (10.5%); 120 (74.07%) patients received 2-4 antibiotics and 25 (15.43%) patients received more than five antibiotics during their stay in the hospital Table 3.1a). By generic name, none of the drugs was prescribed. Meropenem (67, 94.3%), doxycycline (30, 83.3%), linezolid (12, 80%), levofloxacin (22, 78.5%) and ceftriaxone (24, 78.5%) were most commonly prescribed appropriate antibiotics in the initial empirical therapy.

Table 3.3: Antibiotics given before antimicrobial sensitivity reports in the study (n = 334)

Antibiotic category	Number and percent of antibiotic used (n, %)	Number of specific antibiotic used (n, %)	Listing in EML (Yes/No)
Access	86, 25.75	Amikacin (8, 9.3) Amoxicillin/clavulanic acid (3, 3.4) Clindamycin (3, 3.4) Doxycycline (36, 41.8) Metronidazole (29, 33.7) Tetracycline (1, 1.1) Ornidazole (6, 6.9)	Yes Yes Yes Yes Yes No No
Watch	186, 55.69	Cefepime (5, 2.6) Ceftazidime (6, 3.2) Ceftriaxone (35, 18.8) Ciprofloxacin (1, 0.5) Levofloxacin (28, 15.0)- Meropenem (71, 38.1) Pipercillin/tazobactam (20, 10.7) Teicoplanin (2, 1.07) Tobramycin (1, 0.5) Vancomycin (4, 2.1) Azithromycin (6, 3.2) Ofloxacin (2, 1.07) Cefpodoxime (2, 1.07) Rifaximin (2, 1.07) Clarithromycin (1, 0.5)	No Yes Yes Yes No Yes Yes No No Yes Yes No No No Yes
Reserve	28, 8.38	Ceftazidime/avibactam (1, 3.5) Colistin (3, 10.7) Fosfomycin (4, 14.2) Linezolid (15, 53.5) Minocycline (1, 3.5)	Yes Yes Yes Yes No

		Polymyxin-b (1, 3.5) Tigecycline (3, 10.7)	Yes No
Not recommended	34, 10.18	Cefaperazone/Sulbactam (34, 100)	No

Table 3.3 reveals that a total of 334 antibiotics were given before AST report were evaluated to classify into 'Access', 'Watch', 'Reserve (AWaRe), and 'Not Recommended' antibiotics categories. Among 334, 25.75% antibiotics (86) were from the 'Access' category. Notably, 55.69% of the total antibiotics (186 out of 334) were from the 'Watch' category. Antibiotics prescribed from the 'Reserve' group were 8.38% (28). On the other hand, 34 antibiotics (10.18%) were from 'Not Recommended' category. A total of 30 specific antibiotics were frequently prescribed in 162 AST reports and such prescriptions accounted for 334 antibiotics that were examined according to the AWaRe categories and for their listing in the 2021 WHO-EML. Of 30 specific antibiotics, 29 were AWaRe category antibiotics, and the remaining 1 (Cefaperazone/sulbactam) belongs to 'not recommended' category. Among the seven 'Access' antibiotics, 5 are listed in the EML. The five most commonly prescribed 'Access' antibiotics were doxycycline (36, 41.8 %), metronidazole (29, 33.7%), amikacin (8, 9.3%), ornidazole (6, 6.9%), amoxicillin/clavulanic acid and clindamycin each of (3, 3.4%). Among the 15 frequently prescribed 'Watch' category, antibiotics, 8 are listed in the EML. The four most commonly prescribed 'Watch' antibiotics were meropenem (71, 38.1%), ceftriaxone (35, 18.8%), levofloxacin (28, 15.0%), and pipercillin/tazobactum (20, 10.7%). Among the 7 Reserve group antibiotics, 5 are listed in the EML. The most commonly prescribed 'Reserve' antibiotic was linezolid (15, 53.5%).

Table 3.4: Antibiotics given after antimicrobial sensitivity reports in the study (n = 372)

Antibiotic category	Number and percent of antibiotic used (n, %)	Number of specific antibiotic used (n, %)	Listing in EML (Yes/No)
Access	92, 24.72	Amikacin (13, 14.13) Amoxicillin/clavulanic acid (6, 6.52) Doxycycline (41, 44.56) Gentamicin (1, 1.08) Metronidazole (23, 25) Nitrofurantoin (1, 1.08) Trimethoprim/sulfamethoxazole (3, 3.26) Ornidazole (4, 4.34)	Yes Yes Yes Yes Yes Yes Yes No
Watch	179, 48.11	Cefepime (4, 2.23) Ceftazidime (5, 2.79) Ceftriaxone (24, 13.40) Cefuroxime (1, 0.55) Ciprofloxacin (2, 1.11) Levofloxacin (26, 14.52) Meropenem (76, 42.45) Piperacillin/tazobactam (22, 12.29)	No Yes Yes Yes Yes No Yes Yes

		Teicoplanin (4, 2.23) Vancomycin (3, 1.67) Azithromycin (5, 2.79) Ofloxacin (2, 1.11) Cefixime (2, 1.11) Clarithromycin (1, 0.55) Cefpodoxime (1, 0.55) Moxifloxacin (1, 0.55)	No Yes Yes No Yes Yes No No
Reserve	74, 19.89	Ceftazidime/Avibactam (4, 5.40) Colistin (14, 18.91) Fosfomycin (20, 27.02) Linezolid (19, 25.67) Minocycline (4, 5.40) Polymyxin-b (4, 5.40) Tigecycline (9, 12.16)	Yes Yes Yes Yes No Yes No
Not recommended	27, 7.25	Cefaperazone/Sulbactam (27, 100)	No

Table 3.4 reveals that a total of 372 antibiotics were given after AST reports were evaluated to classify into ‘Access’, ‘Watch’, ‘Reserve (AWaRe), and ‘Not Recommended’ antibiotics categories. Among 372, 24.72% of antibiotics (92) were from the ‘Access’ category. Notably, 48.11% of the total antibiotics (179 out of 372) were from the ‘Watch’ category. Antibiotics prescribed from the ‘Reserve’ group were 19.89% (74). On the other hand, 27 antibiotics (7.25%) were from ‘Not Recommended’ category. A total of 32 specific antibiotics were frequently prescribed in 162 AST reports and such prescriptions accounted for 372 antibiotics that were examined according to the AWaRe categories and for their listing in the 2021 WHO-EML. Of 32 specific antibiotics, 31 were AWaRe category antibiotics, and the remaining 1 (Cefaperazone/sulbactam) belongs to ‘not recommended’ category. Out of 8 ‘Access’ category antibiotics, seven are listed in the EML. The five most commonly prescribed ‘Access’ antibiotics were doxycycline (41, 44.56%), metronidazole (23, 25%), amikacin (13, 14.13%), amoxicillin/clavulanic acid (6, 652%), ornidazole (4, 4.34%). Among the 16 ‘Watch’ category antibiotics, of which 10 are listed in the EML. The four most commonly prescribed ‘Watch’ antibiotics were meropenem (76, 42.45%), levofloxacin (26, 14.52%), ceftriaxone (24, 13.40%) and pipercillin/tazobactum (22, 12.29%). Among the 7 ‘Reserve’ category antibiotics, 5 are listed in the EML. The two most commonly prescribed ‘Reserve’ antibiotics were fosfomycin (20, 27.02%) and linezolid (19, 25.67%). Out of 32 antibiotics prescribed, 1 was from ‘Not Recommended’ category and is not listed in the EML.

4. DISCUSSION

In this study, a total of 162 susceptibility reports were collected from 2593 patients enrolled based on the inclusion and exclusion criteria for six months. Among these, the total number of antibiotics prescribed was 706 out of which 334 were prescribed before AST and 372 were prescribed after AST. The total number of encounters prescribed with at least one antibiotic was 17 (10.5%); 120 (74.07%) patients received 2-4 antibiotics. Majority of patients did not have hospital-acquired infections. We found that the proportion of appropriate empirical therapy was generally high (84.05% for Gram-negative bacteria, 95.83% for Gram-positive bacteria). Results were similar to previous studies (Ohnuma et al., 2023) [21]. The mean (SD) age of the patients in the total sample was 55 ± 28 years; which correlates with the previous study conducted by Patel et al., 2017 [23]. Our results are parallel to previous studies which revealed that the male (56.79%) preponderance was more than female (**N**ikki et al., 2019**,** Chowdary et al., 2020) [17, 24]. In the current study antimicrobials were mostly preferred by brand names which was similar to a previous study (Khade et al., 2013) [25] and in contrast to the present study (Das et al 2017) [26].

Discordant empirical antibiotic therapy was associated with antibiotic resistance among pathogens **(**Kadri et al., 2021) [27]**.** In our study majority of patients were hospitalized for a time between 1-5 days was 107 (66%) and patients receiving systemic antibiotics were significantly higher compared to patients not receiving antibiotics (Luo et al., 2023) [6]. It is preferable to keep the number of drugs per prescription as low as to minimize the risk of drug interactions, development of bacterial resistance, and hospital costs. We have not looked at the co-prescribed drugs here, but concentrated only on antibiotics. In our study, three or more antibiotics were prescribed to patients in whom the antibiotics were changed either after reviewing the culture and sensitivity results or due to a lack of improvement in the clinical condition. Three or more antibiotics were started together in seriously ill patients and were prescribed to patients due to the possibility of mixed and suspected infections (Bajpai et al., 2018) [15]. In our study, most of the patients visited General Medicine and were hospitalized and AST was done. This might be due to a high incidence of community-acquired infections or pre-existing chronic illness (Qodrati et al., 2022) [28].

Our samples collected for AST were mostly from urine and blood which directly correlates to the prevalence of UTI and systemic infections reported in hospitalized patients (Vu et al., 2021) [29]. Our findings are in concordance with previous studies in which the most commonly observed co-morbid conditions were diabetes mellitus followed by hypertension which is significant to their prevalence and associated risk (Hermans et al., 2018, Mata-Cases et al., 2019) [30, 31]. All the patients received parenteral antibiotics during the early days of hospitalization and were changed to a systemic route upon recovery and patient compliance. Antibiotics were switched either because the clinical state did not improve or after the culture and sensitivity data were reviewed. In our study, the most commonly identified bacteria isolates were Gram-negative (138/162) reflects the prevalence of infections and resistsance patterns which were similar to previous studies (Masyeni et al., 2018, Al-Naqshbandi et al., 2019) [32, 33]. Most frequently identified Gram-negative organisms were *E. coli* (52) followed by *Klebsiella* spp (27) and *Pseudomonas aeruginosa* (18/162). Most frequently identified Gram-positive organisms were *Streptococcus pneunonia* (5) followed by *Staph. aureus* (4), and *Enterococcus fecium* (4). The results were similar to previous reports where several microorganisms showed optimal sensitivity and resistance to empirical antibiotics (Mao et al., 2019; Chowdary et al., 2020) [34, 24]. This study highlights the fact that almost all of the patients (47.3%) initially receive antibiotics empirically which is similar to the previous study (Bajpai et al., 2018) [15].

To identify the causal organisms and the drugs to which these microorganisms are susceptible, antimicrobial usage in this study was often empirical, lacking laboratory data and antimicrobial sensitivity testing. These results are consistent with prior studies. Given the rise of AMR, care should be exercised while prescribing empirical antibiotics. The study hospital does not follow any national or local antimicrobial recommendations. Prescriptions for empirical antibiotics must be decreased, and local antimicrobial use guidelines must be developed immediately (Nnadozie et al., 2020) [35]. We found that most commonly prescribed antibiotics in the study population both before and after AST results were received for suspected bacterial infections during the entire study period were Meropenem (67, 94.3%), doxycycline (30, 83.3%), linezolid (12, 80%), levofloxacin (22, 78.5%) and ceftriaxone (24, 78.5%) (Chowdary et al., 2020) [24].

The WHO has developed AWaRe metrics to rationalize antibiotic use and minimize the development of antimicrobial resistance (WHO, 2021) [18]. Therefore the prescription pattern of antibiotics has been evaluated systemically using WHO AWaRe classification. In this study, there was high usage of 'Watch' category antibiotics prescribed over 'Access' category. The results have revealed that most commonly used antibiotics are meropenem (67, 94.3%), doxycycline (30, 83.3%), linezolid (12, 80%), levofloxacin (22, 78.5%), and ceftriaxone (24, 78.5%). It is observed that there are vast differences in the prescription of 'Access', 'Watch', and 'Reserve' antibiotics. It is obvious to use certain antibiotics which are not listed and/or 'not recommended' category antibiotics to reduce the severity of infection and to reduce complications. In the present study, the majority of antibiotics used were from 'Watch' category (55.68%) followed by 'Access' category (25.75%), 'Reserve' category (8.38%), and 10.17% from 'not-recommended' category. On the other hand, the use of 'Access' antibiotics including the first-generation cephalosporins was low when compared to the WHO-recommended target of 60%. In a recent study reported that the proportion of 'Watch' group antibiotics was high (Kairi et al., 2020) [36]. The results demonstrated that there is a high need for rationalising in avoiding 'Reserve' and discouraged antibiotics for empirical use in hospitalized patients. More importantly, enough focus must be given in selecting and prescribing antibiotics emphasizing that the use of antibiotics belongs to 'Access' over 'Watch' category.

The recent introduction of the WHO Access, Watch, and Reserve (AWaRe) categories has offered a framework for systematic assessment of antibiotic use and consumption, with a focus on decreasing unnecessary and irrational use of 'Watch' and 'Reserve' antibiotics. In brief, the 'Access' antibiotics are the first and second choices for the empirical treatment. The 'Watch' antibiotics are associated with toxicity concerns and/or resistance potential and are recommended only for specific indications. The 'Reserve' category includes antibiotics of last resort for multidrug-resistant infections (www.who.int) [37]. Accumulating data indicates that there is a considerable global and national variation in the proportion of 'AWaRe' antibiotics used in hospitalized pediatric and adult patients. A recent study reported differences in antibiotic prescribing for the most common surgeries between surgery departments of a teaching and a non-teaching tertiary care hospital (Machowska et al., 2019, Skender et al., 2021) [38, 4]. There is significant variation between departments in industrialized nations, with the surgical department prescribing antibiotics more frequently and for a greater duration of time. This is linked to dosage escalation and frequent non-compliance with local regulations (Sartelli et al., 2020) [39]. The prevalent undesirable state of frequent prescription and availability of 'Watch' over 'Access' antibiotics should be improved by focusing on promoting awareness, changes in prescribing practice, and stringent implementation of national and/or hospital antibiotic policies to restrict their overuse.

According to a recent study, prescription habits are influenced by healthcare workers' knowledge and instruction regarding AMR and antibiotic prescribing (Trikha et al., 2020) [40]. Emerging evidence indicates that adhering to antibiotic policies and guidelines is associated with favorable therapeutic and in-patient outcomes in terms of mortality and duration of hospital stay (Wathne et al.,2019) [41]. It is highly recommended that as part of the WHO National Action Plan, regional and national guidelines can apply this 'AWaRe' categorization in their antibiotic surveillance framework. Furthermore, increasing the use of 'Access' antibiotics while limiting the use of 'Watch' and 'Reserve' antibiotics at the same time is the highest priority for preserving the effectiveness of important antibiotics and minimizing the danger of AMR.

5. LIMITATIONS

The choice and administration of antibiotics by patients who visited the hospital throughout the six-month study period were thoroughly assessed in the current investigation. However, the current study has certain shortcomings. First, determining the quality of diagnosis and evaluating antibiotic choice was outside the scope of this study. Second, the study includes only in-patient data. Third, the small sample size as the study evaluated patient medication data and diagnostic reports generated only during the short period. Fourth, because the research was limited to only one hospital in one city, the results could not be generalized.

6. CONCLUSION

Quickening the availability of culture and sensitivity reports will enable the selection of definitive antibiotic therapy based on susceptibility of bacteria, improve success rate of treatment, patient early recovery, and identify resistant pathogens. Our investigation revealed a concerning trend in the excessive usage of empirical antibiotics, particularly those in the 'Watch' group. The study once again emphasizes the need to re-formulate local guidelines of antimicrobial use based on regional antibiotic susceptibility patterns and using national treatment guidelines as reference only. By carrying out such research and routinely analyzing such data, it would be possible to encourage the responsible use of antibiotics and prevent the spread of bacterial strains that are resistant to them.

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