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REVIVAL OF LOST TREASURES: AN ANALYSIS OF INFREQUENTLY PRESCRIBED ANTIBIOTICS WITH THEIR EMERGING SENSITIVITY PATTERNS

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ABSTRACT

Antibiotic resistance is the alteration in bacteria to resist antibiotics that used to inhibit their growth or kill them. It's one of the leading causes of global mortality. Reduction in antibiotic resistance is observed in bacteria in an antibiotic free environment through mechanisms like phenotypic reversion (1). It requires around $1 billion and 10-15 years to develop an antibiotic, whereas reusing older antibiotics would cost significantly lesser. Thus, this study was done to find the relationship between infrequently prescribed antibiotics in Inpatient Departments (IPD) of a tertiary care hospital & their corresponding antibiotic sensitivity status. This was an observational, retrospective and cross-sectional study. For February 2021, antibiotic data was obtained from IPD prescription records and antibiotic sensitivity results were collected from Antibiotic Sensitivity Testing (AST) method via Kirby Bauer Disc Diffusion records in Microbiology department. The proportions of antibiotics prescribed in IPDs and AST results of antibiotics as per bacterial isolates such as Gram negative bacilli (GNB), Gram positive cocci (GPC) and Non-fermenters (NF) were expressed as percentages. Cumulative frequency cube root method was used to set cut-off frequency for infrequently and **most** prescribed, sensitive and resistant antibiotics. These antibiotics were tabulated along with their sensitivity patterns to compare them. A p value < 0.05 was considered as statistically significant. The

study collected data from 194 IPD prescriptions and 196 patient samples. The most frequently prescribed antibiotic was ceftriaxone and least prescribed ones included chloramphenicol, nitrofurantoin, doxycycline and levofloxacin [each - 1[0.4%]). Commonly resistant antibiotics against GPC were norfloxacin (59[93.7%]), co-trimoxazole (48[76.2%]) and ampicillin (50[70.4%]) and against GNB were ampicillin (90[90%]) and ceftazidime (4[75%]). Least prescribed antibiotics with the least resistance included polymixin B & imipenem (GNB & NF), chloramphenicol (GNB) and nitrofurantoin & gentamicin (GPC & GNB). Infrequently prescribed antibiotics also had reduced resistance like nitrofurantoin (GPC & GNB) and chloramphenicol (GNB). Few most prescribed antibiotics were found to be frequently resistant as cephalosporins like ceftriaxone (GNB) and extended spectrum penicillins like piperacillin-tazobactum (NF). Amidst the evolving antibiotic sensitivity trends, this knowledge is vital for effective treatment of bacterial infections and appropriate implementation of antibiotic stewardship programs.

KEYWORDS: Antibiotic sensitivity pattern, infrequently prescribed antibiotics, IPD prescription, prescription pattern, changing antibiotic sensitivity, Indian antibiotic prescriptions

INTRODUCTION

The phenomenon of change in bacteria to resist antibiotics that used to effectively inhibit their growth or kill them is known as antibiotic resistance (2). The average global antibiotic usage increased by 46% between 2000 & 2018. A prominent rise of 48% increased antibiotic usage was observed in India (3). Today, antibiotic resistance is a growing worldwide dilemma with hazardous effects on human health.

In 2019, antimicrobial resistant infections lead to 4.95 million deaths globally and it is greater than deaths caused by HIV or malaria(4). It is one of the common causes of death worldwide and is estimated to push 24 million more people into extreme poverty in the next decade (5). Around 58,000 neonatal deaths occur each year due to sepsis resulting from first-line antibiotic resistance (6).India accounts for one fourth of the worldwide multi-drug resistant tuberculosis (MDR TB) burden. In 11.4% and 2.5 % of presumptive MDR TB cases, isoniazid mono-resistance & rifampicin mono-resistance was found respectively (7).

During 2008 to 2013, third-generation cephalosporin & fluoroquinolone resistance for E.coli had an increment of 70% to 83% & 78% to 85%, respectively in India. These drugs constitute one of the most commonly prescribed antibiotics in a hospital (8). Moreover, resistance to even newer reserve antibiotics like carbapenems has been found in India with emergence of drug resistance enzymes like New Delhi Metallo Beta-Lactamase (9).

Meanwhile, decrease in resistance was found to older antibiotics like ampicillin and co-trimoxazole in 2014 (10). Presently, these are infrequently prescribed antibiotics and it was demonstrated in a recent study that in an environment free of antibiotics, there is a reduction in bacterial drug resistance. This reduction can vary for each antibiotic, and therefore, is antibiotic specific. While maintaining the original resistance mutations, a bacteria can acquire other mutations through phenotypic reversion to regain its antibiotic sensitive state. This phenomenon has been shown in ampicillin, chloramphenicol, trimethoprim, ciprofloxacin, nalidixic acid and tetracycline (11).

Antibiotic resistance is growing at a much faster rate than development of new antibiotics. It takes around $1 billion and 10-15 years to develop an antibiotic while manufacturing and reusing older antibiotics would cost much lesser (12,13). Therefore, this study aimed to explore the relationship between infrequently used antibiotics prescribed in a tertiary care hospital's Inpatient Departments & their corresponding sensitivity proportion known thorough Antibiotic sensitivity testing [AST]. In addition, it compared the proportions of antibiotic prescribed and the proportions of antibiotics found to be sensitive against different bacteria in a tertiary care hospital in India.

OBJECTIVES

Primary objective:

- To find the relationship between infrequently prescribed Antibiotics in Inpatient Departments of a tertiary care hospital & their corresponding Antibiotic sensitivity status

Secondary objective:

- To find the pattern of antibiotic prescribed in Inpatient Departments of a tertiary care hospital
- To find the pattern of antibiotics found sensitive against different bacteria through Antibiotic Sensitivity Testing in a tertiary care hospital
- To compare the antibiotics most prescribed and the antibiotics most sensitive against bacteria

MATERIAL & METHODS

The present study was an observational, retrospective and cross-sectional study conducted in the Case Record Office attached to a tertiary care hospital, Department of Pharmacology and Department of Microbiology of a Government Medical College in North India.

Prior approval from Institutional Ethics Committee was obtained (Approval number - GMC/IEC/22/GKR/62, dated – 19-03-2022). All procedures followed were in accordance with the ethical standards of the Institutional Ethics Committee on human experimentation and with the revised Helsinki Declaration. Informed consent was not taken since it is a retrospective observational study.

DATA COLLECTION & STATISTICAL ANALYSIS:

The data about antibiotics prescribed in Inpatient Department's was collected from the available Inpatient Department (IPD) records of all clinical departments, like Surgery, Orthopaedics, Paediatrics, Medicine, Obstetrics & Gynaecology, Dermatology and Psychiatry that were submitted in the Case Record Office during February 2021. Each IPD record included the complete prescription file of the patient with his treatment details. No specific randomization method was utilized to obtain the records, but they were obtained as per the records provided by the CRO personnel. The IPD records with incomplete or illegible details were excluded from the study.

The reason for choosing February 2021 was the large amount of Covid-19 cases before and after February 2021 which may have confounded our results due to repeating patterns of Covid-19 treatment instead of a broader range of treatment observed during non-pandemic situations(14).

The data about antibiotic sensitivity results was collected from the available Antibiotic Sensitivity Testing (AST) records in Department of Microbiology during February 2021. The AST was done using Kirby Bauer Disc Diffusion Method. The cutoff diameters for the zones of inhibition to categorize into Sensitive [S], Intermediate [I] & Resistant [R] strains were as per Clinical and Laboratory Standards Institute [CLSI 2021] guidelines.(15)

The antibiotics prescribed in Inpatient Department's and AST levels as per various bacterial isolates like Gram negative bacilli (GNB), Gram positive cocci (GPC) and Non-fermenters (NF) were expressed as percentages. Cumulative frequency cube root method was used to set a cutoff frequency for infrequently prescribed, most prescribed and most sensitive antibiotics. The percentage of each category was calculated as per:

$$\text{Sensitivity [\%]} = \frac{\text{Number of times Antibiotic found S/I/R from the samples}}{\text{Total number of times Antibiotic tested in the samples}} \times 100$$

Infrequently prescribed, most prescribed and most sensitive antibiotics were tabulated along with their sensitivity patterns to compare and provide a comprehensive summary of the pattern of prescribed antibiotics and the antibiotic sensitivity patterns in a tertiary care hospital. A p value of less than 0.05 was considered as statistically significant.

RESULTS

In this study, data was obtained from 194 IPD prescriptions and 196 patient AST results.

Among the 194 prescriptions, total 1677 drugs were prescribed, out of which maximum prescriptions had parenteral drugs - 1014 (60.4%), followed by oral drugs – 620 (36.9%). 622 (37.1%) generic drugs were prescribed and 164 (84.5%) prescriptions had polypharmacy, which included 73 (37.6%) prescriptions with hyperpolypharmacy. Majority of the prescriptions (170 [87.6%]) included antibiotics. Total 281 antibiotics were prescribed, out of which maximum antibiotics were parenteral (265[94.3%]), followed by oral (11 [3.9%]) and topical (5 [1.8%]). The prescription statistics are tabulated in (Table 1).

Cephalosporin class was the most frequently prescribed antibiotic class(126 [45.3%]). Nitrofuran, tetracycline, amphenicol, polymixin B and polypeptide class were least prescribed (1[0.4%]) (Fig. 1). Co-trimoxazole was not prescribed in any IPD prescription (0[0%]).

Among specific antibiotics, ceftriaxone was the most frequently prescribed antibiotics (86 [30.6%]), followed by cefoperazone (32[11.4%]). Many drugs belonged to the least prescribed category including chloramphenicol, nitrofurantoin, doxycycline, levofloxacin and penicillin G [All - 1[0.4%]). Table. 2 depicts and compares the most and least frequently prescribed antibiotics.

The patient samples, as noted from the microbiology laboratory findings, were obtained from various sources with the most common being urine (162 [82.6%]) and least common being cerebrospinal fluid (1[0.5%]) (Table 3).

Vancomycin and linezolid were the most sensitive antibiotics for gram positive cocci, while polymixin B was most sensitive for gram negative bacilli & non-fermenters. The most resistant antibiotics for gram negative bacilli & non-fermenters included ampicillin. Though, not in most resistant category, other commonly resistant antibiotics to gram positive cocci included co-trimoxazole (48[76.2%]) and ampicillin (50[70.4%]).

Table 4 demonstrates the most sensitive and most resistant antibiotics for all bacterial isolates.

None of the most prescribed antibiotics were in the most sensitive category for any bacterial group (Table 5).

The antibiotics from the least prescribed category that were also in the most sensitive category included nitrofurantoin (for gram positive cocci) & polymixin B (for gram negative bacilli & non-fermenters). Nitrofurantoin was prominently sensitive for gram positive cocci (38[86.4%]) & gram negative bacilli (39[75%]) and so was chloramphenicol for gram negative bacilli (10 [71.4%)]). Table 6 compares the least prescribed antibiotics with their respective sensitivity pattern.

The least prescribed antibiotics that also had the least resistance included polymixin B & imipenem (gram negative bacilli & non-fermenters) and chloramphenicol (gram negative bacilli), nitrofurantoin & gentamicin (gram positive cocci & gram negative bacilli) (Table 7).

TABLES

Table 1: Prescription Statistics

S.No.	Prescription Data	n (%)
A.	**Prescription Summary**	
1	Total Prescriptions [n]	194
2	Total Prescribed drugs [n]	1677
3	Total generic drugs [n / %]	622 (37.1%)
B.	**Routes of Administration**	
4	Total Oral drugs prescribed [n / %]	620 (36.9%)
5	Total Parenteral drugs prescribed [n / %] [IV/IM/SC/ID]	1014 (60.4%)
6	Total topical drugs [n / %]	11 (0.70%)
	Total inhalational drugs [n / %]	32 (1.9%)
C.	**Drug Count**	
7	Average number of drugs per prescription [Mean ± SD]	8.644±3.594
8	Prescriptions with Polypharmacy [n / %] [≥ 5 drugs](32)	164 (54.5%)
9	Prescriptions with Hyperpolypharmacy [n / %] [≥ 10 drugs] (15)	73 (37.6%)
D.	**Antibiotic Data**	
10	Prescriptions with Antibiotics	170 (87.6)
10	Total Antibiotics	281 (100)
11	Parenteral Antibiotics	265 (94.3)
12	Oral Antibiotics	11 (3.9)
13	Topical Antibiotics	5 (1.8)

Fig. 1: Prescribed Antibiotic Statistics

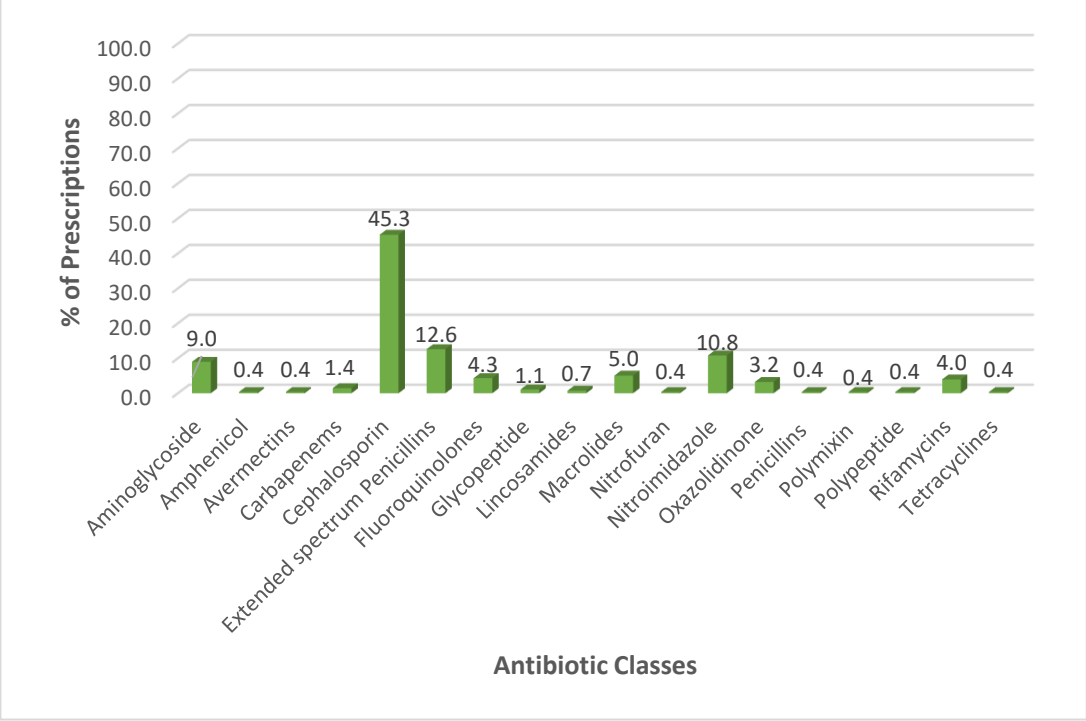

Table 2: Comparison of Most & Least Frequently Prescribed Antibiotics

S.No	**MOST PRESCIBED ANTIBIOTICS[a]**			**LEAST PRESCRIBED ANTIBIOTICS[b]**		
	Antibiotic	n (%)		Antibiotic	n (%)	
1.	Ceftriaxone	86 (30.6)		Bacitracin	1	(0.4%)
2.	Cefoperazone	32 (11.4)		Cefoperazone sulbactum	1	(0.4%)
3.	Metronidazole	29 (10.3)		Chloramphenicol	1	(0.4%)
4.	Amikacin	22 (7.8)		Doxycycline	1	(0.4%)
5.	Amoxyclav	18 (6.4)		Ethambutol	1	(0.4%)
6.	Piperacillin Tazobactum	15 (5.3)		Gentamicin	1	(0.4%)
7.				Imipenem	1	(0.4%)
8.				Isoniazid	1	(0.4%)
9.				Levofloxacin	1	(0.4%)
10.				Neomycin	1	(0.4%)
11.				Nitrofurantoin	1	(0.4%)
12				Ofloxacin ornidazole	1	(0.4%)
13.				Ornidazole	1	(0.4%)
14.				Penicillin G	1	(0.4%)
15.				Polymixin B	1	(0.4%)
16.				Pyrazinamide	1	(0.4%)
17.				Rifampicin	1 (0.4%)	

[*Cumulative Frequency Cube Root Method : Frequency – a: Most Prescribed – 15 to 86 & b: Least Prescribed – upto 1 Co-trimoxazole – not prescribed (0%)]

Table 3: Types of Patient Samples for AST Testing

SAMPLE	**n (%)**
URINE	162 [82.65%]
PUS	27 [13.78%]
SPUTUM	6 [3.06%]
CEREBROSPINAL FLUID	1 [0.51%]
TOTAL	196 (100%)

Table 4: Comparison of Most **Sensitive &** Most **Resistant Antibiotics**

S.No	**BACTERIAL GROUP**	MOST **SENSITIVE ANTIBIOTICS**[c]		**MOST RESISTANT ANTIBIOTICS**[d]	
		Antibiotic	**Sensitivity (%)**	**Antibiotic**	**Resistance (%)**
1.	GPC	Cefipime		Norfloxacin	93.7
		Vancomycin			
		Linezolid	100		
		Nitrofurantoin	86.4		
2.	GNB	Polymixin B	98.5	Ampicillin	90
		Imipenem	90.7		
3.	NF	Polymixin B	100	Ampicillin	
				Amoxyclav	
				Cefixime	
				Levofloxacin	100

[Cumulative Frequency Cube Root Method: Percentage – c: Most Sensitive – 75 to 100% & d: Most Resistant – 88.1 to 100%.
GPC – Gram Positive Cocci, GNB – Gram Negative Bacilli, NF – Non-fermenters]

Table 5: Comparison of Most **Prescribed &** Most **Sensitive Antibiotics**

S.No	**MOST PRESCRIBED ANTIBIOTICS**[a]		**MOST SENSITIVE ANTIBIOTICS**[c]					
			GPC		**GNB**		**NF**	
			Antibiotic	Sensitivity %	Antibiotic	Sensitivity %	Antibiotic	Sensitivity %
1.	Ceftriaxone		Vancomycin	100.0	Polymixin B	98.5	Polymixin B	100
2.	Cefoperazone		Cefipime	100	Imipenem	90.7		
3.	Metronidazole		Linezolid	100				
4.	Amikacin		Nitrofurantoin	86.4				
5.	Amoxyclav							
6.	Piperacillin Tazobactum							

[Cumulative Frequency Cube Root Method: Frequency – a: Most Prescribed - 15 to 86 & Percentage – c: Most Sensitive – 75 to 100%.
GPC – Gram Positive Cocci, GNB – Gram Negative Bacilli, NF – Non-fermenters]

Table 6: Comparison of Least Prescribed Antibiotics & their Sensitivity Pattern

S.No	LEAST PRESCRIBED ANTIBIOTICS[b]		SENSITIVITY (%)					
			GPC		GNB		NF	
			Sensitivity n (%)	Resistance n (%)	Sensitivity n (%)	Resistance n (%)	Sensitivity n (%)	Resistance n (%)
1.	**Chloramphenicol**		NT	NT	10 (71.4)	4 (28.6)	**1 (100)***	0 (0.0)
2.	Gentamicin		34 (50.7)	26 (38.8)	51 (62.2)	29 (35.4)	1 (25)	3 (75)
3.	Imipenem		NT	NT	68 (90.7)	1 (1.5)	6 (100)	0 (0.0)
4.	Levofloxacin		1 (16.7)	5 (83.3)	1 (16.7)	5 (83.3)	0 (0.0)	1 (100)
5.	**Nitrofurantoin**		**38 (86.4)**	6 (13.6)	**39 (76.9)**	12 (23.1)	NT	NT
6.	**Polymixin B**		NT	NT	**67 (98.5)**	1 (1.5)	**6 (100)**	0 (0.0)

[Cumulative Frequency Cube Root Method: Frequency – b: Least Prescribed – upto 1. NT – not tested.
*** - Tested only 1 time**
GPC – Gram Positive Cocci, GNB – Gram Negative Bacilli, NF – Non-fermenters)

Table 7: Comparison of Least Prescribed & Least Resistant Antibiotics

S.No	LEAST PRESCRIBED ANTIBIOTICS (%)[b]		LEAST RESISTANT ANTIBIOTICS[d]					
			GPC		GNB		NF	
			Antibiotic	Resistance %	Antibiotic	Resistance %	Antibiotic	Resistance %
1.	Bacitracin		Vancomycin		**Polymixin B**	1.5	**Polymixin B**	0.0
2.	Cefoperazone sulbactum		Cefipime		**Chloramphenicol**	6.7		
3.	**Chloramphenicol**		Ceftriaxone		**Nitrofurantoin**	23.1	**Imipenem**	28.6
4.	Doxycycline		Erythromycin		**Imipenem**	28.6	Amikacin	60.0
5.	Ethambutol		Linezolid		Piperacillin-Tazobactum	28.9		
6.	**Polymixin B**		**Nitrofurantoin**	0.0	Amikacin	30.0		
7.	**Imipenem**		Amikacin	13.6	**Gentamicin**	35.4		
8.	Isoniazid		**Gentamicin**	27.3	Cefixime	42.9		
9.	**Nitrofurantoin**		Amoxyclav	38.8	Cefipime	50.0		
10.	Levofloxacin			41.7	Norfloxacin	57.5		
11.	**Gentamicin**			50.0				
12.	Ivermectin							
13.	Ofloxacin ornidazole							
14.	Ornidazole							
15.	Penicillin G							
16.	Neomycin							
17.	Pyrazinamide							
18.	Rifampicin							

[Cumulative Frequency Cube Root Method: Frequency – b: Least Prescribed – upto 1 & Percentage – d: Least Resistant – 0 to 62.5%.
GPC – Gram Positive Cocci, GNB – Gram Negative Bacilli, NF – Non-fermenters]

DISCUSSION

In this study, we analysed the prescription patterns in IPDs of a tertiary care hospital in North India in comparison to antibiotic susceptibility patterns of various antibiotics in this hospital.

Most prescriptions (87.6%) included at least one antibiotic (Table 1). Our results are in line with Kujur et al. who conducted a study in Ranchi (Eastern India) (n=200 IPD patients) and found that vast majority (98%) of patients received antibiotics (16). However, Hodosan et al. conducted a study in Romania (n = 175,202 IPD patients) and reported antibiotic prescription in 53.8% patients (17). These differences may arise due to varying patterns of antibiotic sensitivity, hospital antibiotic policies and effectiveness in implementing antimicrobial stewardship (AMS) programs. A stringent AMS program may contribute to reduced irrational usage and decreased resistance of antibiotics.

The most common route of administering the antibiotics was parenteral (94.3%), followed by oral (3.9%) and topical (1.8%) (Table 1). These results are in concordance with Hodosan et al. who found that parenteral antibiotics were prescribed in majority (89.63%) of prescriptions and oral antibiotics in the remaining ones (10.37%) (17).

The most prescribed antibiotic class was cephalosporin (45.3%), followed by extended spectrum penicillins (12.6%) and nitroimidazole (10.8%) and least prescribed class were nitrofuran, tetracycline, amphenicol, polymixin and polypeptide (each – 0.4%) (Fig. 2). These results are supported by Ahmed & Alharbi of 2 years 7 months duration (n – not mentioned), who conducted a study in Saudi Arabia and found the most prescribed antibiotic class in surgery IPD to be cephalosporin (46.6%), followed by nitroimidazole (39.7%) (18). Anupuram et al. conducted a study in Hyderabad (n=200) and found the least prescribed antibiotic classes to be nitrofurans (0.42%), glycopeptide (0.42%) and tetracycline (2.96%) (19).

The most frequently prescribed antibiotic was ceftriaxone (30.6%), followed by cefoperazone (11.4%), while the most infrequently prescribed antibiotics included chloramphenicol, nitrofurantoin, doxycycline, gentamicin, imipenem, ofloxacin ornidazole, levofloxacin, bacitracin and penicillin G (each - 0.4%) (Table 2). These findings are consistent with Hodosan et al. which reported the most prescribed antibiotic to be ceftriaxone (26.46%), followed by metronidazole (13.05%) and cefuroxime (10.96%) and least prescribed antibiotics to be imipenem (0.001%), ofloxacin (0.2%), doxycycline (0.6%) and levofloxacin (1.05%) (17). The proportion for chloramphenicol was not reported.

In the present study, polymixin B (98.5%) and Imipenem (90.7%) were the most sensitive antibiotics to gram negative bacilli (Table 4). Similar to present study, Pattanayak et al. conducted in Odisha (East India) (n = 182 IPD patients) reported high sensitivity of E.coli (gram negative bacteria) to polymixin B (100%) and Chooramani et al. conducted in Lucknow (North India) (n = 1728 patient samples) found carbapenems (42.2% in IPD & 68.6% in OPD) to be among most sensitive antibiotics for gram negative isolates. However, neither study reported any glycopeptide antibiotic to be frequently sensitive for gram negative isolates (20, 21).

In this study, Ampicillin (90%) was the most resistant antibiotic to gram negative bacilli. Though, not in most resistant category, ceftazidime also demonstrated frequent resistance (75%) for gram negative bacilli. (Table 4). These results are again consistent with Pattanayak et al. and Chooramani et al. where cephalosporins including ceftazidime demonstrated high resistance (99.9% in first and 74.4% in second) to GNB. Sneha and Mangayarkarasi conducted in Tamil Nadu (South India) (n = 2687 IPD patients) reported prominent resistance of gram negative isolates to ampicillin (70%) (22).

The present study found cefipime, vancomycin, linezolid (each - 100%) and nitrofurantoin (86.4%) to be most sensitive to gram positive cocci (Table 4). These results are consistent with Sneha and Mangayarkarasi & Chooramani et al. who reported high sensitivity of vancomycin (100% in first & 70% in second), linezolid (100% in first & 64.8% in second) and nitrofurantoin (80% in first & 43.9 % in second) to gram positive isolates (21),(22). In Chooramani et al., sensitivity to nitrofurantoin for gram positive isolates was reported to be higher in OPD (77.6%) than IPD (43.9%) patients, while present study only included IPD patients (21). In addition, Khalid et al. performed a study in Pakistan (n = 422 patient samples) and found cefipime to have 100% sensitivity for gram positive isolates (23). No Indian study could be found in available literature to compare the sensitivity of GPC for cefipime.

In present study, it was found that norfloxacin (93.7%), co-trimoxazole (76.2%) & ampicillin (70.4%) to be frequently resistant for gram positive cocci, though statistically most resistant antibiotic was norfloxacin (Table 4). These findings are supported by Sneha and Mangayarkarasi, who reported high resistance (>70%) of gram positive isolates for these antibiotics (21)). Additionally, Chooramani et al. also reported high resistance of fluoroquinolones to both gram positive (5.2%) & gram negative isolates (10%) ((22).

In present study, polymixin B was the most sensitive antibiotic (100%) against non-fermenters bacteria. Another commonly sensitive antibiotic class for non-fermenters was carbapenems (71.4%) (Table 4). This is in concordance with Grewal et al. who conducted a study in Patiala (North India)

(n=216 patient samples) and reported the maximum proportion of sensitivity for NF by polymixin B (P.aeruginosa – 100%) & imipenem (P.aeruginosa – 83.7% & A.baumannii – 88.2%). (24). Similar results were obtained in Maniyan et al. conducted in Salem (South India) (n =110 patient samples), who reported the highest susceptibility of NF with polymixin B (100% - both P.aeruginosa & A.baumannii), imipenem (79.6% - pseudomonas & 75% - A.baumannii) & meropenem (as imipenem) (25).

While polymixin B is employed as a reserve option for multi-drug resistant (MDR) non-fermenters organisms, carbapenems are commonly used to treat these organisms. However, recently high resistance of MDR P.aeurugonisa has been noted towards carbapenems, as in Soni et al. (66.7% - P.aeruginosa) & Grewal et al. (60.9% - P.aeuroginosa) (24, 26). This indicates the rising prevalence of beta-metallolactamases producing carbapenemases.

In this study, the frequently resistant antibiotics for non-fermenters bacteria were amoxyclav, ampicillin, levofloxacin and cefixime (each – 100% resistance) (Table 4). These results are corroborated by Grewal et al. with maximum resistance for NF reported with amoxyclav (P.aeruginosa – 92.7% & A.baumannii – 70.6%) (24) Levofloxacin and cefixime were usually not tested against NF organism in other studies (24,25,27).

However, it must be noted that in present study due to the low frequency (n=1) of testing of most antibiotics (chloramphenicol, cefixime) against NF bacteria, no definitive conclusions can be made.

In the present study, among the least prescribed antibiotics, relatively higher sensitivity was found in nitrofurantoin (76.9% for gram negative bacilli, 86.4% for gram positive cocci) and chloramphenicol (71.4% for gram negative bacilli) (Table 6). This is in concordance with Chooramani et al. who reported high sensitivity of nitrofurantoin for gram negative isolates (70.7% - OPD & 57.9% IPD) (21). In addition, Alhumaid et al. conducted a study in Saudi Arabia (n = 38,624 patients) and reported that during five years (2015-19) nitrofurantoin sensitivity increased for both gram positive isolates (30.2% increased, p=0.032) and gram negative isolates (36.9% increase, p>0.05), alongside a high MRSA (80.9%) and E.coli (94.5%) sensitivity(28). Moreover, a study conducted by Sood in Jaipur (North India) (n = 483) found chloramphenicol to have high sensitivity (68 %) to multidrug resistant gram negative bacteria (29). This might depict the increased sensitivity of nitrofurantoin and chloramphenicol with infrequent usage over time through mechanisms like antibiotic free environment or phenotypic reversion(11).

However, this might not be applicable for all least prescribed antibiotics as they demonstrated lower sensitivity like co-trimoxazole (23.8% for gram positive cocci and 37.3% for gram negative bacilli) (Table 6). This was also found by Chooramani et al. (29.1% co-trimoxazole sensitivity for gram negative isolates) and Thaddanee et al. (co-trimoxazole —17.3% sensitivity for E.coli & 43.75% for Enterococci) conducted in Gujrat [North India, n = 50]) (30). But, higher sensitivity was reported in studies outside India of co-trimoxazole for gram positive isolates (Alhumaid et al. – 80.65%, done in Saudi Arabia [n=17,566])(26). This indicates the geographical, racial and genetic variance in regain of susceptibility of antibiotics over time with infrequent usage.

In this study, despite being the most prescribed antibiotics, high resistance has been noted in ceftriaxone (62.5% resistance – gram negative bacilli) & piperacillin-tazobactum (71.4% – non-fermenters) (Table 4 & 5). This was supported by Chooramani et al. (gram negative isolates -74.4% resistance for ceftriaxone) & Pattanayak et al. (gram negative isolates - 50.65 % resistance for ceftriaxone) (non-fermenters – 90% resistance for piperacillin-tazobactum) (20, 21). These present findings need to be taken into account before using these drugs as empirical therapy like ceftriaxone, or treating lethal infections like P.aeruginosa.

The strengths of this study include a broad range of antibiotic data collected from all clinical departments and all sources of infections (urinary, bloodstream & body fluids) and it may be the first study conducted in North India with the primary focus on infrequently prescribed antibiotics and their changing susceptibility patterns, as per our systemic search strategy. The search strategy utilized Pubmed, Scopus, Cochrane library, Google Scholar, Directory of Open Accesss Journals (DOAJ),

EMBASE, UpToDate, BioMed Central and Science Direct databases for a systematic search of research projects similar to this project.
Limitations of this study include a small sample size, collection of data from Covid-19 pandemic time which could affect prescriptions with a specific pattern of prescriptions and lack of MIC (Minimum Inhibitory Concentration) data of antibiotics due to unavailability of broth dilution AST method in microbiology laboratory.

CONCLUSION

Antibiotic resistance is a major cause of mortality throughout the world. Though, infrequently prescribed, few older antibiotics appear to have regained sensitivity against bacteria, like nitrofurantoin (for gram positive cocci & gram negative bacilli) and chloramphenicol (for gram negative bacilli). High resistance can be found to some most prescribed antibiotics as cephalosporins like ceftriaxone and extended spectrum penicillins like piperacillin-tazobactum. In view of the shifting antibiotic sensitivity trends, this knowledge can aid in effective treatment of infections. Further studies with greater sample sizes and duration are needed to validate these findings.

CONFIDENTIALITY

All data collected during the study was kept strictly confidential and the investigators did not use any data for any purpose other than conducting the present study.

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