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Original Research Paper

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TRENDS AND CORRELATION BETWEEN ANTIBIOTICS USAGE AND RESISTANCE PATTERN AMONG HOSPITALIZED PATIENTS -A RETROSPECTIVE SURVEILLANCE

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ABSTRACT

Background: Antibiotics are the substances produced by micro-organisms, which selectively kills or inhibit the growth of other microorganisms. To reduce the multi-drug resistance, co-relation between antibiotics usage and resistance pattern were investigated. **Objective:** The primary objective of this study was to characterize the trends and correlation between antibiotic use and resistance patterns in hospitalized patients, including the data on total antibiotics prescription, bed days and antibiotics, antimicrobial sensitivity test. Another objective was to quantify the consumption of each class of antibiotics using the World Health Organizations-Anatomical therapeutic chemical classification system (ATC) and Defined Daily Dose (DDD). **Method:** This is a retrospective study conducted at Government Cuddalore Medical College and Hospital (GCMCH), Chidambaram between 2021 to 2023. **Result:** We conclude third generation cephalosporins(3rd CEPs), beta- fluoroquinolones (FQs) as broad spectrum antibiotics and glycopeptides, oxazolidinone, diglycerine as antibiotics against (MDR) multi-drug resistant pathogens. We found a decrease in total antibiotic consumption in 2021 (18.079%) and an increase in antibiotic consumption in 2023 (28.204%). Among total antibiotic consumption 3rd generation cephalosporin accounts for about 66.842 (40.8%) and against MRO pathogens – polymyxin encountered for about 2.241 (1.37%). ESC consumption reported in significant positive correlation for the MRS occurrence ($p = 0.737$, $r = 0.976$). The most commonly isolated MRO pathogens from 2021 to 2023 were ESBL- producing klebseilla spp. (27.4%) adhere by MRSA (26.64%), ESBL producing E.coli (20.3%).Comparatively, infection rates of ESBL klebseilla spp., MRSA and ESBL E.coli increased throughout the three years. **Conclusion:** In this study, broad spectrum antibiotics such as ESC and BL/BLI comprising 87% of total antibiotic consumption. In addition to that the total usage of BL/BLI and ESC increased every year. In conclusion, overall antimicrobial resistance raised and consumption of broad spectrum antibiotics and antibiotics against MDR pathogens increased in Government Cuddalore Medical College and Hospital.

KEYWORDS : Correlation, Antibiotics, Microbial resistance.

INTRODUCTION

Antibiotics are drugs used to prevent and treat bacterial infections. On the other hand, antibiotic resistance occurs when bacteria change as a result of antibiotic use. A condition in which bacteria grow and become unresponsive to drugs, making treatment difficult and increasing the risk of disease spread, serious illness and death.

Antimicrobial resistance refers to the ability of resistant bacteria to tolerate antibiotics. The ability of microorganisms to resist the growth-inhibiting or destructive effects of an antibacterial agent at clinically achievable concentrations. The organization (WHO) has just issued a warning that the world is "not getting enough antibiotics" and expressed concern that global antibiotic resistance is reaching new heights. bacterial infections. Antibiotic resistance is increasing worldwide:

Bacterial infections are a leading cause of morbidity and mortality. New resistance mechanisms frequently emerge and spread internationally, compromising the ability to treat common infectious diseases. Infections such as pneumonia, tuberculosis, septicemia, gonorrhea and foodborne illnesses are becoming increasingly difficult, if not impossible, to treat. Decades after the first patients were treated with antibiotics, bacterial infections are once again a threat. We are rapidly moving into a post-antibiotic era,in which common infections and minor injuries can once again become life-threatening if prompt and preventive measures are not taken.

METHODS

This is a retrospective study conducted at Government Cuddalore Medical College and Hospital (GCMCH), Chidambaram between 2021 to 2023

Inclusion Criteria

Includes antibiotic prescription and antimicrobial susceptibility test reports.

Exclusion Criteria

Case reports with insufficient data.

Defnitions

Antibiotics

Antibiotics are antimicrobial substances with activity against bacteria which do not include antifungal or antiviral agents.while local agents were excluded.

We converted the amount of antibiotic used into a defined daily dose (DDD) using the WHO anatomical therapeutic chemical classification and then standardized this to 100 patient days. We divided antibiotics into 19 classes: 1st generation cephalosporin, 2nd generation cephalosporin, 3rd generation cephalosporin, 4th generation cephalosporin, aminoglycosides, beta-lactamase inhibitors, carbapenem, fluoroquinolones, glycopeptides, lincoromide, macrolides, monobactam, metronidazole, oxazolidinone, penicillin, polymycin, tetracycline, tigecycline and trimethoprim/sulfonamides. Other antibiotics such as amphenicol, streptogramin, fosfomycin were excluded because they are rarely used. We grouped 3rd generation cephalosporin, 4th generation cephalosporin, beta-lactamase inhibitors and fluoroquinolones as broad-spectrum antibiotics and carbapenems, tigecycline, glycopeptide, oxazolidione and polymycins and antibiotics against multidrug-resistant pathogens. The remaining antibiotic classes were grouped as broad-spectrum antibiotics.

Major Bacterial Pathogens And Antimicrobial Resistance

We investigated antimicrobial susceptibility testing for major bacterial pathogens such as Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Protein mirabil is, Methicillin-resistant Staphylococcus aureus (MRSA), and Acinetobacter baumannii. Antimicrobial susceptibility testing was performed on patient samples: blood, pus, urine, ascites fluid, synovial fluid, and cerebrospinal fluid. Antibiotic susceptibilities were determined using a semi-automated system in the Department of Microbiology. R (resistance) or I (intermediate) was defined in the report as resistance.

Statistical Analysis

The Jonckheere-Terpstra test was used to assess the trends in Antibiotics use, pathogens proportions and Antimicrobial resistance rates over time.

Study Defnition

Six groups of antibiotics classified as[Antibiotics for systemic use] in accordance to the Anatomical Therapeutics Chemical (ATC) classification system were included in this study. The broad spectrum antibiotics selected for this study were Amoxicillin / Clavulanate, Ampicillin/ sulbactum, piperacillin / tazobactum, cefotaxime, ceftriaxone, ceftazidime, cefepime, ciprofloxacin and levofloxacin. We categorized carbapenems, glycopeptidases, oxazolidinone and polymyxin as antibiotics against multi drug resistant organisms (MRO's). Extended-spectrum cephalosporins (ESC) are cephalosporins with more potent activity against gram negative microbes than first generation agents. The following formula was to calculate the defined daily dose (DDD) per 100 hospital admissions.

$$Number\ of\ DDD\ per\ year = \frac{total\ antibiotics\ usage(g) for\ inpatients\ adults\ in\ a\ year}{DDD\ (from\ WHO)}$$

$$Number\ of\ DDD\ per\ 100\ admissions = \frac{Number\ of\ DD\ per\ year}{total\ admission\ for\ the\ particular\ year} \times 100$$

The MROS types investigated in this study were methicillin-resistant Staphylococcus aureus (MRSA), extended spectrum beta lactamase (ESBL) producing Klebseilla species, ESBL producing Escherichia coli, MRO-Acetobacter baumannii, carbapenem resistant enterobactericeae and vancomycin resistant enterococci.

Table 1: Consumption Of Anti-microbial Agents For Parental Use From 2021 To 2023 (DDD/100 Admission)

	2021	2022	2023	p-value	Total
BROAD SPEECTRUM ANTIBIOTCS					
Beta-lactamase inhibitors	64.112	65.215	81.683	0.059	70.34 (42.96%)
Amoxicillin-Clavulanate	34.601	31.116	51.051	0.1807	38.92 (23.7%)
Ampicillin-salbactum	12.102	8.514	11.583	0.179	10.73 (6.55%)
Piperacillin-tazobactum	17.409	25.585	19.049	0.118	20.68 (12.6%)
Extended Spectrum Cephalosporins	56.037	60.201	84.287	0.137	66.842 (40.8%)
Ceftriaxone	39.021	40.108	52.908	0.087	44.01 (26.8%)
Cefotaxime	10.248	11.526	19.806	0.324	13.26 (8.46%)
Cefepime	5.128	5.579	7.825	0.142	6.18 (3.77%)
Ceftazidime	1.252	2.011	2.182	0.176	1.815 (1.10%)
Cefoperazone	0.189	0.686	1.2578	0.534	0.711 (0.43%)
Cefoperazone-Salbactam	0.199	0.291	0.308	0.121	0.266 (0.16%)
FLUROQUINOLONES	3.918	4.595	4.062	0.856	4.1921 (2.56%)
Ciprofloxacin	3.297	3.998	3.708	0.034	3.668 (2.24%)
Levofloxacin	0.621	0.597	0.354	0.183	0.524 (0.32%)
SUBTOTAL	124.067	130.011	170.032	0.089	141.37 (86.35%)
ANTIBIOTICS AGAINST MRO					
Carbapenems	10.102	12.162	17.416	0.193	13.22 (8.07%)
Imipenem-cilastatin	0.888	1.954	1.083	0.866	1.308 (0.798%)
Meropenems	8.212	8.102	12.306	0.240	9.54 (5.82%)
Ertapenem	1.002	2.106	4.027	0.936	2.378 (1.152%)
POLYMYXINS	2.1106	2.103	2.516	0.034	2.241 (1.37%)
Polymyxin B	0.089	0.071	0.194	0.591	0.118 (0.072%)
Colistin	2.017	2.032	2.322	0.043	2.123 (1.296%)
Glycopeptide (vancomyicn)	5.871	6.652	8.272	0.090	6.889 (4.21%)
SUBTOTAL	18.079	20.791	28.204	0.143	22.35 (13.65%)
TOTAL	142.146	150.802	198.236	0.096	163.72 (100%)

RESULTS

Overall consumption and trends of parenteral antibiotics. Table 1 shows overall consumption of antimicrobial and their corresponding classes for parenteral use. The entire consumption of six classes of antibiotics monitored was 163.72 DDD/100 admissions for the three years period. There was a 39.4% and 31.5% urge in antibiotic use in 2023 compared to 2021 and 2022 (142.146 DDD/100 admissions in 2021, 150.802 DDD/100 admission in 2022 and 198.236 DDD/100 admissions in 2023, $p<0.001$).Besides, the consumption of Broad-spectrum antibiotics is increased by 37% and 30.7% in 2023 from 2021 and 2022 (124.067 DDD/100 admissions in 2021, 130.011 DDD/100 admission in 2022 and 170.032 DDD/100 admissions in 2023, $p<0.001$). Antibiotics against MRO showed a stand up trend in 2023 by 56% and 35.6% from 2021 and 2022, respectively (18.079 DDD/100 admissions in 2021, 20.791 DDD/100 admission in 2022 and 28.204 DDD/100 admissions in 2023, $p<0.001$).

Beta-Lactamase inhibitors was the most commonly prescribed antibiotic groups (42.96%,70.34 DDD/100 admissions), continued by Extended Spectrum Cephalosporins (40.8%, 66.842 DDD/100 admissions), carbepenems (8.07%, 13.22 DDD/100 admissions), glycopeptides (4.21%, 6.889 DDD/100 admissions), fluroquinolones (2.56%, 4.192 DDD/100 admissions) and ploymyxins (1.37%, 2.241 DDD/100 admissions) (Table 1). The usage of broad-spectrum antibiotics and antibiotics against MRO were 86.3% (141.37/163.72 DDD/100 admissions) and 13.7% (22.35/163.72 DDD/100 admissions), respectively.

The top five most oftenly prescribed antibiotics, which encountered for 73.39% of all antibiotic usage, were amoxicillin-clavulanate, ampicillin-salbactam, piperacillin-tazobactam, ceftriaxone and cefepime. All the antibiotics showing greater use throughout the study period except for ampicillin-clavulanate, cefepime, meropenem and ertapenem was significantly greater ($p<0.05$ throughout the 3

years observation).

Beta lactamase inhibitor was the most utilized antibiotic group, with 27.4% and 25.2% increase in 2023 from 2021 and 2022, respectively (64.112 DDD/100 admissions in 2021, 65.215 DDD/100 admissions in 2022 and 81.683 DDD/100 admissions) (Table 1).

Comparatively, the annual Extended spectrum cephalosporins usage revealed a 50.4% and 40% increase in 2023 from 2021 and 2022, respectively (56.037 DDD/100 admissions in 2021, 60.201 DDD/100 admissions in 2022 and 84.287 DDD/100 admissions in 2023).

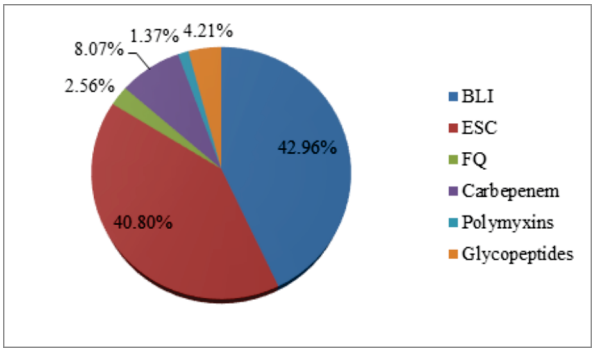

Figure 1: Consumption of antibiotics by subgroups from 2021 to 2023. BLI= beta-lactamase inhibitors, ESC= extended spectrum cephalosporins, FQ= fluroquinolones.

Table 2: Rate of MRO infection per 100 admission from 2021 to 2023. *Significant trend (J-T test on monthly data) at p<0.05

Organisms	2021	2022	2023	p-value	Total %
Methicillin-resistant Staphylococcus aureus (MRSA)	0.091	0.101	0.112	<0.0001	0.101 (26.64%)
Extended spectrum beta-lactamase (ESBL)-producing klebsiella spp.	0.083	0.112	0.119	<0.0001	0.104 (27.4%)
Extended spectrum beta-lactamase (ESBL)-producing Echerichia coli	0.045	0.078	0.108	<0.0001	0.077 (20.3%)
Multidrug-resistant organisms (MRO) Acinetobacter baumannii	0.061	0.093	0.051	<0.0001	0.068 (17.9%)
Carbapenem-resistant Enterobacteriaceae (CRE)	0.023	0.034	0.029	1	0.028 (7.38%)
Vancomycin-resistant enterococci (VRE)	0.003	0.002	0.000	<0.0001	0.001 (0.26%)

Trends of MRO infection rates. The most commonly isolated MRO pathogens between 2021 and 2023 was ESBL-producing klebsiella spp. (27.4%), followed by MRSA (26.64%), ESBL-producing Echerichia coli (20.3%), MRO Acinetobacter baumannii (17.9%), CRE (7.38%) and VRE (0.26%) (table 2). Comparartively, infection rates of ESBL Klebsiella spp, MRSA and ESBL E.coli raised throughout the three years.

Correlation Between Antibiotic Consumption And Mro Infection Rates

Increasing BI/BLI consumption indicate negative correlation for MRO occurrence A.baumannii (r= -0.260, p= 0.02) and CRE (= -0.627, p= 0.474). The utilization of ESC reported in significant positive correlation for occurrence of MRSA (p= 0.737, r= 0.976), ESBL producing Klebsiella spp. (r= 1.005, p= 0.759), ESBL producing E.coli (r= 0.744, p= 0.562) and MRO A.baumannii (r= 0.656, p= 0.496). Similar to ESC, FQ also indicated significant positive correlation for occurrence of MRSA (r= 0.154, p= 0.117), ESBL producing Klebsiella spp. (p= 0.121, r= 0.160), ESBL producing E.Coli (r= 0.117, p=0.089). Carbapenem resulted positive correlation with ESBL Klebsiella spp. (r= 0.712, p=0.538) and ESBL E.coli (r= 0.527, p= 0.398). Similarly, polymyxins were accomplished with positive correlation for resistance of ESBL producing Klebsiella spp. (r= 4.050, p= 3.058), MRO A.baumannii (p= 2.00, r= 2.649) and CRE (p= 0.823, r= 1.090). VRE occurrence negatively correlated with the glycopeptides consumptions (r= 0.94, p= 0.011).

Table 3: Correlation between antibiotic consumption and MRO occurrence. BL/BLIs = beta lactam/beta-lactamase inhibitors, ESC = extended-spectrum cephalosporin (third generation and fourth generation cephalosporins), FQ = fluoroquinolones. Significant result *p < 0.05, **p < 0.01.

ORGANISM	ANTIBIOTIC GROUP	CORRELATION	
		P-VALUE	CORRELATION COEFFICIENT (PEARSON'S r)
MRSA	BL/BLIS	1.711	1.291
	ESC	0.737	0.976
	FQ	0.117	0.154
	CARBAPENAM	0.523	0.692
	POLYMYXINS	2.970	3.933
	GLYCOPEPTIDES	1.122	1.486
ESBL-producing Klebsiella spp	BL/BLIS	1.762	2.333
	ESC	0.759	1.005
	FQ	0.121	0.160
	CARBAPENAM	0.538	0.712
	POLYMYXINS	3.058	4.050
	GLYCOPEPTIDES	1.155	1.529
ESBL-producing E.coli	BL/BLIS	1.305	1.728
	ESC	0.562	0.744
	FQ	0.089	0.117
	CARBAPENAM	0.398	0.527
	POLYMYXINS	2.264	2.998
	GLYCOPEPTIDES	0.855	1.132
MRO A. baumannii	BL/BLIS	1.152	1.525
	ESC	0.496	0.656
	FQ	0.079	0.104
	CARBAPENAM	0.352	0.466
	POLYMYXINS	2	2.649
	GLYCOPEPTIDES	0.755	1
CRE	BL/BLIS	0.474	0.627
	ESC	0.204	0.270
	FQ	0.032	0.042
	CARBAPENAM	0.145	0.192
	POLYMYXINS	0.823	1.090
	GLYCOPEPTIDES	0.311	0.411
VRE	BL/BLIS	0.016	0.021
	ESC	0.007	0.009
	FQ	0.001	0.001
	CARBAPENAM	0.005	0.006
	POLYMYXINS	0.029	0.038
	GLYCOPEPTIDES	0.011	0.014

DISCUSSION

The study revealed the antibiotic use and resistance pattern in a tertiary care teaching hospital in Chidambaram, Tamil nadu, India. This study showed that 85% of antibiotics prescribed was for empirical therapies. Initially, Antibiotics were prescribed and given for patient only based upon the clinical assessment. Later, after identification of the causative

microorganism, clinicians detect the most appropriate antibiotic, which shows sensitive to particular pathogen-results improvement in overall patient outcomes.

In this study, broad spectrum Antibiotics such as ESC and BL/BLI comprising-87% of total antibiotic utilization.

In addition to that, the total usage of BL/BLI and ESC tends to be raised every year.

However, pursuing and following a protocol for Antimicrobial stewardship will be a successful approach to decrease unnecessary and unsuitable use of antibiotics and to reduce Antibiotics resistance among patients.

LIMITATIONS

The study is a retrospective observational study, it doesn't confirm the actual relationship between antibiotic use and MRO infection rate. Simultaneously due to the distinct dosage requirement, antibiotic usage was measured using DDD,that may be inappropriate in certain cases such as kidney impairment. Hence, it may not indicate the prescribed daily dose for all patient.

Hence, there is a absence of patient specific data for elaborated risk factor evaluation. In addition, all data points are necessary to signify the correlation between antibiotic usage and MRO's infection.

CONCLUSION

The comprehensive data represents a true sign for antibiotic usage and resistance pattern. Broad spectrum antibiotic and Antibiotic against MRO consumption raised significantly throughout the study Meanwhile the antimicrobial resistance trend in hospital had decreased except for MRSA and ESBL.

Simultaneously, ESC and FQ usage was positively correlated with the MRSA occurrence, ESBL producing Klebsiella spp., E.coli and MRO A.baumannii resistance.

Routine monitoring, receiving and enforcement of Antimicrobial Stewardship (AMS) will be further helpful to overcome the crucial threats by MRO's.

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