

# Restricted High-End Antibiotics monitoring and policy adherence rate in a tertiary care hospital

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## ABSTRACT

**Background:** AMR is an emerged silent global pandemic leading to significant mortality and morbidity with a great cause of concern to tackle. Improved access to antibiotics and surveillance of antibiotic consumption are the key component to prevent AMR. AMSP implements strategies to ensure the right drug, dosage, route, and duration of antimicrobial therapy and promotes infection prevention and control measures. Considering this, the current interventional study aims to portray the effect of restricted High-End Antibiotic (HEA) usage monitoring from January to December 2022 (pre intervention) and January 2023 to December 2024 (post intervention) from a tertiary care hospital.

**Materials and Methods:** Between pre and post intervention periods, the usage of HEA(meropenem, imipenem, ertapenem, doripenem, colistin, polymyxin B, tigecycline, fosfomycin, ceftazidime-avibactam+/- aztreonam, vancomycin, linezolid, teicoplanin, daptomycin, cefepime and ceftaroline) were monitored towards their trend, appropriateness, whether clinical samples were sent for culture/sensitivity testing before starting HEA, frequency of escalation and de-escalation followed.

**Results:** Patient with 45 to 70 years of age, urosepsis (25%) and sepsis/ shock (35%) were found to be high risk groups. MRP, CL, PB, TIG, FOS, CAZ-AVI+/-AZT, VAN, LZ and TEI are the high priority HEA with significant reduction in meropenem usage over the period of time. The recovery rate of patients was found to be 60% with 8% mortality rate.

## Conclusion:

The usage of HEA was significantly less in wards when compared to CCU. MRP, LZ, VAN and PB were found to be the high priority HEA. Following intervention significant reduction evidenced with TEI, TIG, CL, and FOS.

**Keywords:** Antimicrobial stewardship, high end antibiotics, restricted antibiotics, antimicrobial trend, defined daily dose and antibiotic consumption

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## INTRODUCTION

Globalization led to exchange of opportunity, wide growth in technology, trading and economy in tandem, it also created a massive silent pandemic called Antimicrobial Resistance (AMR).<sup>1</sup> The emergence of Multi Drug Resistant (MDR) and Pan Drug Resistance (PDR) bugs caused enough health

disaster worldwide.<sup>2</sup> The biological and functional competence of the microbes to make the antimicrobial molecules ineffective created great survival issue among the community. Factors like over the counter sale, inadequate, in discriminate, irrational usage of antimicrobial agents, lack of awareness on AMR at the community level, extensive use of antibiotics among livestock's,

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aquaculture and also increased environmental contamination by pharmaceutical wastes favours major role on emergence of AMR.<sup>3</sup> Non-prescribed antibiotic consumption, suboptimal dosing, wrong route of administration and poor quality of pharmaceutical products, also adds additional pressure towards emerged AMR.<sup>4</sup>

The global consumption of antimicrobials in food animals was estimated to be 200,235 tons by 2030.<sup>5</sup> One-Health approach is an effective initiative against the dynamics of AMR. Global Research on Antimicrobial Resistance (GRAM) project estimated that 1.91 million people might potentially die due to AMR in 2050.<sup>6</sup> The Access, Watch and Reserve (AWaRe) group of antibiotic guidelines by WHO is an effective initiative to make potentially optimal usage of antibiotics among the prescribers.<sup>7</sup> Likewise many AMR initiative guidelines and protocols are formulated and being practised.<sup>8</sup> Still there are large gaps in implementing these policies. It is mainly because of lack of effective monitoring force to educate, execute, audit, analyse and to reframe the process in all levels of healthcare settings.

Antimicrobial Stewardship Program (AMSP) refers to integrated interventions designed to improve and to measure appropriate usage of antimicrobial agents by promoting the selection of optimal drug regimen, dose, duration and route of administration.<sup>9</sup> The use of antimicrobials can be monitored by measuring their total use, Days of therapy (DOT), Defined Daily Dose (DDD) and restricted High End Antimicrobial (HEA) usage.<sup>10,11</sup> Considering these parameters, this interventional study was aimed to monitor the usage of restricted HEA, their indication and appropriateness in a tertiary care hospital.

#### Materials and methods:

During January to December 2022 (pre intervention period/ phase1) and January 2023 to December 2024 (post intervention period/phase2), after obtaining institute research and institute ethical committee approval, this descriptive cross-sectional, prospective study was conducted in a tertiary care hospital, Puducherry. Study population includes all adult in-patients admitted in various speciality and Critical Care Units (CCU). Patients shifted from other healthcare centres, already on any of the listed HEA with/without microbiology culture reports were excluded. Institute AMSP committee formulated the list of restricted HEA agents in align with the local resistance pattern, spectrum of antimicrobial activity, potential toxicity, clinical condition and its cost factor. Meropenem(MRP), imipenem(IMP), ertapenem(ETP), doripenem(DOR), colistin(CL), polymyxin B(PB), tigecycline(TIG), fosfomycin(FOS), ceftazidime-

avibactam+/-aztreonam(CAZ-AVI-AZT, vancomycin(VAN), linezolid(LZ), teicoplanin(TEI), daptomycin(DAP), cefepime(FEP) and ceftaroline(CFT-F) were listed as restricted high-end antibiotics.<sup>7,10,12</sup> This policy also stated that these restricted drugs shall be prescribed only with proper clinical/ diagnostic indications. The consultant and above cadre (unit chief) were only permitted to prescribe from the above list.

#### Intervention and post intervention period/ phase 2:

Using previous year audited data and local antimicrobial resistance pattern, antibiotic policy and guidelines was formulated and updated. Updated high-end antibiotics monitoring form also was shared to all the stakeholders. Multiple department wise meetings, flipped classes, individual desktop teaching and open-ended discussions, were made for all the prescribers, nursing staffs, pharmacists and administrative heads periodically. Targeted antimicrobial agents usage was daily reviewed towards its indication and appropriateness. During monthly meetings, the policy adherence rate, advantages of collecting and sending appropriate clinical samples for culture and sensitivity (C/S) testing before starting antimicrobials, evidence based prescription practices, importance of escalation and de-escalation of therapy following microbiological reports were discussed. Regular discussions were made with the prescribers and pharmacists based on the review and feedback. Depending upon the need, individual educational sessions also got executed aiming for improved policy adherence rate<sup>7</sup>.

#### Defined Daily Dose (DDD) calculation:

Total DDDs Consumed = Strength \* Pack Size \* Packs Consumed/ DDD of Molecule/formulation.<sup>11,13</sup>

#### Institute Human Ethics Committee approval reference details:

MGMCRI/ 2025/02/04/IHEC/74.

#### Result:

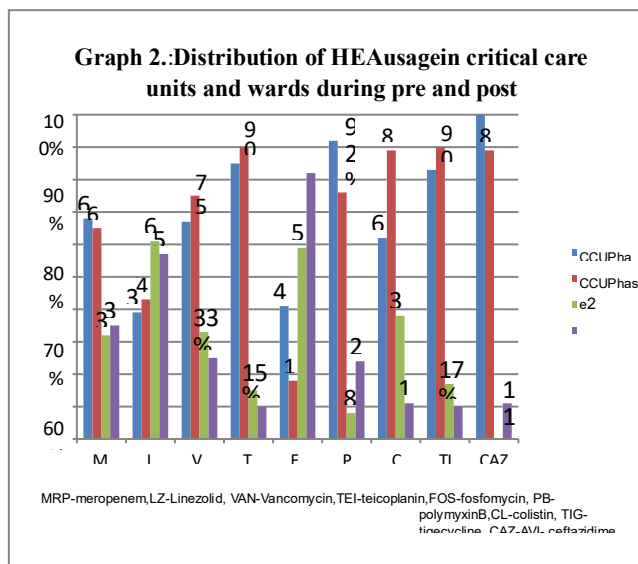
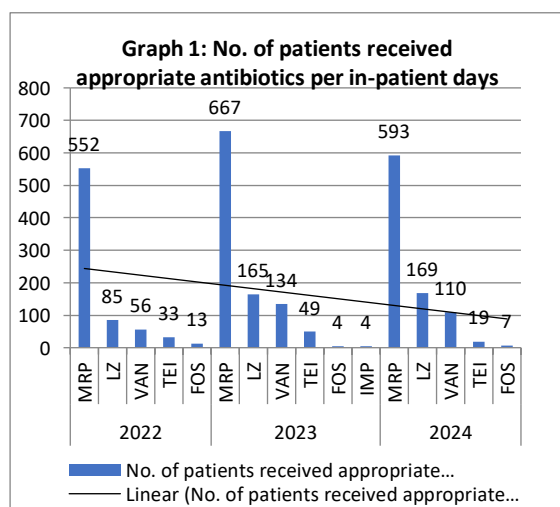
A total of 694 in-patients between January to December 2022 (pre intervention period) out of 1,11,782 in-patient days and 1730 in-patients out of 2,38,707 in-patient days from January 2023 to December 2024 (post intervention period) involving all departments were recruited in this study. The proportion of HEA consumption in pre-intervention period was 6.2 per 1000 in-patient days. During post-intervention period, it was 7.1 (2023) and 7.4 (2024) per 1000 in-patient days. The overall HEA consumption in post intervention period was 7.2 per 1000 in-patient days. Male and female patients with

45 to 70 years of age were found to be the vulnerable age group who exhibited greater consumption of HEA in both phases followed by other age groups. Significantly during phase 2, female gender with 45-70 years of age received more quantity of HEA when compared to others (table 1).

In phase 1, significant amount of patients with urosepsis (25%) and patients with sepsis/ shock (23%), followed by patients with GIT / hepatobiliary and skin soft tissue infections (15%) received at least a minimum of one high end antibiotics. Patients with sepsis/ shock, skin and soft tissue infections followed by urosepsis and patients with LRTI were found to receive more amount of HEA during 2023 and 2024 (table 2). Majority of the patients were identified to be presented with multiple clinical diagnoses irrespective of total number of patients.

Based on recommended antibiotic policy MRP, CL, PB, TIG, FOS, CAZ-AVI-AZT, VAN, LZ and TEI are the high priority high-end antibiotics were utilized predominantly in both pre and post intervention period. Imipenem,ertapenem, doripenem, daptomycin, cefepime and ceftarolineantibiotics were not prescribed among any of these patientswithout specific indication.The usage of MRP showed significant reduction during the post intervention period (62%) than pre-intervention period (76%). Usage of VAN and LZ during phase 2 showed significant increase when compared to other drugs (graph 1).

Out of 67% MRP usage in phase 1, 68% of the drugs were utilized among CCU patients and 32% for general ward patients. Similarly during phase 2 (62%), among CCU patients 65% and in wards 35% of MRP usage was documented. Linezolid, VAN, TEI, CL, TIG usage in CCU patients are



increased during post intervention period, when compared to phase1. Fosfomycin, PB, CAZ-AVI in CCU showed significant reduction in their usage (graph 2).Prescription of CL, PB, TIG and CAZ-AVI was only based on the MIC reports done by microbroth dilution method.

Compared to initial phase, in post intervention period, the percentage of appropriate clinical sample ordering for culture and sensitivity before starting empirical antibiotics showed significant improvement except 80% forlinezolid.In phase 1, a total of 712 patients clinical samples were sent for C/S, 15% of them showed sterile/normal flora grown, among these 72% of patients were continued with same empirical drugs with varying days of therapy. Similarly, in phase 2, out of 1966 samples sent for C/S, 24% of these samples were found to be sterile/normal flora grown, of which 46% of these patients received continuation of the same empirical HEA due to patient’s worsened clinical condition which is of great concern. Out of 57% resistant MRP empirical therapy, 34% patients were escalated with higher antibiotics and 21% of them were continued with same as per clinical response evidenced by the clinical team in case of phase 1. Similarly, in phase2, MRP was found to be resistant among 44% of patients, of which 42% were prescribed with higher antibiotics and 7% of these patients were continued with the same empirical drug as per clinician’s advice. Likewise, all other HEA also showed significant de-escalation rate over the period of time following intervention (table3).Analysis of DDDcalculation from January to December 2024 also explores thatmajor HEA consumption happened among CCU patients. Significantly, MRP, VAN, CL, PB, CAZ-AVI were most commonly used antibiotics when compared to LZ. Linezolid was mostly used among ward patients than CCU patients (table 4).

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**Table 1: Gender and age wise distribution of patient who received HEA**

Age (in years)	Pre intervention period		Post intervention period	
	2022 (n=694)		2023&2024 (n=1730)	
	MALE	FEMALE	MALE	FEMALE
< 1	2%(9)	3%(7)	7%(74)	7%(41)
1-<19	3%(12)	3%(7)	4%(51)	4%(21)
19-<25	4%(18)	2%(6)	4%(46)	2%(13)
25-<45	21%(89)	27%(69)	21%(244)	18%(107)
45-70	53%(232)	51%(132)	51%(582)	56%(330)
>70	17%(74)	15%(39)	13%(147)	13%(74)
Total	63%(434)	37%(260)	66%(1143)	34%(587)

**Table 2: Diagnosis based distribution of HEA usage**

Diagnosis	Phase 1 (2022)	Phase2 (2023+2024)
Head injury	7%(54)	0.5%(11)
Sepsis/ Shock	23%(185)	35%(684)
Skin & soft tissue infections	15%(120)	25%(497)
Urosepsis	25%(205)	18%(344)
Meningitis/ encephalitis	5%(45)	6.5%(113)
Gastrointestinal and hepato biliary infection	15%(124)	5%(101)
Respiratory tract infection	10%(88)	10%(205)
Total	821	1955

**Table 3: Analysis of High End Antibiotics prescription pattern**

Antibiotics	Phase 1 (2022)	Phase 2 (2023+2024)
Amoxicillin	15%	25%
Clindamycin	15%	25%
Vancomycin	5%	6.5%
Meropenem	15%	5%
Respiratory tract infection	10%	10%
Total	821	1955

LZ	85	96% (82)	4% (3)	31% (26)	62% (16)	68% (56)	89% (50)	20% (16)	0	0	0
VAN	56	84% (47)	16% (9)	57% (27)	74% (20)	43% (20)	90% (18)	19% (9)	0	0	0
TEI	33	79% (26)	21% (7)	31% (8)	75% (6)	69% (18)	88% (11)	35% (9)	0	0	0
FOS	13	54% (7)	46% (6)	43% (3)	29% (2)	71% (4)	10% (0)	14% (1)	0	0	0
PB	55	100% (55)									
CL	19	100% (19)									
TI	6	100% (6)									

**2023-2024 Post intervention period (n=2,123 in-patients)**

MRP	1260	97% (1216)	3% (44)	23% (83)	32% (90)	33% (40)	45% (179)	34% (16)	44% (531)	4% (22)	7% (37)
LZ	334	80% (268)	20% (66)	25% (6)	73% (48)	75% (22)	49% (99)	45% (21)	0	0	0
VAN	244	86% (210)	14% (34)	50% (105)	56% (59)	50% (105)	32% (34)	56% (17)	0	0	0
TEI	68	84% (57)	16% (11)	40% (3)	48% (11)	60% (34)	62% (21)	44% (25)	0	0	0
FOS	119	82% (9)	18% (2)	22% (2)	100% (2)	78% (7)	71% (5)	22% (2)	0	0	0
PB	152	100% (152)									
CL	35	100% (35)									
TI	10	100% (10)									
CAZ	9	100% (9)									

**Table 4 :2024- CCU & ward level DDD value of HAE usage**

Antibiotics	CCU level DDD value											
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
MRP	50	51	69	48	113	115	46	79	54	50	45	38
LZ	23	13	70	72	128	108	124	24	21	98	29	35
VAN	14	21	10	14	137	186	61	25	37	113	37	58
TEI	0	0	0	0	146	458	35	20	24	82	35	88

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			0						1			
			6						4			
PB	2.3	1.5	2.7	1.1	41.9	54.3	4.0	4.4	5.1	1.7	2.1	9.1
CL	0	0	0.2	0	0.3	0.34	0	0.1	0.1	0.0	0.0	0.0
CAZ-AVI	0	0.5	0	0	0.13	0	0	7	3.2	0	0.4	0
<b>Ward level DDD value</b>												
Anti biotics	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
MRP	1.7	1.9	1.2	2.1	10.8	8.59	9.0	9.4	1.2	9.3	1.8	1.5
LZ	1.6	0.2	1.6	1.4	1.07	7.36	6.3	7.4	2.0	9.4	6.8	7.9
VAN	4.0	4.0	0.9	8.9	1.96	1.53	3.1	2.5	5.1	1.4	4.1	2.3
TEI	0	1.1	0.2	0	0.86	0	0	0	0.5	0.1	0.6	0
PB	2.8	1.3	4.3	3.4	0	0	0	1.8	1.8	1.2	1.6	0.9

### Discussion:

Injudicious and inappropriate use of antimicrobial agents was identified as proven predisposing cause for emerged resistant bugs.<sup>14</sup> It was approximately estimated that 20-50% of antibiotics prescriptions are found to be unnecessary and it led to various untoward effects like prolonged hospitalization, significant increase in health care expenditure and drastic raise in AMR universally.<sup>15</sup> The increase in healthcare seeking behaviour among public had also lead to more use of broad spectrum, much costly antibiotics to manage the emerged resistant organisms.<sup>16</sup> Worldwide about 36% increase in antibiotics consumption among human was reported during 2000 to 2010.<sup>17</sup> As per literature, India was found to be one of the largest consumers of antibiotics.<sup>18</sup> With available data the sales and use of newer group of antibiotics in India were found to be significantly high.<sup>19</sup> Mainly due to unregulated over-the-counter antibiotic sale, India attributes 23% of retail sale when compared to Brazil, Russia, China and South Africa.<sup>20</sup> Studies identified high inequalities in antibiotic usage within countries (2018), especially India which was found to have highest relative deviation in antibiotics.<sup>21</sup>

The integral component of AMSP is formulation of antibiotic policy as per local sensitivity pattern, periodic updating, and analysis of antibiotic consumption with review of audited reports.<sup>22</sup> Effective AMS program includes restricted antimicrobials agents monitoring as the core component of formulary system.<sup>10</sup> Restriction of High-End Antibiotic (HEA) and preauthorization plays pivotal role in preventing AMR in the healthcare settings.<sup>22,10</sup> Based on the institute antibiotic policy and individual susceptibility pattern, the AMSP team made a closed

monitoring of each HEA antibiotics usage by incorporating a pre authorization form in phase 2.

Considering the prevailing resistant pattern of bugs and antibiotic policy in conjunction with existing patient health condition, the high- end antibiotic monitoring program got initiated among all in-patients. The overall percentage of HEA usage during pre and post intervention was 6.2 and 7.2 per1000 in-patient days. The overall MDR rate in phase2 was 36% in wards and 51% in CCU. Comparison of pre intervention period MDR rate was not possible because of lack of data. Initially, male gender (53%) with age group between 45-70 years of age was found to be the most vulnerable patients to receive more HEA. In contrast during phase 2, female patients (56%) with the similar age groups were found receive majority of HEA which was found to be comparable with other study findings.<sup>23,24</sup>

For 13% of patients before starting antibiotics, appropriate clinical samples were not sent for culture and sensitivity testing (phase 1). Following intervention it significantly reduced to 7%. Except FOS (82%) for patients with cystitis and LZ (57%) for skin soft tissue infections, all other HEA usage among ward patients showed significant reduction from phase 1 to phase 2. Escalation of antibiotic was done as per culture report for patient with 34% MRP resistance in initial phase, with mild improvement in intervention phase of 42%. Following MRP in vitro resistance, either FOS, CL, PB or TIG was initiated based on their susceptibility pattern and patient clinical condition. For patients with pan drug resistant bugs, based on MIC and synergy testing, Ceftazidime-avibactam+/- aztreonam was prescribed. Even though MRP usage as empirical therapy was resistant, 21% of patients from pre and 7% from post intervention period received the same drug because of clinical improvement witnessed by treating team. The overall unjustified usage of HEA in phase 1 and phase 2 (patients received HEA but culture sterile/ normal flora grown and number of patient received HEA but drug was resistant by in-vitro test) was 15% and 10% respectively in case of MRP usage (table3).

Defined Daily Dose is the assumed daily average maintenance dose per day for a drug. DDD per 100 bed-days is to compare and to monitor the antibiotic consumption in a hospital.<sup>25,26</sup> It is mainly used for assessing the change in drug utilization over the period of time and also can be used to make international comparisons as a standard of metrics among adult patients. In a national level study across the country, the highest annual DDD value of 30.5 was recorded in Delhi (2013) and the lowest of 6.6 values was recorded in Madhya Pradesh in 2017.<sup>22</sup> DDD value of HEA in the current study showed fluctuating pattern over the period of time in both locations (CCU and wards). To streamline the HEA utility, review and feedback strategies plays significant role. Increase in the mortality has association with inappropriate or delay in empirical therapy.<sup>27,28,29</sup> In phase 2, the recovery rate was found to be 60%, 14% of patients got shifted to

step down wards and they showed slow recovery. Due to comorbid conditions and other individual issues 18% of these patients were referred to higher centre or discharged against medical advice and the mortality rate was found to be 8%. Lack of Phase 1 data on MDR rate, morbidity and mortality statistics and DDD values are the major limitations of this study.

### Conclusion:

The overall consumption of HEA in pre and post intervention periods was 6.2 and 7.2 per 1000 in-patients days. Compared to phase 1, female patients between the age group 45-70 years were found to be more vulnerable to receive majority of HEA in phase 2 (56%). Urosepsis (25%) and sepsis/shock (35%) were found to be commonest clinical indication to initiate HEA. The overall usage of MRP from 67% was reduced to 62% following intervention. De-escalation of MRP following resistant culture report in phase 1 from 21% was significantly reduced to 7% in phase 2. In contrast, usage of LZ, VAN and FOS showed significant increase in post intervention period. Thus monitoring the optimal use of each antimicrobial agent, a comprehensive analysis, review, effective feedback and policy update are mandatory in all levels of healthcare settings. Therefore an effective integrated antimicrobial stewardship approach can be formulated to prevent AMR.

**Conflict of interest:** None

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