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Original Article

A 4-Year Prospective Study on Anti-fungal and Reserved Antimicrobial Drugs under Antimicrobial Stewardship Program

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ABSTRACT

Introduction: In 2018 and 2021, CIMS hospital conducted an audit to analyse the quality of antifungal use. We conducted a follow-up audit after four years of the antifungal stewardship programme (AFS) to evaluate the program's long-term effects. We assessed antifungal usage in Medical & surgical Patients receiving systemic antifungals using a pre-set score. Antibiotics and its classes designated as antimicrobial reserved products are intended to be used only in the treatment of confirmed or suspected infections caused by multidrug-resistant organisms. **Materials and Methods:** The research was conducted in a medical & surgical unit at tertiary care hospital during a four-year period. The sensitivity pattern was identified after the laboratory data were processed. Some of the newer AMs were labelled as "Reserve," requiring the completion of an authorization form prior to prescription. **Results:** Patients treated with antimicrobial drugs in medical and ICU wards were assessed. The results of both the audits revealed that there was a decrease in the irrational cases of both reserved antimicrobial and antifungal cases in successive years. The year 2020 showed fewer irrational cases of antifungals. **Conclusion:** With time the use of correct dosage regimen, proper route of administration and proper handling of patients has led to decrease in the irrational cases of antimicrobials.

Key words: Antibiotic, Antifungal, Audit, Reserved antimicrobial, Resistance.

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INTRODUCTION

Fungal infections are a constant and severe danger to human health, accounting for nearly 1.5 million fatalities each year globally.[1,2] Invasive candidiasis has a 30–40 percent death rate, disseminated cryptococcosis has a 20–30 % mortality rate, and invasive aspergillosis has a comparable proportion.[3,4] As a consequence of harsh treatments (e.g. anticancer chemotherapy, long-term corticosteroid treatment, or organ transplant) and immunosuppressive diseases like HIV/AIDS, these infections are extremely frequent in immunocompromised individuals. Antifungal agents' discovery is more difficult than antibacterial drug development as fungi are eukaryotes, and many putative therapeutic targets are also present in humans, posing a significant risk of host toxicity.[5]

Antibiotic resistance has reached a dangerously high level, acting as a global concern; microorganisms are evolving new defence mechanisms and propagating them across geographical locations and species, threatening decades of progress in treating common infectious diseases.[6,7] The development of resistant strains to currently available antifungal medicines has prompted extensive research into novel treatments that target the production of fungal lipids, proteins, and cell walls.[8] Antifungal resistance is a natural selection process in which organisms improve their capacity to live and thrive in the presence of a medication. Antimicrobial resistance is common in nature, and microorganisms develop different ways to fight antibiotic activity.

Antibiotic resistance is linked to longer hospital stays, higher treatment costs, and higher mortality and morbidity rates. In developing countries, the problem is significantly worse. In India and Nigeria, for example, about 19,400 and 56,500 infants died in 2012 due to serious antibiotic-resistant infections.[9] Antibiotic resistance also has a major adverse impact on the economy. If left untreated, it is predicted that the globe will pay annual costs of almost 1 trillion US dollars by 2030.

In recent years, the occurrence of systemic fungal infections has increased, with the greatest increases occurring in patients awaiting treatments and in ICUs (intensive care units).[10] The problem remains despite substantial progress in postoperative therapy, surgical procedure, and the rise of fungal infection. The broad use of antifungal prophylaxis for all patients for liver transplant does not appear to be warranted. Infection remains a severe problem despite the abundance of antifungal agents, as well as immunosuppressive and medicinal procedures.[11]The difficulties in managing infectious fungal infection (IFI) complicates antifungal stewardship (AFS). There is a growing number of high-risk immunocompromised patients, which, when paired with poor local diagnostics and a lack of prescriber awareness of infectious fungal infection, results in high rates of incorrect prescribing (25 to 75%).[12] Specialized action is possible as a result of this. Antifungal resistance becomes a growing challenge for human health and global food security, and stewardship may be able to assist.[13-14]

Several antibiotics are mostly kept for hospital settings, because of their economic effectiveness and to combat the increasing antibiotic resistance threat. In some situations, antibiotics reserved for hospital usage may be prescribed in outpatients for severe infections or when no other treatment options are available. These antibiotics are considered as reserved antibiotics.

MATERIALS AND METHODS

Study Setting

The research was conducted in a surgical ward with 350 beds in a tertiary care CIMS hospital.

Inclusion Criteria and Exclusion Area

Patients with microbial infections have been included in the study. Patients with various ailments were not allowed to participate in the trial.

Study Location

CIMS hospital, Gujarat.

Study Period

This study is based over a period of 4 years (from 2018 to 2021) for reserved antimicrobial audit and 4 years (from 2018 to 2021) for anti-fungal audit. During the study period, a retrospective prospective analysis of all the patients who were admitted to the surgical ward was performed. On a daily basis, the AMs prescribed, and the dosage were recorded. Daptomycin, Tigecycline, Collis tine, and Caspofungin were placed on restricted from use, and at the start of the trial, a «Reserve AM indent form» [Table 1] was implemented to see how it affected AM consumption.

Data Collection

The data was collected from a CIMS hospital by using an organised audit form that covered the patient's age, gender, type of condition, drug duration, and irrational drug use in the medical ward in which the patients were admitted during study. Reserved antimicrobial data and antifungal audit of medications prescribed to medical & surgical ward patients,frequency and mode of administration, antimicrobial prescription base,and re-dosing were gathered and evaluated.

RESULTS

Reserved Antimicrobial AuditReserved anti-microbial contains antibiotics and its classes which should be reserved for diagnosis of suspected or confirmed infections due to the organisms that are multi-drug-resistant. Reserve antibiotics should be considered "last resort" treatments that must be available, but their use must be limited to very particular patients and conditions when all other options have ended in failure. To sustain their effectiveness, these drugs could be conserved and prioritised as essential goals of international and national stewardship initiatives incorporating monitoring and utilisation reporting. Caspofungine, Collistine, Tigecycline, and Daptomycin are 4 antimicrobials or its classes that have been identified.

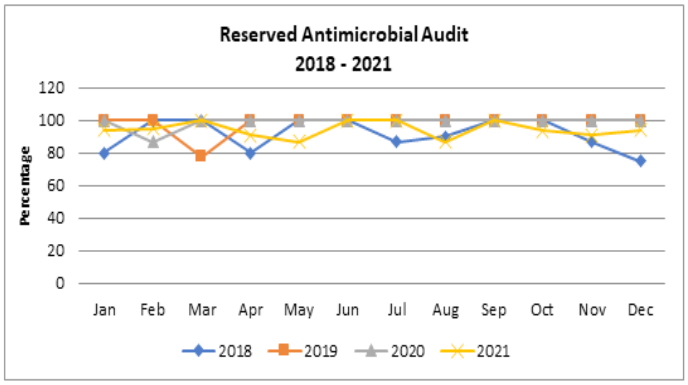
In the current study, the observation of 4-year reserved antimicrobial audit is represented in graph 1 from the year 2018 to 2021. As we saw

Table 1: **Reserve Antibiotic Indent form.**

List of reserved antibiotics:	Tigecycline, Caspofungine, Daptomycin, Collistine	
Name/Age of patient:		
IPID:	Ward:	Prescribing date:
Provisional Diagnosis:		
Probable infection site:	Bloodstream/ Respiratory/ Diabetes/ Urinary / hypertensive/ Any other	
Indication:	Culture based / Empirical / Prophylactic	
Antibiotic prescribed:		
Sign/Department-		

Table 2: **Reserved Antimicrobial Audit.**

Month	Year	Total cases	Reserved antimicrobial cases	Irrational
Jan	2018	440	10	2
	2019	450	15	0
	2020	462	19	0
	2021	472	17	1
Feb	2018	350	13	0
	2019	309	11	0
	2020	467	15	2
	2021	490	19	1
Mar	2018	392	7	0
	2019	412	9	2
	2020	494	12	0
	2021	464	9	0
Apr	2018	415	5	4
	2019	460	7	0
	2020	442	8	0
	2021	478	11	1
May	2018	316	10	0
	2019	312	9	0
	2020	363	11	0
	2021	386	15	0
Jun	2018	325	6	0
	2019	312	9	0
	2020	350	8	0
	2021	335	11	0
Jul	2018	325	15	2
	2019	410	6	0
	2020	343	6	0
	2021	392	16	0
Aug	2018	356	10	1
	2019	390	11	0
	2020	423	9	0
	2021	451	15	0
Sep	2018	399	7	0
	2019	359	4	0
	2020	398	5	0
	2021	375	9	0
Oct	2018	250	9	0
	2019	261	10	0
	2020	297	7	0
	2021	310	15	1
Nov	2018	297	15	2
	2019	378	12	0
	2020	438	13	0
	2021	406	11	1
Dec	2018	345	12	3
	2019	394	17	0
	2020	424	14	0
	2021	455	17	1



Graph 1: Represents the data of reserved antimicrobial audit from year 2018 to 2020.

in graph, there were increased usage of reserved antibiotics over the following successive years. In 2018, use of reserved antibiotic in surgical prophylaxis was found to be 91.52 % on average. By the end of 2019, the average surge to the value of 98.14%. In year 2020, the average remains around 98.88%. But in year 2021, a decline was observed in rational use of reserved antibiotic with an average of 96.51%.

The data (Table 4) indicates statistically no significant difference between the reserved antibiotic usagein 2019 (*p>0.05) as compared to 2018. In 2020, statistically significant difference can be observed (*p<0.05) in reserved antibiotic usage as compared to 2018 and in year 2021, a decline in rational use ofreserved antibiotic can be observed with statistically no significant difference as compared to 2018(*p>0.05).

Antifungal Audit

In CIMS hospital, a 4-year prospective audit of systemic antibiotic treatment was conducted to determine the pattern of use of systemic antifungal drugs. Patients undergoing surgery were given prophylactics, and data on the following parameters were recorded, as shown in Table 3, including the antifungal cases, irrational usage of antifungal treatment, and total case of surgery. Table 3 shows that, from 2018 to 2021, the use of a stewardship programme in term of antifungal prophylaxis increased both procedure outcomes and knowledge.

The data assessment of the antifungal surgical prophylaxis seen at the CIMS hospital is shown in graph 2. The data for the 4 years from 2018 to 2021 is visually presented. Antifungals were given in all surgical operations, and the majority of antifungals were given by IV in the post-operative period, according to the findings. The graph depicts a progressive rise in the rational use of antibiotics both before as well as during surgery. The use of antifungals in surgical prophylaxis was found to be 92.28 % on an average in 2018. This number was seen to be gradually growing throughout the years. By the end of the year, the average had jumped to 97.22 %. In year 2020, the average reduced to 97.10% and in year 2021 it remains around 97.07%. This is strong indication of antifungal usage becoming more rational over time. As may be seen in the graph, recent times have reached the highest peak. One of the key reasons in the systemic usage of antifungals might be this.

Graph 2: Represents the data of antifungal audit from year 2018 to 2021.

The data (Table 5) indicated statistically no significant difference between the antifungal usagein 2019 (*p>0.05) as a significant increase in the rational use can be observed as compared to 2018. In 2020 and 2021, rational antifungal usageremains constant as compared to 2018 with statistically no significant difference between them(*p>0.05).

Table 3: Antifungal Audit.

Month	Year	Total cases	Anti-fungal cases	Irrational
Jan	2018	450	29	3
	2019	462	32	0
	2020	443	39	2
	2021	471	31	1
Feb	2018	309	29	0
	2019	467	32	0
	2020	395	35	1
	2021	408	25	0
Mar	2018	412	15	0
	2019	494	19	0
	2020	446	17	3
	2021	391	21	1
Apr	2018	460	20	2
	2019	442	17	0
	2020	475	26	0
	2021	451	16	0
May	2018	312	5	0
	2019	363	9	2
	2020	329	9	0
	2021	412	11	1
Jun	2018	312	4	0
	2019	350	9	1
	2020	342	5	0
	2021	362	3	0
Jul	2018	410	14	3
	2019	343	13	0
	2020	395	18	0
	2021	382	11	0
Aug	2018	390	13	0
	2019	423	16	0
	2020	405	11	1
	2021	423	16	0
Sep	2018	359	10	1
	2019	398	12	0
	2020	364	9	0
	2021	417	18	1
Oct	2018	261	12	3
	2019	297	9	0
	2020	319	11	0
	2021	296	15	0
Nov	2018	378	13	0
	2019	438	15	0
	2020	385	12	0
	2021	428	19	0
Dec	2018	394	17	1
	2019	424	19	0
	2020	365	11	0
	2021	382	16	0

Table 4: **Paired Sample Test of Reserved Antimicrobial Audit 2018 – 2021.**

Paired Differences									
		Mean	Standard Deviation	Standard Mean Error	95% Confidence Interval of the Difference		t	d_f	Significance (2-tailed)
					Lower	Upper			
Pair 1	2018 - 2019	-6.62000	12.96223	3.74187	-14.85581	1.61581	-1.769	11	.105
Pair 2	2018 - 2020	-7.36083	11.31324	3.26585	-14.54893	-.17274	-2.254	11	.046
Pair 3	2018 - 2021	-4.98333	8.27737	2.38947	-10.24252	.27586	-2.086	11	.061

Table 5: **Paired Sample Test of Antifungal audit 2018 – 2021.**

Paired Differences									
		Mean	Standard Deviation	Standard Mean Error	95% Confidence Interval of the Difference		t	d_f	Significance (2-tailed)
					Lower	Upper			
Pair 1	2018 - 2019	-4.94250	12.96613	3.74300	-13.18079	3.29579	-1.320	11	.213
Pair 2	2018 - 2020	-4.82833	11.22500	3.24038	-11.96036	2.30369	-1.490	11	.164
Pair 3	2018 - 2021	-4.79333	10.56457	3.04973	-11.50574	1.91907	-1.572	11	.144

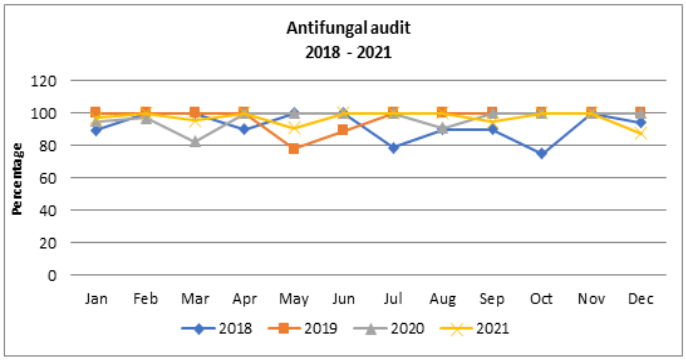
DISCUSSION

Antibiotics and antibiotic classes that should be reserved for the treatment of proven or suspected illnesses caused by multidrug-resistant organisms are classified as reserved antimicrobials.

Clinical auditing is used to enhance the quality of treatment. The best way to assess the quality of treatment is a point of contention. The two major methods are to look at either the process (for example, chosen elements of clinical management) or the result (for example, patient outcomes) (e.g., mortality or morbidity). The more complicated to assess is the outcome.[15-16] Individuals or small groups working in one or more hospitals or general practises produced most internal audit reports, which focused on procedure.[17] There seem to be no prior accounts of clinical audits conducted by a large group of physicians who provide a comprehensive clinical service to a health authority and specified community.

In this study we have focused on reserved antimicrobial audit and antifungal audit of the patients treating with antibiotic and antifungal drugs in medical and ICU wards. The antifungals were administered by IV route. The case notes of all patients receiving antibiotics and systemic antifungals were reviewed daily and the appropriateness of therapy was determined. The irrational cases were noted for all the 4 years. The findings revealed that in 2018 more irrational cases were seen in both the audits as compared to the number of irrational cases in 2019, 2020 and 2021. From 2019 to 2021, there was much decrease in the irrational cases of the drugs.

Using a multi-pronged strategy that includes post-prescription evaluation and feedback, teaching, and the creation of clinical guidelines, many institutions have effectively adopted antifungal stewardship initiatives. Over the course of six years, one research examined 636 prescriptions, 72 percent of which came from adult and paediatric hematology-oncology services.[18] The ASP gave input to the main teams on diagnostic tests,



Graph 2: Represents the data of antifungal audit from year 2018 to 2020.

TDM, and antifungal prescription, and found that ASP recommendations were followed with a high degree of compliance (88 percent). Patient outcomes were good in 47 of 63 (75%) cases of IA and 52 of 60 (87%) cases of IC, while antifungal costs were constant. Over the course of a year, second research looked at high-cost antifungals in 173 patients at a tertiary hospital.19 During the evaluation - 70 (78.7%) voriconazole, 45 (88.2%) micafungin, 3 (27.3%) caspofungin, and 78 (62.4%) liposomal amphotericin B prescriptions, the ASP offered clinical advise.

In patients with filamentous fungal infections, a comparable approach in Spain was able to show a substantial decrease in antifungal expenditures without an increase in the incidence of IFI or 12-month mortality.20 Shah et al. looked at the effect of antifungal susceptibility findings in 103 patients who had been given an echinocandin for candidemia; 89 of them were later discovered to have fluconazole-sensitive strains, but only 35 (39%) were changed to fluconazole.21 While antifungal susceptibility

testing is a useful tool, this research emphasises the necessity of combining AS interventions to get the best results.

CONCLUSION

Antibiotic and antifungal resistance is becoming more of a problem, whether owing to inherently resistant bacteria or strains with evolved resistance. Antimicrobial selections that are more effective and cost-effective enhance results and save expenses. In conclusion, we found a substantial shift in the use of antibiotics and antifungals in the hospital after four years of both reserved antimicrobial audit and antifungal audit, with an improvement in the optimum choice of medication, microbiological adjustment, and route of administration. As a result, the number of irrational cases has decreased in recent years. The result showed that in 2018, reserved antibiotic in surgical prophylaxis usage was found to be 91.52% on average which was increased in successive years. In 2019, average use of reserved antibiotic was found to be 98.14%. In 2020, it was 98.88% and in year 2021, it was 96.51%. Similarly, the use of antifungals in surgical prophylaxis was found to be 92.28% in 2018 and it was also increased with years with an average of 97.22% in 2019, 97.10% in 2020 and 97.07% in 2021.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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