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Implementation of Antimicrobial Stewardship Program During COVID-19 Era: Cost Effectiveness and Mortality Rates

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Abstract: The growing spread of antimicrobial resistance is a major problem on a global level that has provoked several health and government organizations to call for action to counteract the problem. The frequent misuse of antibiotics is prevalent within hospital settings, especially during the COVID-19 era. The introduction of antibiotic stewardship initiatives has demonstrated the capability to decrease both unwarranted antibiotic consumption and the prevalence of drug-resistant microbes. Educating individuals is a pivotal element of such programs. Nevertheless, the impact of educational efforts targeting appropriate antibiotic usage has yet to be thoroughly evaluated. Ibrahim Bin Hamad Obaidullah Hospital (IBHOH) and Old Geriatric Hospital (OGH) in Ras Al Khaimah, UAE, are 250-bed secondary hospitals managed by Emirates Health Services (EHS). We classify antimicrobial agents as "controlled" or "uncontrolled." Controlled agents require approval from an Infectious Diseases (ID) consultant and clinical pharmacist and a web-based antimicrobial control system is used for this purpose. The Antimicrobial Stewardship Program (ASP) was implemented starting in October 2021 the ASP team reviews cases based on the "5 Rs" principle, records their decisions in the hospital's Electronic Medical Record (EMR) and discontinues controlled antimicrobial medication if disapproved within 48 h. Uncontrolled agents do not require ID physician approval. The consumption of antibiotics during the Pre-implementation period (period 1) from 1 April 2021 to 30 September 2021 and the post-implementation period (period 2) from 1 October 2021 to 30 March 2022 was recorded. The need for individual informed consent was waived for this study as it was considered a surveillance activity. Statistical analysis involved the use of the student's t-test for parametric data and either the chi-square test or Fisher's exact test for nonparametric data, as deemed appropriate. Significance was established when the p-value was less than 0.05. These analyses were conducted using MedCalc® version 12.3.0, developed by MedCalc software in Mariakerke, Belgium. A total of 1583 patients were admitted in the pre-implementation period compared to 2718 patients admitted in the post-implementation period. During the pre-implementation period, 118 patients died compared to 103 patients who died in the post-implementation period. Compared with the pre-implementation period, there was a significant decrease of more than 69% in total antimicrobial consumption with a more than 75% reduction in controlled antibiotic consumption, specifically colistin, linezolid and meropenem. There was a significant reduction in patient mortality between the pre-implementation period and the post-implementation period ($p<0.0001$) A focused ASP program is effective in controlling the use of controlled antimicrobial agents, reducing hospital mortality. minimizing financial burden and promoting cost-effectiveness.

Keywords: Antimicrobial Stewardship, Antimicrobial Resistance, Controlled Antimicrobial Use, COVID-19

Introduction

Approximately 20-50% of antibiotic usage in acute care hospitals is considered inappropriate or unnecessary (Pollack and Srinivasan, 2014). Such improper use of antimicrobials has adverse effects on both patients and the wider community (Al-Tawfiq *et al*., 2015; Owens Jr, 2008). The misuse of antibiotics not only contributes to the rise of antibiotic resistance but also leads to increased healthcare expenses (Pollack and Srinivasan, 2014; MacDougall and Polk, 2005). Unfortunately, we are witnessing a significant surge in bacterial resistance, compounded by a decline in the number of new antibiotics being discovered and approved each year (Fishman *et al*., 2012; Boucher *et al*., 2009). As a solution, the Antimicrobial Stewardship Program (ASP) was created to ensure the appropriate utilization of antibiotics, decrease the overuse of antimicrobial agents and prevent the development of resistance (Owens Jr, 2008; MacDougall and Polk, 2005).

ASPs have gained increasing importance in recent years to optimize the usage of antimicrobials, ensuring adherence to guidelines and enhancing patient care. These programs have also demonstrated their effectiveness in reducing Antimicrobial Resistance (AMR) (Laxminarayan *et al*., 2013; Goff *et al*., 2017).

Since its emergence in late 2019, the advent of the new Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) has piqued the interest of medical professionals and researchers worldwide. The potential influence of this virus on Antimicrobial Resistance (AMR) has also been a topic of exploration. Recent studies conducted in the past couple of years have revealed that patients diagnosed with Coronavirus Disease (COVID-19) often receive antibiotic prescriptions, despite bacterial co-infections being relatively infrequent (Langford *et al*., 2021).

The primary aim of Antimicrobial Stewardship Programs (ASPs) is to counter the escalating threat of AMR by optimizing antibiotic usage. However, numerous established ASPs have been paused, diverting resources and personnel toward addressing the COVID-19 crisis (Tomczyk *et al*., 2021). In a survey carried out in the UK, more than 60% of participating institutions noted an adverse impact of COVID-19 on regular ASP operations, resulting in reduced stewardship rounds, multidisciplinary meetings and prevalence surveys.

Studies conducted in hospitals with hospitalized patients have provided evidence that ASPs can enhance compliance with antimicrobial guidelines and reduce the unnecessary use of antibiotics. This, in turn, has resulted in better patient outcomes and a decrease in both hospital-acquired infections and rates of AMR (Davey *et al*., 2013; Leuthner and Doern, 2013; Feinstein *et al*., 2017). The most effective strategies employed in ASPs include prospective audit and feedback, preauthorization and tailored treatment recommendations specific to each healthcare facility (Emberger *et al*., 2018).

According to surveillance on antimicrobial resistance in Abu Dhabi, United Arab Emirates (UAE), there is a significant prevalence of multidrug-resistant pathogens, which is accompanied by an upward trend in resistance rates (Al-Zarouni *et al*., 2007; Rotimi *et al*., 2008).

Recently, the UAE hospitals have implemented an ASP with the goal of enhancing the appropriate utilization of antimicrobial medications. The introduction of this program aims to improve patient health outcomes and mitigate the emergence of resistance (Khanem *et al*., 2012; Abu-Gharbieh and Fahmy, 2012; El Hassan *et al*., 2015; Alghamdi *et al*., 2018).

Hence, the current study was carried out in a secondary care hospital in Ras Al Khaimah to assess the implementation of its ASP and its effect on antibiotic consumption and patient outcomes.

Methods

Ibrahim Bin Hamad Obaidullah Hospital (IBHOH) and Old Geriatric Hospital (OGH) are 250 beds secondary hospitals. Both hospitals are under Emirates Health Services (EHS), in Ras Al Khaimah, UAE. During the period of the study, both hospitals were converted into referral centers in the northern Emirates zone for COVID-19 cases.

At IBHOH and OGH, antimicrobial agents are categorized as "controlled" or "uncontrolled." Controlled agents consist of certain types of cephalosporins (third- and fourth-generation), carbapenems, extended-spectrum penicillins, fluoroquinolones, glycopeptides, colistin, oxazolidinones (linezolid), tigecycline and daptomycin. Typically, the primary prescribers of these antimicrobial agents for admitted patients at IBHOH and OGH are the in-charge or on-duty residents.

For hospital-wide usage, prescribing any controlled antimicrobial agents necessitates permission from an Infectious Diseases (ID) consultant and clinical pharmacist. To facilitate this process, a web-based antimicrobial control system using a predesigned Google form was introduced in April 2019. Within this system, the ID physician and clinical pharmacist utilize the health information system to review the clinical and laboratory presentation, culture reports and images of each patient who is prescribed controlled antibiotics.

The ASP team engages in discussions regarding these cases and assesses the suitability of therapy for each individual case. The team defines appropriateness based on the "5 Rs" principle, which encompasses ensuring the right drug, the right indication, the right dose, the right frequency and the right duration of treatment. References used to determine appropriateness include practice guidelines from the Infectious Diseases Society of America (Pappas *et al*., 2009; Patterson *et al*., 2016; Baddour *et al*., 2015), international stewardship guidelines (Dellit *et al*., 2007) and standard treatment

recommendations for antimicrobial therapy (Leekha *et al*., 2011; Gilbert *et al*., 2017). The ASP team's decision will be recorded in the hospital's Electronic Medical Record (EMR) system.

In the event that a decision of disapproval is reached, the unit-dose delivery system will cease providing the antimicrobial medication after 48 h. The prescribing physician will be promptly informed to make adjustments to the prescription. No approval is required for the use of uncontrolled antimicrobial agents.

Outcomes

This retrospective study was planned to review the clinical records of all patients admitted to Ibrahim Bin Hamad Obaidullah Hospital (IBHOH) and Old Geriatric Hospital (OGH), RAK, UAE. The study duration will be divided into 2 periods (6 months each). Pre-implementation period (period 1) is from 1 April 2021 to 30 September 2021 and post post-implementation period (period 2) is from 1 October 2021 to 30 March 2022. The study included all patients who received at least one day of systemic antibiotics as empiric medication or therapeutic therapy during their hospitalization.

The primary outcome was the cost of consumption of all the controlled antimicrobials audited by the ASP team. Secondary outcomes included the overall hospital mortality during the study period.

Calculation of Antimicrobial Consumption

At the end of each month, the clinical pharmacist receives the consumption per unit for all medication dispensed through the PYXIS (automated dispensing cabinets). This system ensures that consumption is the real administered medications not only what was issued from the pharmacy. 2nd step, the clinical pharmacist filters the antimicrobial agents depending on the approved list by the ASP committee. In 3rd step, the final cost per consumption will be calculated according to the official price list per unit which comes monthly from the AX team (the team responsible for counting and stock management). Lastly, data will be reviewed by the ASP team before being announced to the hospital leaders, for data analysis and further modification in our practice.

Data Analysis

Student's t-test was used for statistical analysis for parametric data and either the chi-square test or Fisher's exact test was utilized for nonparametric data, as deemed appropriate. Significance was established when the p-value was less than 0.05. This data analysis was conducted using MedCalc® version 12.3.0, developed by MedCalc Software in Mariakerke, Belgium.

Ethical approval and consent to participate. The study was approved by the Ministry of Health and Prevention Research Ethics Committee/RAK subcommittee (MOHP/REC/2022/26-2022-F-M). Individual informed consent was waived for the conduct of this study by these committees as it was deemed a surveillance activity.

Results

A total number of 1583 patients was admitted in the pre-implementation period compared to 2718 patients admitted in the post-implementation period. During the pre-implementation period, 118 patients died compared to 103 patients who passed away in the post-implementation period. Monthly data is listed in Table 1.

Review of antibiotics usage prior to and after the ASP was done. The consumption data for the pre-ASP period and the post-ASP period were analyzed. A significant reduction of more than 69% in antimicrobial consumption was observed (Table 2) with more than 75% reduction in controlled antibiotic consumption specifically colistin, linezolid and meropenem.

There was a significant reduction in patient mortality between the pre-implementation period and post-implementation period ($p<0.0001$) (Table 3).

Imipenem, meropenem, carbapenems, fluoroquinolones and antifungal agent consumption have shown significant reduction within the 6 months of the ASP program Fig. 1(a-f).

Table 1: Monthly data for total patient admission, mortality and antimicrobial consumption

	Month	Total Admission (n)	Total mortality (n)	Antimicrobial consumption per month (AED)
Period 1	Apr-21	241	16	1256663
	May-21	242	7	1078129
	Jun-21	322	23	1627773
	Jul-21	234	33	2211046
	Aug-21	140	26	1153471
	Sep-21	404	13	7637520
	Total	1583	118	8090834
Period 2	Oct-21	389	14	6130720
	Nov-21	408	14	2462210
	Dec-21	397	13	2673020
	Jan-22	694	23	3652470
	Feb-22	429	23	4155510
	Mar-22	401	16	5715470
	Total	2718	103	2478941

Table 2: Comparison between antimicrobial consumption cost during the pre-implementation and post-implementation periods

	Period 1	Period 2	p-value
Antimicrobial consumption cost (AED)	1348472±506652	402341±152641	0.0198

Table 3: Comparison of patient mortality during the pre-implementation and post-implementation periods

	Discharged	Mortality	X	p-value
Pre-ASP period	1465	118		
Post-ASP period	2615	103	27.5	<0.0001

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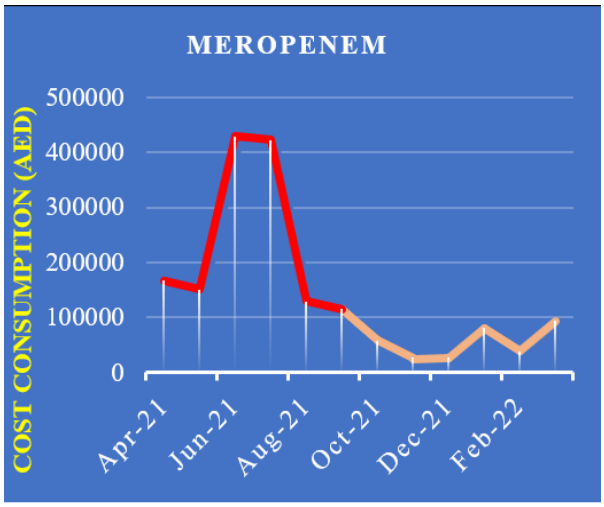
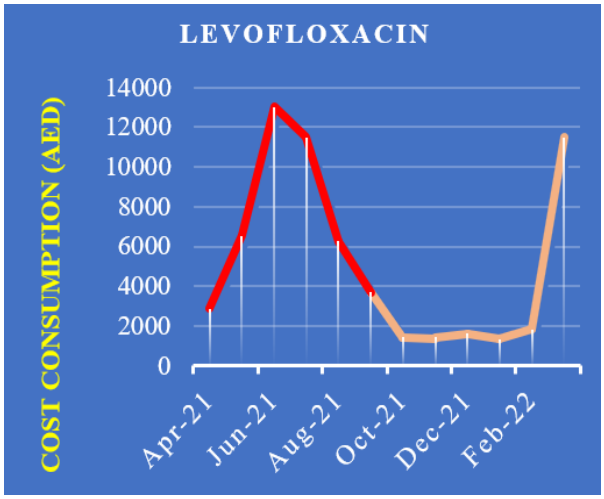


(a)



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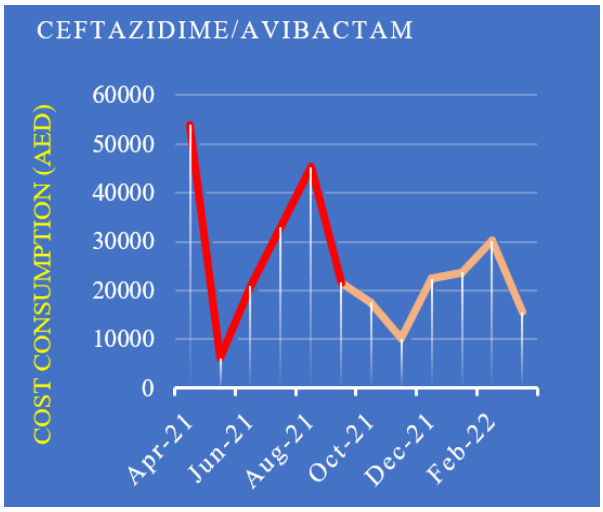

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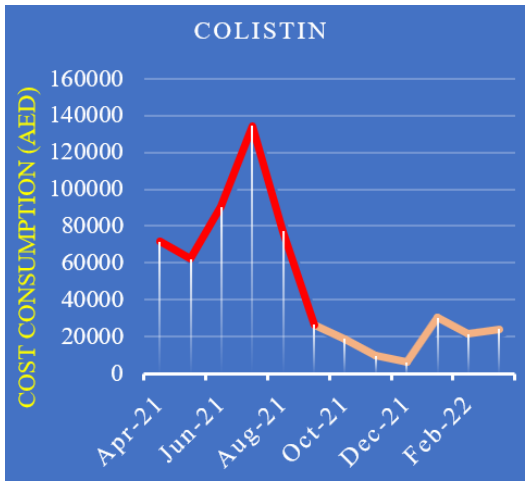

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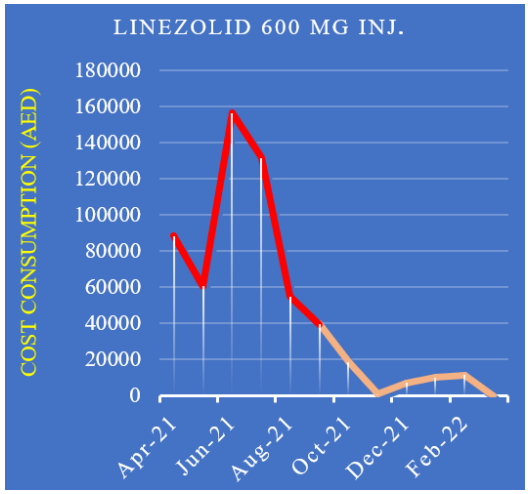

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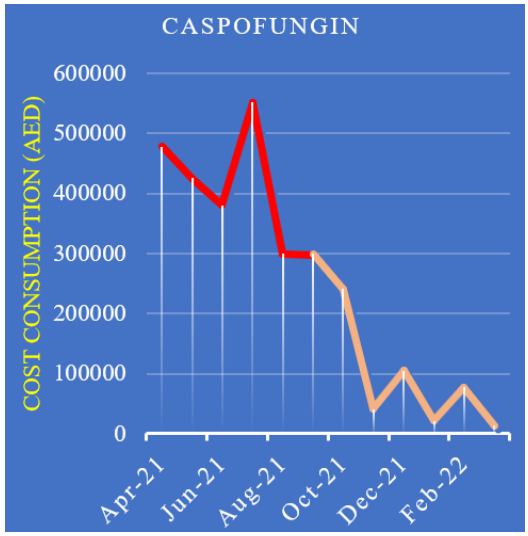

(f)

Fig. 1: Antimicrobial consumption rates within 6 months of ASP program

Discussion

In our study, we clearly demonstrated the effectiveness of the ASP program in reducing the overall use of antibiotics among inpatients and implementing restrictions on antimicrobial agents within a short timeframe. The available evidence indicates that an effective ASP necessitates a well-coordinated and interdisciplinary approach involving multiple measures. However, assessing the precise impact of each measure can be difficult because various control measures are implemented simultaneously. Moreover, differences in patient safety culture and prescribing practices among institutions can lead to variations between them. What might be successful in one institution could face challenges in another due to cultural disparities. As a result, institutions should embrace strategies with higher chances of success and implement cost-effective measures.

Theoretically, healthcare providers are supposed to adhere to local and international guidelines that promote both the efficacy of antibiotics and the risk of antimicrobial resistance while treating patients. In real-world clinical settings, practitioners often prioritize the immediate benefits of antimicrobial treatment over its potential to cause resistance (Metlay *et al*., 2002). When a patient's condition is unstable, they usually opt for antibiotics with a broad spectrum such as meropenem or imipenem and these are frequently continued unless microbiological studies clearly support a reduction in antibiotic intensity.

Education forms a crucial pillar for the success of an ASP (Tseng *et al*., 2012; Cisneros *et al*., 2014). A well-prepared educational initiative equips physicians with knowledge regarding antimicrobial use, drug resistance and the management of infectious diseases (Cisneros *et al*., 2014). It has been demonstrated that educational interventions can enhance prescribing skills, induce changes in prescribing patterns and assist prescribers in adhering to guidelines (Kamarudin *et al*., 2013). An institution-based educational training can incorporate regional data alongside country guidelines, promoting the use of antimicrobial therapies that align with the institution's specific needs and preferences (Hanberger *et al*., 2014). These programs can influence clinicians' prescription practices during patient evaluations, encouraging the selection of appropriate treatment regimens that align with stewardship strategies such as formula restriction and review processes.

At IBHOH and OGH, the ID physician held regular face-to-face meetings with the main prescribing clinicians to emphasize the importance of using controlled antimicrobial agents judiciously. These sessions are done using PowerPoint presentations. The objective was to guide clinicians in their thought process regarding the empirical use of antimicrobials, emphasizing the importance of not exclusively relying on antibiotics with a broad spectrum and promoting the effectiveness of the de-escalation strategy according to individual culture results. Educational approaches that encourage self-reflection, small-group learning and discussions have a higher likelihood of influencing behavioral changes (Stålsby Lundborg and Tamhankar, 2014).

However, our study has several limitations. First, the data collection was retrospective, conducted in IBHOH and OGH hospitals and involved a limited number of patients over a short duration. This restricted the capacity to evaluate the program's clinical and epidemiological influence. Furthermore, the analysis was unable to evaluate any changes in prescribing clinicians' behavior.

Conclusion

In conclusion, our research indicates that a concentrated ASP initiative aimed at primary prescribing clinicians effectively manages a particular category of antibiotics and reduces hospital mortality and infection rates, it is also cost-effective as we saved about 1.6 million USD within 6 months after applying for our program without increasing the mortality rate.

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Author’s Contribution

Safaa AlKhiami and Anass Qasem: Designed the study and wrote the manuscript with support.

Hussien Mohamed and Ali Abdalla: Collected the data.

All authors discussed the results and contributed to the final manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

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