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Original Research Article

Implementing an antibiotic cycle program to reduce antimicrobial resistance while optimizing antibiotic usage: a sobering experience from a tertiary care facility in northern Mumbai

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ABSTRACT

Background: The increase of antimicrobial resistance and the scarcity of new broad-spectrum antibiotics is a major challenge. Antibiotic cycling is one tactic that increases antibiotic homogeneity to the greatest extent possible and can aid in controlling resistance pattern, but this approach has not undergone a thorough evaluation. The study's objective was to examine the effects of an antibiotic cycling strategy on the antimicrobial susceptibility profile by avoiding and alternately using beta lactam/beta lactamase inhibitors over a period of many years.
Methods: During the four-year trial period, from January 2018 to December 2021, an antibiotic cycling protocol was applied for indoor patients. Piperacillin/tazobactam and cefoperazone/sulbactam were alternately rotated and withheld for the full year. Using the hospital's antibiogram as a guide, antibiotics were chosen for cycling. Data obtained from positive clinical cultures were used for preparing antibiogram.
Results: The general susceptibility profile of the most prevalent species remained stable or showed a minor increase in sensitivity. While piperacillin/tazobactam susceptibility failed to approach statistical significance, the antibiogram for cefoperazone/sulbactam indicated a 4% increase in susceptibility with a shift to the left of the minimum inhibitory concentration (MIC).
Conclusions: Antibiotic cycling is a controversial idea, yet it can be a successful technique to achieve either stability or a continuous decrease in resistance to a chosen antibiotic. Additionally, for meaningful outcomes, the antibiotic selected and the length of cycling must be in accordance with the hospital's antibiogram.

Keywords: Antibiotic cycling, Antimicrobial stewardship, Antimicrobial resistance, Cefoperazone, Piperacillin

INTRODUCTION

Antimicrobial resistance (AMR) has been a growing threat worldwide making the treatment of patients difficult, costly, or even impossible. Every year AMR kills about 700,000 people worldwide- a number that was predicted to reach upto10 million by 2050.[1] The impact is most obvious on vulnerable patients, resulting in prolonged illness and increased mortality. Even the economic impact of AMR is devastating. A loss of USD $100 trillion is estimated, and global GDP may decrease by 3.5%. The World Bank estimated that 28 million people are likely to be pushed into poverty as a direct consequence of disease due to resistant pathogens.[2] AMR has thus become a challenge to global development invoking its political dimensions.

As a response, antibiotic stewardship programs aimed to optimize the rational and prudent use of antibiotics. These programs attempt to control the antimicrobial resistance

by reducing overall antibiotic consumption but also to optimize the choice of the antibiotic, dosing and administration route.[3] Dependence on one class of antibiotic to treat an infection or a regional population, despite optimal dosing and duration of treatment allow selective pressure on organisms.

Hence, cycling or mixing antibiotics can be an important component from a population perspective of antimicrobial stewardship. Antibiotic cycling involves the planned removal of the antimicrobial in a specific unit with the intention of reintroducing that antimicrobial at a predetermined time in the future. The main purpose of cycling is to decrease the resistance to a particular antibiotic when that antibiotic is no longer used. In addition to restriction, annual rotation helps to alter the selective pressures and thus preventing emergence of resistance.[4] This is in contrast to mixing, whereby equal portions of a target population receive different antimicrobial agents at any given time.

Hence, the objective of the present study was to retrospectively analyse the antibiogram of common pathogenic organisms to determine the impact of scheduled change of antibiotic usage over the study period of four years.

METHODS

Study period and location

A retrospective interventional study was conducted at 250-bedded NABH accredited tertiary-care hospital located at Northern Mumbai, which caters population, form both urban and rural areas adjacent to Mumbai city.

Study was conducted for a period of four consecutive years from January 2018 to December 2021. Hospital has a well-planned infection control committee and robust infection control team with single pharmacy. All guidelines and protocols followed in hospital are as per NABH (national accreditation board for hospitals and healthcare providers) standards. Antibiotics cycling policy was planned as a part of antimicrobial stewardship programme. Based on hospital's antibiogram, most commonly used antibiotics with concerning rise in resistance were selected for rotation for a period of one year from January 2018. Two of the beta lactam/beta lactamase inhibitors namely cefoperazone/sulbactam and piperacillin/ tazobactam were withhold alternatively for complete one year (Table 1). All clinical samples from indoor patients with suspected infection received in microbiology laboratory were processed and antibiotic sensitivity testing done using automated Vitek2 compact system.

Results were reported according to Clinical and Laboratory Standards Institute methods.[5] Antibiograms of four years were prepared for analysis.

Table 1: The implementation of antibiotic cycling protocol during the four-year study period.

Year	Antibiotic on hold
2018	Cefoperazone/Sulbactam
2019	Piperacillin/Tazobactam
2020	Cefoperazone/Sulbactam
2021	Piperacillin/Tazobactam

Study source

Patients admitted in intensive care units (ICU) and indoor wards from January 2018 to December 2021, with suspected infection were the source for microbiological sampling. Audits for monitoring antibiotic usage were done by both active and passive surveillance methodology. Infection control nurse noted all non-compliances related to antibiotic cycling protocol and on the spot feedback were given to healthcare workers for correction and prevention. Notification from wards was given to pharmacy department whenever withhold antibiotic was prescribed by physicians. Approval for use of holiday antibiotic were given as per the indication and justification discussed with infection control team.

Inclusion criteria

All the patients admitted in the hospital with positive bacterial cultures, requiring antibiotic intervention were included in the study. Antibiotic cycling protocol was implemented for indoor patients only.

Exclusion criteria

Outdoor patients requiring antibiotic interventions and those admitted patients who did not require antibiotics were excluded from the study. Cycling protocol was not implemented for outdoor patient department.

Data collection tool and technique

All the indoor patients with positive bacterial culture reported in microbiology laboratory from January 2018 to December 2021 were recorded. Data was compiled in Microsoft excel software and analysis was done using excel tools. Trends in antibiotic sensitivity pattern were noted from antibiogram. The study was conducted with approval from institutional ethics committee.

RESULTS

Total 5382 isolates obtained from clinically significant samples during the study period of four years. The overall antibiotic susceptibility of cefoperazone/sulbactam and piperacillin/ tazobactam were noted (Figure 1). It was observed that cefoperazone/sulbactam showed 4% increase in susceptibility percentage. While no change observed in piperacillin/tazobactam. It did not reach statistically significant results.

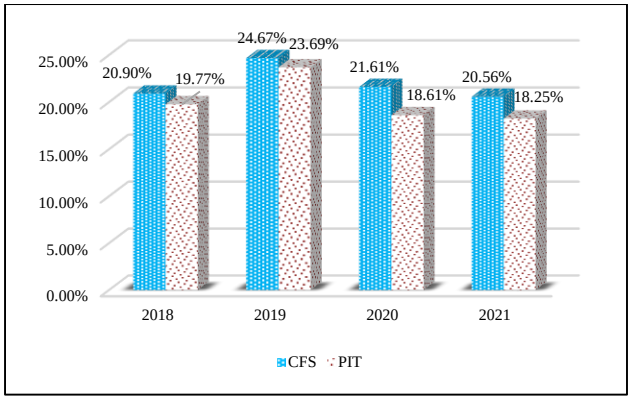

Figure 1: Trends of antimicrobial susceptibility pattern for beta lactam/beta lactamases over the study duration of four years.

While observing the distribution of MIC values for both antibiotics over the study period of four years, it was noted that cefoperazone/sulbactam showed leftward shift of MIC value from higher to lower concentration, while no such significant observation noted with piperacilln/tazobactam (Figures 2 and 3).

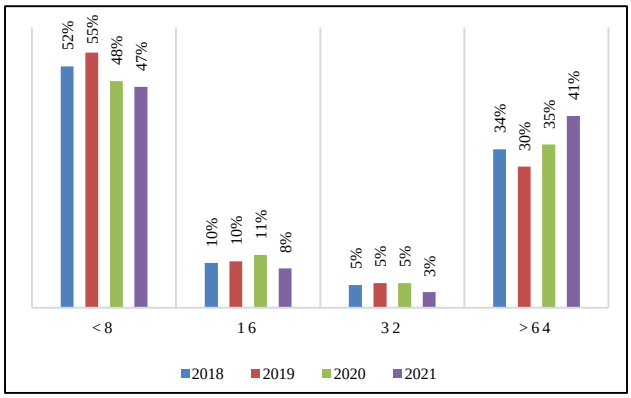

Figure 2: Distribution of MICs of cefoperazone/sulbactam over the study period of four years.

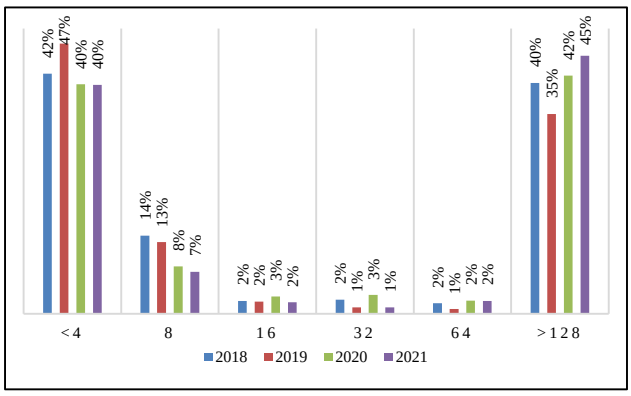

Figure 3: Distribution of MICs of piperacillin/tazobactam over the study period of four years.

DISCUSSION

The increasing incidence of infections caused by multidrug resistant organisms worldwide are associated with increased costs, morbidity and mortality.[6] The main factors for spread of antimicrobial resistance are irrational prescribing of antibiotics, patients not finishing their treatments, overuse of antibiotics in livestock and fish farming, poor infection control practices and poor sanitation.[7] Infection control policies are unlikely to prevent emergence of resistance, but they are quite essential to decrease the spread of antimicrobial resistant bacteria.

Besides effective infection control policies, second most effective component is antimicrobial stewardship. The strong selective pressure created due to excessive and inappropriate usage facilitate the emergence of resistance. Antimicrobial stewardship can help by optimizing the selection, dosage and duration of antimicrobial therapy.[8] Once antimicrobial stewardship has been optimized, potential antibiotic utilization strategies identified by national consensus guidelines can be developed, including restriction of antibiotics, combination therapy and antibiotic cycling.[9]

Hence, strategic plan is needed to combat the chain of events. Antibiotic cycling is one of the concepts that can be effective if implemented stringently for longer duration of time. Cycling aims to create maximum antibiotic homogeneity during consecutive periods that differs from antibiotic mixing which aims to create maximum antibiotic heterogeneity. The aim of the present study was to analyse the effect of antibiotic cycling protocol on antibiotic susceptibility pattern by withholding and rotating the usage of antibiotics.

In the present study, cefoperazone/sulbactam and piperacillin/tazobactam were used for antibiotic cycling protocol. Cefoperazone which is a third-generation cephalosporin with broad spectrum antimicrobial activity against gram-positive and gram-negative organisms, covers hospital acquired organisms too.[10] The combination with the beta lactamase inhibitor sulbactam has been used to treat various infections like hospital-acquired infections, febrile neutropenia, sepsis, intra-abdominal infections and gynecological infections.[11-13]

Similarly, piperacillin is an ureidopenicillin which was intended as an antipseudomonal antibiotic originally, now only available as an 8:1 combination with the β-lactamase inhibitor tazobactam. Tazobactam is a β-lactam sulphone that possess little intrinsic antibacterial activity itself, which has high affinity for many non-chromosomally mediated β-lactamases. The combination has a broad spectrum of activity against most gram-positive and gram-negative aerobic and anaerobic bacteria, including many β-lactamase producing bacteria.[14]

Present study showed that cefoperazone/sulbactam is having better result as compared to piperacillin/ tazobactam. It was noted that sensitivities remain steady throughout the study period with minor increase in susceptibility percentage. While observing the distribution of MIC values for both antibiotics, it was noted that cefoperazone/sulbactam showed leftward shift of MICs. Isolates showed shift of MICs from higher to lower side. On the other hand, no change observed in piperacillin/tazobactam, it did not reach statistical significance. It was observed that significant results for both antibiotics were lesser from the year 2020. One of the major reasons might be decrease in sample load due to COVID-19 pandemic and disproportionate usage of antibiotics universally. Hence, from the observation, it was concluded that cefoperazone/sulbactam is an ideal drug for cycling. Similarly, Guclu et al study showed that cefoperazone/sulbactam and piperacillin/tazobactam have equal effectivity and safety for the empirical treatment of Gram-negative nosocomial infections but cefoperazone/ sulbactam might be an appropriate alternative to piperacillin/tazobactam for antibiotic cycling or mixing strategy to reduce antibiotic resistance.[15]

Many studies had shown that antibiotic cycling proved to be effective in critical ill patients. Raymond et al study noted that rotation of empirical antibiotic therapy seems to be a promising method to reduce infectious mortality in an ICU.[16] Gruson et al study proved that rotation of antibiotics could help to avoid ventilator-associated pneumonia.[17] The study concluded that it could greatly improve the susceptibilities of the potentially antibiotic-resistant gram-negative bacilli responsible for late-onset ventilator-associated pneumonia. Similar observation given by Raineri et al that, despite global microbial flora not being affected, antibiotic rotation may reduce the incidence of VAP caused by antibiotic-resistant gram-negative bacteria in the ICU, such as *Pseudomonas aeruginosa* and its application may also improve antibiotic susceptibility.[18] Also, Bennett et al reported that implementation of an antibiotic rotation protocol in surgical ICU resulted in overall improvement in the antibiotic susceptibility profile of gram-negative microorganisms compared to medical intensive care unit, where such a protocol was not used.[19]

If antibiotic cycling and antibiotic mixing were compared, it was observed that a cycling programme is more effective against dual resistance compared with mixing.[20] In critically ill medical patients, a strategy of monthly rotation of anti-Pseudomonas beta-lactams and ciprofloxacin may perform better than a strategy of mixing in the acquisition of *P. aeruginosa* resistant to selected beta-lactams.[21]

As per the distribution of organisms concerned, cycling was associated with preserved antibiotic susceptibility among Gram-negatives, but not with gram positives.[22] Rotational usage practices are likely to be most appropriate for drugs active against gram-negative bacilli because of the wide choices available for rotation. Future availability of new agents that are active against resistant gram-positive organisms will present the opportunity to cycle these agents for example as vancomycin substitutes. Nevertheless, such strategies need careful monitoring of clinical outcomes and resistance. Multicenter controlled trials that follow carefully designed protocols are most likely to produce statistically significant and clinically meaningful results.[23]

However, there are many studies that showed negative observations related to antibiotic cycling protocol. Van Loon et al reported that cycling of homogeneous antibiotic exposure is unlikely to control the emergence of gram-negative antimicrobial resistance in intensive care units.[24] Other studies did not reach definite conclusions even using mathematical modeling.[25,26]

Present study suggested that implementing a cycling protocol, the susceptibility pattern remained either steady or improved. However, the limitation of antibiogram based guideline is that it does not provide unlimited duration of utility. The shifts in antibiotic usage will eventually lead to a change in resistance patterns. Thus, it is important to update antibiogram and antibiogram based guidelines on a regular basis. Moreover, cycling duration should be short in order to maintain the benefits associated with rapid cycling periods, but it should be long enough not to frustrate the prescribing practitioners. Studies performed more recently have used cycle durations of 1 to 4 months to achieve this balance, although the optimal duration is not known.

In present study, many hurdles were faced while implementing the policy in hospital but smooth collaboration between the clinicians, microbiologists, pharmacists and infection control officers helped to achieve the success. A healthy discussion has been shown to have a positive impact on changing prescribing patterns and compliance to antibiotic cycling policy in the hospital.

To conclude, antibiotic stewardship programs are considered important to reduce antibiotic resistance, but the effectiveness of strategies like, antibiotic cycling have not been determined rigorously. Significant results can be possible if cycling protocol is followed properly and appropriate surveillance strategies used to overcome the daily challenges.

Present study had some limitations that opens the door for further studies like different patient population and prescribing practices were not categorized. Hence, it's difficult to draw conclusion regarding merits of antibiotic cycling. In addition, it is important to study the pattern of antibiotic susceptibilities without antibiotic cycling too. Second, single center retrospective study without controlled comparison group was conducted. Hence, prospective studies are required. Third, microbiologic data and culture sites of origin were only derived from

antibiograms created from clinical cultures. It only reflects submitted specimens with potential to underestimate actual number of infections. Fourth, COVID-19 pandemic altered the antibiotic usage pattern of physicians that might affected the overall susceptibility pattern.

Besides all limitations in implemented strategies and suboptimal study designs, present study showed that cycling can be a successful strategy in stabilizing or decreasing resistance. Consequently, surveillance on the evolution of the resistance patterns and antibiotic consumption should be done.

CONCLUSION

Although antibiotic cycling is a subject of considerable criticism but it helps to achieve either sustained steady susceptibilities to the cycled antibiotics or improvement in susceptibility. Cycled antibiotics and its duration should be chosen based on hospital local antibiogram. Along with other infection control practices and monitoring the compliance to policy, notable differences observed. Though damage, which was done, cannot be reversed but experimentation with existing antibiotics can help to increase grip over progressive antibiotic resistance.

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