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REVIEW ARTICLE

ANTIMICROBIAL STEWARDSHIP PROGRAMMES

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ABSTRACT

Antimicrobial resistance (AMR) is an emerging public threat. There is a need to develop antimicrobial treatment guidelines, including a plan to reduce AMR at the community and hospital level. We present a literature review to study the strategies used and the effectiveness of antimicrobial stewardship programmes (ASPs). ASPs are cost-effective, reduce antimicrobial resistance, improve clinical outcomes, and alter prescribing behaviour without compromising short-term outcomes. They not only help reduce hospital stay but also the duration of antibiotic therapy thus leading to significant cost savings and reduction in infection by resistant organisms like *Clostridium difficile* and *Acinetobacter baumannii*. Prospective audit with intervention and feedback to physicians and restriction or prior approval of antibiotics are the two most effective strategies commonly used in most ASPs. Thus, ASPs lead to an overall reduction in the antimicrobial consumption.

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Introduction

Antimicrobial resistance (AMR) has caused immense harm to the health of the population thereby affecting global economy.[1] Four ways of fighting antimicrobial resistance could include preventing infections, tracking data on resistant organisms, antimicrobial stewardship programmes (ASPs) and developing new drugs and diagnostic tests.[2] Studies have shown an increasing trend in the development of resistance to commonly used antimicrobials in pathogens e.g. ciprofloxacin and fluoroquinolone resistant *Salmonella enteric serovar Typhi*, Methicillin resistant *Staphylococcus aureus* (MRSA), extended spectrum β-lactamase (ESBL) producing *Klebsiella pneumoniae*, multi-drug resistant (MDR) *Mycobacterium tuberculosis* among others.[3]

Antimicrobial stewardship programs (ASPs)

ASPs are programs that help in appropriate use of antimicrobials. Thus, they reduce the incidence of drug-resistance, improve outcome, and decrease the spread of MDR organisms. The core aspects of ASPs include multidisciplinary team meetings, antimicrobial policies with optimization of dose, rotation of antibiotic use to prevent resistance, antibiotic restriction policy and quick and safe conversion to oral antibiotics from parenteral antibiotics.[4,5] There are some strategies that could provide the basis for an ASP. These strategies can be used alone or in combination.

A)Prospective audit with intervention and feedback: A review of antimicrobial therapy by an infectious diseases (ID) physician or a clinical pharmacist with/without training in antimicrobial stewardship who is not a part of the treatment team with face to face interactions and feedback given to the treatment team, who can suggest changes to the antimicrobial prescription in comparison to hospital guidelines.

B)Preauthorization: Preauthorization requires obtaining approval prior to the use of certain antibiotics. This requires expertise and staff to complete the authorizations in time. This can optimize the initiation of antimicrobial therapy and avoid unnecessary use of antibiotics.

C)Facility-specific treatment guidelines can optimize and help establish recommendations for antimicrobial selection especially for common conditions such as community acquired pneumonias, urinary tract infections and surgical prophylaxis. These could be based on local antibiotic susceptibilities, patient mix, and drug formulary options available.[6]

A Cochrane review by Davey P et al[7] studied two broad interventions to improve antibiotic policy: restrictive/preauthorization techniques, which requires pre-approval and enables physicians optimize initiation of antibiotic therapy, and enablement techniques, which provides advice and feedback to physicians to optimize antibiotic therapy after it has been started. Evidence was found that interventions especially enabling techniques led to increased compliance with hospital antibiotic policy and a decrease in the duration of antibiotics and length of stay in hospital without increasing patient deaths. Both techniques were successful in achieving appropriate antibiotic stewardship although enablement techniques helped increase the effect of interventions including the restrictive techniques.

Effectiveness of ASPs

We discuss the evidence to show that ASPs are cost-effective, improve clinical outcomes, alter prescribing behaviour, and reduce antimicrobial resistance.

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Antimicrobial resistance

In a study done in Taiwan by Chang et al[8], an educational programme targeting the major prescribing clinicians was conducted and implemented for the use of imipenem, meropenem and glycopeptides. The programme resulted in a significant reduction in antibiotics consumption. The reduction in the total inpatient antibiotics was 13%, in carbapenems 29.8%, in imipenem and meropenem 34.9%, and in glycopeptides 27%, in the 3-month post educational and 6-month post-ASP period. The prescription of antibiotics for inpatients decreased significantly by 16.2%. Besides, the rate of carbapenem-resistant *Acinetobacter baumannii* reduced from 70.8% in the pre-ASP period to 29.6% in the post-ASP period. It showed that a focused educational program can significantly reduce the prescription of specific antibiotic classes. It also proves that ASPs have the potential to reduce antimicrobial resistance and alter physician prescribing behavior thereby reducing the incidence and cost of treating infections caused by MDR organisms.

Altering prescribing behavior and cost-effectiveness

In a study done by Malani AN et al[9], an ASP at community teaching hospital targeting 8 antimicrobials caused a 50% reduction in the chances of developing infection with *Clostridium difficile* infection (CDI). Besides the reduction in CDI, there was not only a 13.3% reduction in antimicrobial cost per patient day but also a 15.2% decrease in the antimicrobial budget and a 25.4% reduction in the daily doses of these antimicrobials. These 8 target antimicrobials were namely voriconazole, tigecycline, meropenem, linezolid, ertapenem, daptomycin, caspofungin and aztreonam. Thus, a community ASP can be made successful with limited but dedicated resources, such as a pharmacist and ID physician.

Clinical outcomes

In a systematic review and meta-analysis by Schuts et al[10], the following strategies were found most useful in ASPs - namely bedside consultation by an infectious disease physician (most useful in cases of bacteremia due to *Staphylococcus aureus*), use of preauthorization for a list of restricted antibiotics, conversion from intravenous to oral treatment, therapeutic drug monitoring, de-escalation of therapy and the use of guidelines based empirical therapy. These objectives showed significant benefit for one or more of the following patient outcomes – namely clinical outcomes, adverse events, costs, and bacterial resistance rates. Guideline – adherent empirical therapy and de-escalation reduced risk of mortality by 35% and 56% respectively. Restrictive antibiotic policies were associated with reduced rate of drug-resistance. These objectives can help guide hospitals stewardship teams to enhance the quality of antibiotic use.

Another systematic review by Kaki et al[11], to study the evidence for antimicrobial stewardship interventions in the intensive care unit (ICU), identified six intervention types: studies pertaining to antibiotic restriction or pre-authorization; infectious diseases physician consultation; implementation of de-escalation protocols; the use of guidelines for antibiotic prophylaxis or treatment in the ICU; reassessment of antibiotics used on a pre-specified day of therapy; as well as the implementation of computer assisted decision support. Stewardship interventions were associated with a total decrease in the use of anti-microbials, a lower antimicrobial cost to patients and shorter duration of antibiotic therapy. Besides these, inappropriate use of antibiotics decreased, and fewer adverse events were seen. Stewardship interventions when continued beyond the 6-month period showed a reduction in antimicrobial resistance rates. These interventions were not associated with an increase in nosocomial infection rates, length of stay or mortality. This review concluded that antimicrobial stewardship efforts are associated with improved use of antimicrobials especially in the intensive care unit, with improvement in the rates of antimicrobial resistance and adverse events without seeing a compromise in short-term clinical outcomes.

There is paucity of data studying the importance of ASPs in pediatric and neonatal intensive care units. However, Mukhopadhyay et al[12] have suggested that promising strategies do exist despite the challenges of implementing AMS in the premature infant. Some strategies could include stopping antibiotics after 36 hours of incubation of blood culture, using ampicillin and gentamicin for early onset sepsis, restricting the use of vancomycin in late-onset sepsis to avoid adverse events related to its use and using strategies to administer empirical antibiotics in culture negative infection in very low birth weight preterms.

Cost – effectiveness

Karanika et al[13] in their systematic review and meta-analysis found that implementation of ASPs caused a decrease in total antimicrobial consumption and the use of restricted antimicrobial agents by 19.1% and 26.6% respectively. Besides, in intensive care units, the antimicrobial consumption was reduced by 39.5%. The implementation of ASPs not only brought about a decrease in the use of broad spectrum antibiotics such as carbapenems and glycopeptides by 18.5% and 14.7% respectively but also a decrease in the overall antimicrobial cost by 33.9%, and the length of hospital stay. The implementation of ASPs led to a decrease in infections due to methicillin-resistant *Staphylococcus aureus*, imipenem-resistant *Pseudomonas aeruginosa* and extended-spectrum beta lactamase *Klebsiella spp.* Thus hospital ASPs not only resulted in an overall reduction in infections due to specific antimicrobial-resistant pathogens and length of hospital stay but also a significant decrease in antimicrobial consumption and cost, the benefit of which was seen more in the critical care setting.

Clostridium difficile infection

Antimicrobial stewardship intervention (ASi) should decrease healthcare-associated *C. difficile* infection (HA-CDI).[14] In a study conducted by DiDiodato and McArthur[14], ASi as a prospective audit and feedback done daily resulted in a significant reduction in the risk of *C. difficile* infection on the medicine wards as compared to the surgery wards, besides having an independent effect of overall reduction in antibiotic utilization. Most of the ASi consults resulted in discontinuation of antimicrobials especially the quinolones and

cephalosporins and the overall acceptance rate of ASi recommendation was 67.4%. This study shows us that a similar ASi along with hand hygiene practices could be implemented in most hospitals globally thus reducing unnecessary antimicrobial exposure, the risk of HA – CDI and antimicrobial resistance.

In a systematic review and meta-analysis by Baur et al[15] aimed to study the evidence of the effect of ASPs on the incidence of infection and colonization with antibiotic-resistant bacteria showed that ASPs helped reduce the incidence of infections and colonization with MDR gram negative bacteria by 51%, ESBL producing gram negative bacteria by 48%, MRSA by 37% and *C. difficile* infections by 32%. ASPs along with infection control measures such as hand-hygiene interventions were more effective than when implemented alone. The reduction in the incidence of infections and colonization with resistant bacteria and *C. difficile* infections was seen more in hemato-oncology patients. These results provide governments and hospital administrators, with the necessary evidence for implementing ASi such as antibiotic cycling, audits, and prospective feedback to reduce infections from antibiotic-resistant bacteria.

ASPs may prevent *C. difficile* infections by limiting exposure to certain classes of antibiotics. In a systematic review and meta-analysis by Feazel et al[16] restrictive ASPs (either prior approval or removal from pharmacy) of certain antibiotics such as cephalosporins or fluoroquinolones helped reduce the incidence of C. difficile infections especially in the geriatric population. Reduction in CDI incidence through restrictive ASPs can result in significant reduction in costs and increase savings for hospitals, insurers, and society.

In a study by Del Arco et al[17], compliance with the ASP intervention led to treatment optimization. This was attained by reducing the antibiotic spectrum and adjusting the dose, dosing interval and the duration of therapy. Overall, 93% of the treatment recommendations were accepted after the intervention period as compared to 89% before the intervention. Empirical antibiotic treatment evaluated fell from 46% to 31%. The main drugs assessed were imipenem/meropenem, cefepime, ertapenem, linezolid and aztreonam in that period. The use of these restricted antibiotics decreased from 37% to 21% in that time. The rate of imipenem sensitivity of the *P. aeruginosa* strains isolated increased by 10% and the strains of ESBL producing *K. pneumoniae* decreased by 13% over three years. Significant savings in annual costs were obtained. Thus, ASPs not only contribute to preventing antimicrobial resistance but also to the financial cost of antibiotic treatment.

ASPs prevent antimicrobial resistance and reduce the resistance of gram-negative bacilli thus leading to huge savings in cost of treating drug resistant infections.

Conclusion

We conclude that ASPs are cost-effective, reduce antimicrobial resistance, improve clinical outcomes, and alter prescribing behaviour without compromising short-term outcomes. They also help reduce length of hospital stay and duration of antibiotic therapy thus leading to significant cost savings and reduction in infection by resistant organisms like *C. difficile* and *A. baumannii*. Prospective audit with intervention and feedback worked well in most studies and restriction of antibiotics led to a reduction in *C. difficile* infection. These programmes led to an overall reduction in the antimicrobial consumption.

Compliance with Ethical Standards

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References:

1. Naylor NR, Zhu N, Hulscher M, Holmes A, Ahmad R, Robotham JV. Is antimicrobial stewardship cost-effective? A narrative review of the evidence. Clin Microbiol Infect. 2017;23:806-811.
2. Centers for Disease Control and Prevention, 2013. Antibiotic Resistance threats in the United States, 2013. [Online] Available at: https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf Accessed on 22nd February 2020.
3. Kumar SG, Adithan C, Harish BN, Sujatha S, Roy G, Malini A. Antimicrobial resistance in India: A review. J Nat Sci Biol Med. 2013;4:286-91.
4. Bertollo LG, Lutkemeyer DS, Levin AS. Are antimicrobial stewardship programs effective strategies for preventing antibiotic resistance? A systematic review. Am J Infect Control. 2018;46:824-836.
5. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159-77.
6. Centers for Disease Control and Prevention, 2019. The Core Elements of Hospital Antibiotic Stewardship Programs:2019. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. [Online] Available at https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf Accessed on 22nd February 2020.
7. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2:CD003543.
8. Chang YY, Chen HP, Lin CW, Tang JJ, Hsu TY, Weng YC, et al. Implementation and outcomes of an antimicrobial stewardship program: Effectiveness of education. J Chin Med Assoc. 2017;80:353-359.
9. Malani AN, Richards PG, Kapila S, Otto MH, Czerwinski J, Singal B. Clinical and economic outcomes from a community hospital's antimicrobial stewardship program. Am J Infect Control. 2013;41:145-8.
10. Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:847-856.
11. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother. 2011;66:1223-30.

12. Mukhopadhyay S, Sengupta S, Puopolo KM. Challenges and opportunities for antibiotic stewardship among preterm infants. Arch Dis Child Fetal Neonatal Ed. 2019;104:F327-F332.
13. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic Review and Meta-analysis of Clinical and Economic Outcomes from the Implementation of Hospital-Based Antimicrobial Stewardship Programs. Antimicrob Agents Chemother. 2016;60:4840-52.
14. DiDiodato G, McArthur L. Evaluating the Effectiveness of an Antimicrobial Stewardship Program on Reducing the Incidence Rate of Healthcare-Associated Clostridium difficile Infection: A Non-Randomized, Stepped Wedge, Single-Site, Observational Study. PLoS One. 2016;11:e0157671.
15. Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, Tacconelli E. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis. 2017;17:990-1001.
16. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. J Antimicrob Chemother. 2014;69:1748-54.
17. Del Arco A, Tortajada B, de la Torre J, Olalla J, Prada JL, Fernández F, et al. The impact of an antimicrobial stewardship programme on the use of antimicrobials and the evolution of drug resistance. Eur J Clin Microbiol Infect Dis. 2015;34:247-51.