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ANTIMICROBIAL STEWARDSHIP STRATEGY TO REDUCE LENGTH OF STAY AND COST OF ANTIBIOTIC CONSUMPTION: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Reducing the cost of care and length of stay for patient in hospital are important to monitor the benefits of implementing an antimicrobial management program. An antimicrobial management program is a strategy to decrease Antimicrobial Resistance (AMR) that affect to the treatment of the patient. One of the antimicrobial management programs is Antimicrobial Stewardship Programs (ASP). This study aims to determine the appropriate strategies in the application of Antimicrobial Stewardship Programs (ASP) that can reduce the length of stay and cost of antibiotic consumption for patient in hospital.

Methods: This study was a systematic review that used PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. Data obtained from Electronic databases ProQuest and Medline (PubMed) that published five years times span. By using keywords such as antimicrobial stewardship, antimicrobial resistance, length of stay, length of the hospital and patient cost to find the relevant journal.

Results: The search found 3,541 studies, of which 26 studies were included in the systematic review. After excluded the article review, there were 9 studies that used quasi-experimental, observational cohort studies and Randomized Control Trial (RCT). These studies conducted majority in Europe and USA, only 1 study that conducted in Asia. Analysis of the studies found out that 6 of 9 studies mentioned if ASP can reduce the length of stay of the patient in hospital. Only 3 of 9 studies that examined the effect of ASP in cost of care and these 3 studies mentioned ASP can reduce the cost of care.

Conclusion: This study showed that implementing ASP can reduced the length of stay and antibiotics consumption among patient in hospital by manage the antimicrobial use, conduct audits and feedback in an appropriate step, and intravenous to oral switch program.

Keywords: Antimicrobial stewardship, length of stay, cost of care

INTRODUCTION

Antimicrobial resistance (AMR) threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi. An increasing number of governments around the world are devoting efforts to a problem so serious that it threatens the achievements of modern medicine. A post-antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility for the 21st Century[1].

Antimicrobial stewardship Programs is a coordinated, quality improvement strategy designed to encourage the appropriate use of antimicrobial agents to optimize clinical outcomes while minimizing collateral antimicrobial effects. This can promote prudent, effective prescribing through optimization of antimicrobial selection, dosage, duration of treatment, and route of administration. The goals of antimicrobial stewardship are to achieve optimum clinical outcomes and to ensure cost- effectiveness and minimum unintended consequences, including toxic effects, selection of pathogenic organisms, and resistance. For several stewardship objectives, there is abundant, although low-quality, evidence on clinical outcomes, adverse events, costs, and resistance rates in hospitals [2].

Outcome measures for quality of care are increasingly used to monitor and compare hospital performance, to identify areas for improvement. Three outcome measures that are commonly used in various countries to evaluate the quality of care in hospitals are in-hospital mortality, readmissions, and long length of stay (LOS). Length of Stay as a clinical outcome is a potentially important measure of ASP effectiveness. LOS is an important factor in healthcare cost analysis. the speed of identification of disease-causing bacteria also affects the speed of clinical decision making which greatly affects the patient's LOS.

Antimicrobial Stewardship Programs (ASP) may require additional resources, such as hospital personnel and equipment, to be effective and be sustainable. As such, the upfront costs associated with these additional resources can be a potential barrier to individuals who have not yet implemented an ASP. With the growing importance of measuring the impact of ASP and health economic evaluations, there has been an increasing number of studies that have evaluated the clinical and economic impact of ASP in the last few years [3].

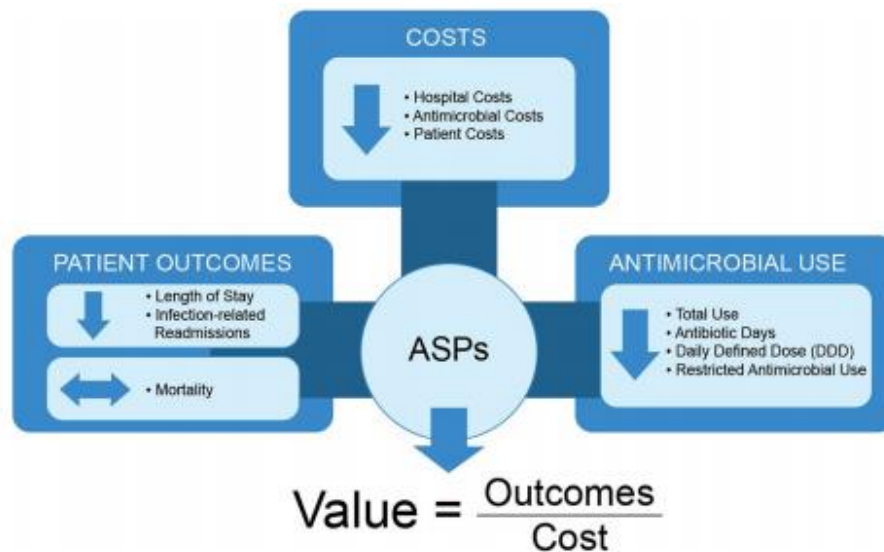


Figure 1. Conceptual value framework for implementation (Nathwani, 2019)

An ASP aims to improve antibiotic prescribing, minimize harm, reduce antibiotic resistance and HCAI, and promote cost-effective prescribing. Outcomes from the interventions generally fell into three categories: antibiotic use, patient outcomes, and economic outcomes. To improve patient outcomes and safety and to reduce AMR and healthcare costs by promoting the judicious use of antibiotics. Some core elements identified in successful ASP include leadership commitment, prescriber accountability, drug expertise and education of clinicians and patients, among other [4,5]. There has been an increasing number of studies that have evaluated the clinical and economic impact of ASP in the last few years [4]. Operational costs were

defined as the total direct hospital costs associated with patient treatment for bacterial infection, typically including costs associated with Length of Stay, diagnostics, and treatment. A few studies also measured costs associated with human resources. All included studies measured costs from the hospital perspective and reported either total hospital costs or per patient costs both pre- and post-intervention [5].

METHOD

This systematic review follows the recommendations by the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. We searched using an electronic database, such as Proquest and Pubmed database published not more than five years. The included studies were broadly classified as reporting on study experimental, study cohort, which can be comparing clinical outcomes before and after the intervention. Research conducted in the various regions of the world but the selected article is mostly in developing countries because they are highly exposed to an impact on the incidence of antimicrobial resistance (AMR).

Based on the search with keyword Antimicrobial Stewardship and Length of stay results obtained as many as 3541 articles (3252 articles from Proquest and 289 articles from Pubmed) that are considered to be following the objectives of the study. Some of the keywords or Medical Subject Heading (MeSH) terms used in the search were: "Antimicrobial Stewardship," "Antimicrobial resistance," "length of stay," length of the hospital ", "patient cost,". Then we carried out screening from full-text articles in English, Scholarly Journals and published not more than 5 years, from 2014 to 2019, whether the title of the article is the same or not. After screening there were 782 articles, then screening again the based method of research, There are 26 articles that eligible for the study. Furthermore, 9 articles were included in supplemental searching. In parallel to the updated search, and seventeen articles contain article review and protocol study are excluded. We worked to synthesize the quantitative results of all these 9 studies (Fig. 2). A total of nine articles that we have studied, six of them were quasi-experimental before-after studies. the other articles are observational cohort studies, two articles and the other are a randomized controlled trial. The majority of the studies analyzed were conducted in Europe (55%), in the USA (33%) and 1 study was conducted in Asia. Most of the study implemented at the hospital of the university hospital affiliated with the university.

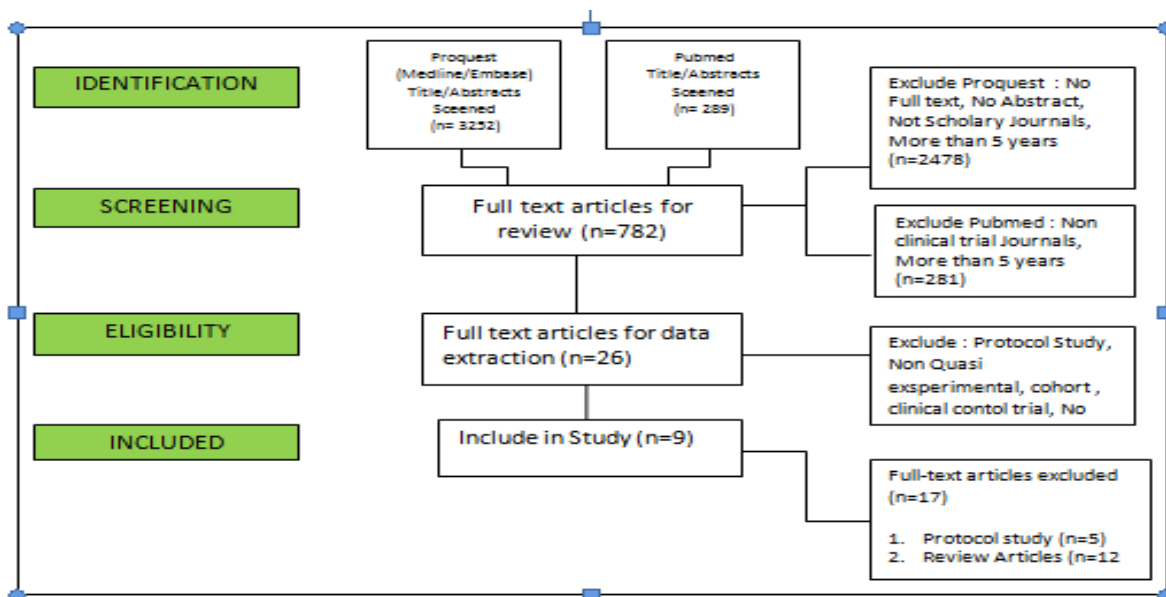


Figure 2. Chart of the research method

RESULTS

A total of nine articles that we have studied, six of them were quasi-experimental before-after studies and the other articles are observational cohort studies, two articles and the other are a randomized controlled trial. The majority of the studies analyzed were conducted in Europe (55%), in the USA (33%) and 1 study was conducted in Asia. Most of the study implemented at the hospital of the university hospital affiliated with the university.

Reducing Inappropriate antimicrobial use

Reducing inappropriate antimicrobial usage is the key to stewardship. Several methods of reducing inappropriate antimicrobial use have been suggested, including preventing the initiation of or stopping unnecessary treatment, restricting durations to the shortest effective course, and reducing the use of broad-spectrum antimicrobials [17].

Implementation Antimicrobial Stewardship Programs with audit and feedback by the team regularly for every patient admitted obtained result that Median of LOS is a shorter 1Day Post- (5days, IQR3 – 8vs. 4, IQR 2 – 7; $p < 0.001$). The time for LOS significantly shorter post-ASP (HR 1.18, 95% CI 1.09 – 1.27). The 30-day repeated was significantly higher post-ASP (HR 1.24, 95% CI 1.08 -1,42). The total cost of antimicrobial use decreased by 14% pre-to post-ASP, with a decrease of 5.3% means antimicrobial cost/1000PD ($P = 0.5$). The cost of consumption for fluoroquinolones decreased 29% pre-to post-ASP ($P < 0.05$). IV (-4.2%), digestion (-7.6%), and broad-spectrum (-9.5%) Cost all decreases non-significant [6].

At the study of the relationship between adherence to national antibiotic guidelines and mortality, re-admission and length of stay in inpatient hospitals in Norway multicentre, there was a trend towards shorter LOS when guideline-compliance treatment was prescribed at the start of treatment (40,47 days, $p = 0.087$) SHR 1.17, 95% CI (1.02, 1.34), $p = 0.025$). These results are supported by competing for risk analysis of LOS in which the adherent group is associated with a 17% increase in discharge rates, compared with the non-adherent group [8].

Audit and feedback

Intervention conducted on research about antibiotic utilization was Feedback every morning from ASP Pharmacist to the physician after the pharmacist reviewed the patient's medical record or by phone if it needs to follow up immediately. Of the 16 antibiotics that meet these criteria in the surgical ward, all except Amoxicillin/clavulanic acid, Cefazolin, and ceftriaxone show decreased utilization during the intervention period. Of the 18 antibiotics that meet the criteria in the respiratory wards, a minor increase in utilization is observed for amoxicillin, amoxicillin/Clavulanic acid, Ampicillin, azithromycin, Cefazolin, Ceftazidime, and Cephalexin. The utilization of 11 other antibiotics decreased after PAAF initiation. Of 16 antibiotics in a medical ward, utilization increased for amoxicillin/clavulanic acid, ceftriaxone, and cephalexin, while the use of all other antibiotics showed a decrease [7].

Study about the benefits of a combination of rapid diagnostic tests and an active re-evaluation of antibiotic therapy 72 hours after the onset of bloodstream infection (BSI) shows that re-evaluation at 72 hours correlated with more days of optimal therapy on total duration, as well as the rate of starting optimal therapy within 24 h [$p < 0.0001$, analysis of variance (ANOVA)]. The total duration of antibiotic therapy decreased in the third study period ($p = 0.002$, ANOVA) and LOS was significantly shorter in the third study period ($p = 0.04$, ANOVA) compared to the first or second study periods (mean 2 days and 5 days, respectively). Both 15and 30-day mortality was similar among the three study periods ($p = 0.90$) [14].

Intravenous to oral switch program

Switching to an oral agent can reduce the need for intravenous devices, which can pose a risk of catheter-related blood flow infections. Early replacement also reduces the complexity of care and can (for soft and respiratory tissue infections) so that it can have an impact on saving drug procurement costs and treatment time without affecting clinical care. For the transition to be effective and safe, oral agents must have good bioavailability and are known to be effective against identified or suspected pathogens. It must be able to reach the right concentration at the site of infection and should not be used where there is a lack of evidence for indication. Besides, patients must respond to their initial therapy without worrying about malabsorption [17].

In this review, The study comprised two cohorts: the prospective cohort to assess the effectiveness of a sequential intravenous-to-oral antibiotic switch algorithm and early discharge, and the retrospective cohort group that patients who had been prescribed IV treatment with glycopeptides, lipopeptides, or linezolid for more than 72 h who did not change to oral antibiotics daily microbiology and/or pharmacy antibiotic reports were used to identify potential candidates for inclusion among hospitalized patients with a confirmed gram-positive infection. intravenous-to-oral antibiotic. switch therapy was defined as a switch occurring within 5 days after the start of IV therapy., the result The duration of hospitalization was significantly shorter in the prospective cohort compared to the retrospective group that did not switch to oral drugs (16.7 ± 18.7 vs 23 ± 13.4 days, $P < 0.001$).

Title (Year)	Authors	Setting	Intervention	Comparators	Outcome	Study Design
1 Impact to Prospective Audit and Feedback Antimicrobial Stewardship Program at a Veterans Affairs Medical Center: A Six-Point Assessment (2016)	Haley J.Morrill, Aisling R. Caffrey, Melissa M. Gaitanis, Kerry.LaPlante	Providence Veterans Affairs Medical Center (PVACM), teaching hospital licensed for 119 beds.In September 2012,	Antimicrobial Treatment guidelines Implementation Antimicrobial Stewardship Programs, audit and feedback by the team regularly for every patient admitted	Standard treatment without ASP	The median LOS was 1day shorter post-ASP (5days, IQR3–8vs. 4, IQR 2–7;p<0.001). In unadjusted analysis, time to discharge (LOS) was significantly shorter post-ASP HR 1.18, 95%CI 1.09–1.27). Total antimicrobial costs decreased 14%pre-to post-ASP, with anon-significant 5.3% decrease in mean antimicrobial costs/1000PD(p=0.5). length of stay did not change significantly following the introduction of PAAF	quasi-experimental study (before-after)
2 Every antibiotic, every day: Maximizing the impact of prospective audit and feedback on total antibiotic use (2016)	<u>Campbell, Tonya J;</u> <u>Decloe, Melissa;</u> <u>Gill, Suzanne;</u> <u>Ho, Grace;</u> <u>McCready, Janine;</u>	Michael Garron Hospital (MGH), a 490-bed urban community teaching hospital in Toronto, Ontario, Canada.	Feedback every morning from ASP Pharmacist to the physician after pharmacist reviewed the patient's medical record or by phone if it needs to follow up immediately	Standard ASP treatment without Prospective audit feedback (PAAF)	On the surgical wards, daily antibiotic costs were reduced by 35% from \$5.64 to \$3.66 per patient day (p<0.001). on the respiratory ward, Costs decreased from \$9.40 to \$5.51 per patient day following PAAF, representing a 41% reduction (p<0.001 on the medical wards, antibiotic costs declined from \$3.35 to \$2.17 per patient day, indicating a 35% decrease (p<0.001).	Quasi-experimental (before-after)

Title (Year)	Authors	Setting	Intervention	Comparators	Outcome	Study Design
3 The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study (2019)	Jannicke Slettli Wathne, Stig Harthug Lars Kåre Selland Kleppe, Hege Salvesen Blix, Roy M. Nilsen, Esmita Charani and Ingrid Smith	three emergency care and teaching hospitals in Western Norway [6]. Hospital A and B are tertiary care hospitals with 1100 and 600 beds, respectively. Hospital C is a secondary care hospital with 160 beds	antibiotic guidelines	Standard treatment without antibiotic guidelines	LOS analysis, there was a trend towards shorter LOS when guideline-adherent treatment was prescribed at treatment onset (-0.47days, p =0.087)	observational cohort studies

Title (Year)	Authors	Setting	Intervention	Comparators	Outcome	Study Design
4 Comparison of Prior Authorization and Prospective Audit with Feedback for Antimicrobial Stewardship (2014)	Jimish M. Mehta, PharmD, MSCE1, Kevin Haynes, PharmD, MSCE2, E. Paul Wileyto, PhD2, Jeffrey S. Gerber, MD, Ph.D., MSCE3, Daniel R. Timko, PharmD, BCPS4, Steven C. Morgan, PharmD, et al	Hospital of the University of Pennsylvania, a 776-bed tertiary care academic medical center in Philadelphia	Formulary restriction with prior authorization and prospective audit with feedback to prescribers. Reviews conducted by the ASP to recommend changes in agent selection, dosing, or duration of therapy.	ASP without the strategy. use of select agents after approval from an ASP team member	increased LOS by 1.94 days/1,000-PD (P = .016 and .004) Antibiotic consumption increase	Quasi-experimental study (before-after)

Title (Year)	Authors	Setting	Intervention	Comparators	Outcome	Study Design
5 Postprescription review improves in-hospital antibiotic use- A multicenter randomized controlled trial (2015)	P. Lesprit, A de Pontfarcy, M.Esposito-Farese, H.Ferrand, J.L Mainardi, M. Lafaurir, P Parise, C. Rioux, F. Tubach and J.C Lucet	Total 246 patient (123 control and 123 patient get the intervention) from Four University-affiliated hospitals in Paris. Two surgical or medical wards per hospital which have a high-level antibiotic consumption.	Systematic post-prescription review performs by ASP Infection disease physician on day 1 and day 3-4.	ASP infection Disease Physician performed no systematic post-prescription review	The median time of hospitalization was 4,0 days (IQR 2,0 – 6,0 days) Median total cost per patient decreased from €1646 (IQR €114,6 – €3986) to €1626 (IQR €90,7 - €3967) The difference was not significantly different between control and intervention	A multicenter randomized controlled trial

Title (Year)	Authors	Setting	Intervention	Comparators	Outcome	Study Design
6 Effectiveness of sequential intravenous-to-oral antibiotic switch therapy in hospitalized patients with Gram-positive infection: the SEQUENCE cohort study (2016)	D. Rodriguez-Pardo, C. Pigrau, D. Company, V. Diaz-Brito, L. Morata, I. C. de Diego, L. Sorlí, S. Ifimie, R. Pérez-Vidal, G. García-Pardo, T. Larrainzar-Coghen, B. Almirante	115 in the perspective and 132 in the retrospective cohort. Forty-five retrospective patients (34 %) were not changed to oral antibiotics, and 87 (66 %) were changed to oral antibiotics without following the proposed algorithm.	The study comprised two cohorts: the prospective cohort to assess the effectiveness of a sequential intravenous-to-oral antibiotic switch algorithm and early discharge, daily microbiology and/or pharmacy antibiotic reports were used to identify potential candidates for inclusion among hospitalized patients with a confirmed gram-positive infection. intravenous-to-oral antibiotic. switch therapy was defined as a switch occurring within 5 days after the start of IV therapy.	retrospective cohort group that patients who had been prescribed IV treatment with glycopeptides, lipopeptides, or linezolid for more than 72 h who did not change to oral antibiotics	The duration of hospitalization was significantly shorter in the prospective cohort compared to the retrospective group that did not switch to oral drugs (16.7 ± 18.7 vs 23 ± 13.4 days, P < 0.001).	a prospective cohort with a retrospective historical comparison cohort study

Title (Year)	Authors	Setting	Intervention	Comparators	Outcome	Study Design
7 Antimicrobial stewardship program (ASP): an effective implementing technique for the therapy efficiency of meropenem and vancomycin antibiotics in Iranian pediatric patients (2019)	Aliakbar Rahbarimanesh, Sayed Yousef Mojtahedi, Payman Sadeghi, Maryam Ghodsi, Sara Kianfar, et al	135 children in Children's Hospital affiliated to the University of Medical Science	ASP team including specialist physicians and pharmacists in infectious diseases.	Standard treatment without ASP	Decreasing Length of stay from 22,7 ±1,9 to 15,6 ± 2,8 days (p=0,015)	quasi-experimental study
8 Effects of clinical pathway implementation on antibiotic prescriptions for pediatric community-acquired pneumonia (2018)	<u>Donà, Daniele;</u> <u>Zingarella, Silvia;</u> <u>Gastaldi, Andrea;</u> <u>Lundin, Rebecca;</u> <u>Perilongo, Giorgio;</u> et al	120 pre- and 86 post-intervention Pediatric Emergency Departement of the Department for Women and Children Health at Padua University Hospital Italy	implemented a Clinical Pathway (CP) for Community-Acquired Pneumonia	Standard treatment and ASP Clinical Pathway	no statistical difference in length of therapy (median LOT from 11 pre-CP to 10 post-CP, p = 0.06).	quasi-experimental study (before-after)

Title (Year)	Authors	Setting	Intervention	Comparators	Outcome	Study Design
9 A 72-h intervention for improvement of the rate of optimal antibiotic therapy in patients with bloodstream infections	R. Murri, F. Taccari, T. Spanu, T. D'Inzeo, I. Mastrososa, F. Giovannenze, G. Scoppettuolo, G. Ventura, C. Palazzolo, M. Camici, S. Lardo, B. Fiori, M. Sanguinetti, R. Cauda, M. Fantoni	1100-bed university hospital in Rome, Italy	A bedside Infectious Disease Consultancy (study period 1). (study period 2). (study period 3)	UDCI was called by a ward physician when patients had positive blood cultures (study period 1).	LOS was significantly shorter in the third study period (days) 24.2 ± 20.7 from 29.7 ± 29.3 in the first study ($p = 0.04$)	prospective, single-center, pre-post quasi-experimental study

DISCUSSION

Reducing inappropriate antimicrobial usage is the key to stewardship. Several methods of reducing inappropriate antimicrobial use have been suggested, including preventing the initiation of or stopping unnecessary treatment, restricting durations to the shortest effective course, and reducing the use of broad-spectrum antimicrobials [17].

Length of Stay as a clinical outcome is a potentially important measure of ASP effectiveness. LOS is an important factor in healthcare cost analysis. The speed of identification of disease-causing bacteria also affects the speed of clinical decision making which greatly affects the patient's LOS. The evolving field of rapid diagnostics has set the stage for a period of intense progress in antimicrobial de-escalation (ADE) strategies. ADE is a strategy that aims to change a broad spectrum antimicrobial to narrow the spectrum of therapy and minimize the patient's exposure to antimicrobials as soon as clinically possible [14]. The benefits associated with de-escalation have indicated decreased costs, low risk of adverse drug events, and less selective pressure for resistance and superinfections [15].

On the other hand in this review also found results at one tertiary hospital in Philadelphia, where formulary restrictions with prior authorization and prospective audits with feedback to prescriptions were carried out, reviews have been conducted by ASP to recommend changes in agent selection, dosage, or duration of therapy, but the results of LOS increase of 1.94 days / 1,000-PD ($P = 0.016$ and 0.004) increased antibiotic consumption. There are several potential limitations for the study. First, process steps, such as antimicrobial use, are considered inadequate when ASP is used without intervention because these results do not show direct clinical benefit. Standard and validated clinical indicators have not been established in this study. substantial knowledge gaps in management research. Another important limitation is that the influence of factors other than ASP changes cannot be fully excluded. During the 4 years of this study, changes in patient demographics, levels of bacterial resistance, or hospital characteristics can have an impact on the pattern of antimicrobial use [9].

A significant reduction in antibiotic consumption also can highly promote patients' satisfaction and their expectations by decreasing medical costs and long-term disability for patients. Although the present research was limited by its quasi-experimental design, the obtained results in pediatric patients along with the evaluation of care quality can be verified by conducting further studies with larger sample size and multi-center sampling. Furthermore, the efficiency and satisfaction with the available ASP may potentially improve the therapy optimization by incorporating a prospective audit-and-feedback intervention [12]. The availability of services with sufficient capacity to take on stewardship activities, such as diagnostics, on-site microbiology laboratories, medical infection specialists, and clinical pharmacy services, will have a significant impact on which strategies are chosen and implemented [17]

This systematic review investigating Implementation Antimicrobial Stewardship Programs, and how to optimizing patient outcome in LOS. Prospective audit and feedback have the potential to improve antimicrobial use and outcomes. Several studies could not establish a significant impact on LOS. A longer study is needed which is divided into several periods after the application of ASP and a combination of strategies to strengthen the control of antimicrobial use. No significant LOS or an increase in LOS indicates that the application of ASP alone is insufficient. Regular audits and feedback should be done to improving the rate of optimal antibiotics therapy as reported in research Murri, at all, where a significant decrease in LOS after the audit was conducted at 72 hours after the first therapy of antibiotics, to increase [14]. The interventions include the publishing of antibiotic guidelines for hospitals that do not have yet, publishing clinical pathways, conduct audits and feedback regular by the ASP team, discuss and consultation with the ASP team consisting of clinical pharmacists, microbiologists, and physician, restrict antibiotic use and conducted a review of the selection, dosage, and duration of therapy.

CONCLUSION

From this study, we know that implementation guidelines for Antimicrobial Stewardship can be a strategic policy to reduce health care cost. Most of the study found that involving health care team, especially clinical pharmacists, microbiologist and physician can result better outcome. The strategy to decrease Antimicrobial Resistance (AMR) is how to manage antimicrobial use, conduct audits and feedback in an appropriate steps, discuss and consult with a strong and trained team, immediately identify the causative bacteria, select selective antimicrobials, a the right dosage and duration of use of appropriate antibiotics Continuous training is required for the ASP team to make more significant results of implementation guidelines.

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