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EXPERT OPINION

Antimicrobial stewardship programs – cost-minimizing or cost-effective?

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Antimicrobial stewardship programs (ASPs) are aimed to improve patient care and health care outcomes. It is encouraging to find ASP interventions to be cost-saving in many cost-minimization analyses in literature. Nevertheless, the cost-effectiveness of ASP interventions, measured in cost per quality-adjusted life-years, is less well-established. This Editorial aims to explore the barriers in assessing clinical effectiveness of ASPs and provide suggestions to conduct cost-effectiveness analysis of ASPs.

Keywords: antimicrobial stewardship program, cost-effective, cost-minimizing, mult-drug resistance

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1. Introduction

Resistance is an inevitable consequence of antimicrobial usage. However, inappropriate and excessive antimicrobial use promotes this further. Antimicrobial misuse or overuse is a leading cause of antimicrobial resistance development. Antimicrobial stewardship programs (ASPs) are aimed to improve patient care and health care outcomes through two titers of impact. Immediate impact on patient care is achieved by optimizing antimicrobial therapy in antimicrobial selection, dosing, route of administration and duration of therapy, and as a result, reducing the unintended consequence of antimicrobial treatments, such as drug toxicity and *Clostridium difficile* colitis. The long-term impact is to prevent or restrain antimicrobial resistance by reducing antimicrobial misuse.

Infectious Disease Society of America (IDSA) recommends a multi-disciplinary antimicrobial stewardship team including an infectious disease physician, a clinical pharmacist with infection diseases training, a clinical microbiologist, an information system specialist, an infection control professional, and a hospital epidemiologist. The core active antimicrobial stewardship strategies should include the prospective monitoring of antimicrobial use with direct feedback, and formulary restriction and preauthorization requirements for target agents, while education, clinical guidelines and pathways and intravenous (i.v.)-to-oral (PO) switch are suggested as supplemental strategies [1].

2. Effectiveness assessment

Despite the well acceptance of ASP as a routine measure of quality improvement, the effectiveness of ASPs is often less well qualified or quantified for a few reasons. Multiple interventions are usually included in the ASP, making it difficult to assess one specific intervention. The types of ASP interventions often aimed at the prescribers to change prescribing behaviors and are therefore limiting the feasibility to conduct randomized controlled trials when ASP implementation is system-wide change of practice. Outcome assessment in the pre- and post-ASP implementation periods becomes the most commonly employed study design. Most reported

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findings in ASP outcome studies established association, not definite causality, between ASP activities and the index outcome parameters.

Unlike other treatment programs or strategies, the clinical impact of ASPs extends beyond the patients receiving ASP interventions to prevention of future multi-drug resistant bacterial infections through curbing antimicrobial resistance. To capture the full clinical effectiveness of ASP interventions on the change of infection rate for multi-drug resistant nosocomial bacteria would require the support of long-term surveillance data as well as a control group without ASP [2].

The target antimicrobial agents covered by the ASPs are mostly broad-spectrum agents and/or costly agents (also typically with broad spectrum of coverage), such as carbapenems, floroquinolones, agents against methicillin-resistant *Staphylococcus aureus*, broad-spectrum cephalosporins and beta-lactams, and antifungals [2-4]. In reality, most of ASP interventions are reacted to or flagged up by the primary physicians' orders of target antimicrobial agents, and the interventions are mostly to reduce unnecessary overuse of broad-spectrum agents. The process goals of the ASP are therefore changing the use of a target agent to another spectrum-appropriate agent without compromising the clinical outcomes such as mortality rate and readmission rate [2,3,5-7]. Incidence of *C. difficile* colitis has been frequently assessed as an indicator of unintended consequence of antimicrobial misuse or overuse [2,3].

3. Economic assessment

IDSA suggested that an effective ASP can be financially self-supporting [1]. Many cost analyses of ASP in literature lately were conducted using the approach of cost-minimization analysis [8] that costs of alternatives (with and without ASP) with no therapeutic difference in clinical outcomes are compared. The economic outcomes of ASP primarily focused on the change of drug budget as a result of reduced use of target antimicrobial agents while the clinical quality indicators shifted to the safety of ASP interventions that ASP did not associate significant change in mortality and readmission [3,5-7]. The findings all supported that ASPs are cost-minimizing. Recent literature further encourages the use of supplemental strategies such as i.v.-to-PO switch and therapeutic substitution. These interventions are considered as low-hanging fruit because they require fewer resources and less effort and potentially result in early success of substantial cost-savings [9]. On the other hand, very limited outcome research on ASP was conducted in the approach of cost-effectiveness analysis in which cost and quality-adjusted life-years (QALYs) gained are the primary outcome measures [8].

4. Expert opinion

It is encouraging to find ASP interventions to be cost-saving or cost-minimizing in current literature and it provides financial incentive for healthcare administrators to support the implementation or substantiation of ASP interventions. Nevertheless, the intended aims of ASPs to improve patient care and health care outcomes (other than economic outcome) still require quantification.

The challenge of assessing cost-effectiveness of ASP mainly stems from the unique scope of clinical impact of ASP that extended from the intervened cases to the prevention of future infections caused by multi-drug resistant pathogens. It is difficult in assessing the short-term and long-term benefits of ASP in a single study, plus the study design was limited by the system-wide program implementation to make it infeasible to conduct randomized, controlled trials. In addition, the lack of qualified research clinicians also presents a challenge to design and conduct appropriate studies in most ASPs outside of academic settings.

Decision analytical model might be the most practicable option to assess cost-effectiveness of ASP interventions. It has been used widely to evaluate short-term and long-term outcomes of various clinical scenarios such as anticoagulation management for stroke prevention, testing and treatment strategies for influenza infection, screening programs of multi-drug resistant bacteria for the prevention of nosocomial infection [10-12]. Through the incorporation of expected consequences during the course of antimicrobial treatment with and without ASP interventions, both expected cost and clinical outcomes could be mathematically simulated under the pre-described assumptions. Influential factors affecting the cost-effectiveness of ASP could also be identified by decision analysis. One study reported using a decision analytic model to compare the costs and clinical outcome of bacteremic patients receiving treatment with or without ASP consult, and the cost per QALY gained was found to be favorable for ASP intervention [13].

The clinicians who have participated in ASPs would agree that the ASP interventions benefit patients by more than cost-savings in antimicrobial cost. The economic benefits of ASPs are well-established and the future outcome research of ASP should extend to quantification both short-term and long-term economic as well as clinical benefits of ASPs.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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