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State of the Science Review

Are antimicrobial stewardship programs effective strategies for preventing antibiotic resistance? A systematic review

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Antimicrobial stewardship
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Background: Antimicrobial stewardship programs (ASPs) have been proposed as a solution for the global burden of antibiotic resistance, despite the lack of evidence on the subject.
Objective: To analyze the role of ASPs in reducing bacterial resistance to antibiotics in hospital settings.
Data sources: A review in PubMed, Scopus, LILACS, and SciELO databases was performed. The period analyzed was January 1, 2012-January 4, 2017.
Eligibility criteria: Studies that related ASPs to bacterial resistance.
Data extraction: All studies that did not focus on ASPs were removed. Antifungal and antiviral programs were excluded.
Results: Only 8 studies had quasi-experimental designs, and none were controlled trials. ASP strategies and microorganism-antibiotic pairs evaluated varied widely. Seven studies were classified as presenting clearly positive results, 3 had limited positive results, 7 had doubtful results, 4 had negative results, and 5 had noninterpretable results. The implementation of new infection control practices occurred in 7 studies.
Limitations: There are yet few studies on this matter, and most of them have inadequate study designs. Great heterogeneity between study features was detrimental to drawing evidence-based conclusions.
Conclusions: There is no solid evidence that ASPs are effective in reducing antibiotic resistance in hospital settings. We uphold the need for more studies with appropriate study designs, standardized ASP interventions targeting common microorganism-antibiotic pairs, and avoiding simultaneous implementation of infection control practices.

The antibiotic era began in 1923 with the discovery of penicillin by Alexander Fleming. Antimicrobial resistance was already a problem of global public health in the 1940s, a few years after the introduction of antibiotics into clinical practice. The World Health Organization, together with member states and collaborators, produced in 2014 for the first time a document that portrays the exact magnitude of the situation concerning bacterial resistance in the world.[1] The study clearly states that resistance to common bacteria has reached alarming levels. According to the World Health Organization report, groups of key antibiotics no longer work for half of the patients in several countries: carbapenems, which are administered to treat infections caused by *Klebsiella pneumoniae*, and fluoroquinolones, indicated for treatment of urinary infections, have been proven ineffective against pathogens in >50% of patients.[1] The emergence of antimicrobial resistance is a threat to public health.[2,3]

Behind this scenario lies the extraordinary genetic ability of these microorganisms. A wide range of biochemical and physiologic mechanisms may be involved in the development of bacterial resistance,[4] and the lack of knowledge about the complex relationship between pathogen exposure to drugs and the development of resistance justifies the few advances in resistance prevention and control. The most obvious and probably most costly example regarding public health (morbidity and mortality) concerns bacteria. In 2009, databases[5] listed >20,000 potential resistance genes of 400 different types.

The development of bacterial resistance to antimicrobial agents is triggered by the selection of resistant organisms[6] during individual or populational antibiotic-based treatments.[7-9] Another form of contact of individuals with resistant species is through agriculture: because antibiotics are used as growth supplements in livestock,[2,10] resistant bacteria of these animals may reach consumers through consumed animal products.[10]

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To reduce the selective pressure that favors highly resistant pathogens, a set of structured programs have been globally implemented in medical settings. Antimicrobial stewardship programs (ASPs) are coordinated programs aimed at promoting the appropriate use of antimicrobials, improving patient outcomes, reducing the emergence of antimicrobial resistance, and decreasing the spread of infections caused by multidrug-resistant organisms.[11-16] ASPs include a wide variety of strategies: multidisciplinary groups, medical education on antimicrobial prescription, antibiotic cycling, restriction of antibiotic use, combining therapies, dose optimization, and conversion of parenteral administration to oral administration are among the main elements considered.[11-16]

ASPs are not based on consolidated scientific evidence, and their widespread adherence is in part because of the financial savings provided by the policy of restricting the prescription of drugs.[11-16] Although many attempts to associate antibiotic consumption and acquisition of resistance by organisms have been made, the results are inconsistent. This association is not uniform among all antibiotic-microorganism pairs.[17,18]

OBJECTIVE

Aiming to analyze the role of the strategies grouped under the definition of ASPs in reducing the emergence of bacterial resistance to antibiotics in hospital settings, this review article tries to answer the question, “Do we have enough evidence to state that ASPs are effective strategies for preventing antibiotic resistance?”

METHODS

Information sources and search strategy

We performed a literature search in Scopus, PubMed, LILACS, and SciELO databases from January 1, 2012-January 4, 2017. We used the following combined terms for the searching strategy, adapted to each database specific syntax: (“antimicrobial stewardship” OR “antibiotic stewardship”) AND (“antibiotic resistance” OR “antimicrobial resistance”). Only studies with humans and in English were included. We only obtained articles that clearly stated antimicrobial stewardship programs/ASPs. We did not include articles that performed programs or interventions that could be grouped under that definition but were not characterized by the authors as an ASP.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram showing the flow of information through the different phases of this systematic review is shown in **Figure 1**.

Study selection

The number of records identified through database searching included only those results whose titles were relevant to the article, that is, titles that related stewardship programs to bacterial resistance. Studies with titles that did not suggest a focus on ASPs or described antifungal or antiviral programs were excluded. Review articles were not included in the analysis. In the screening phase,

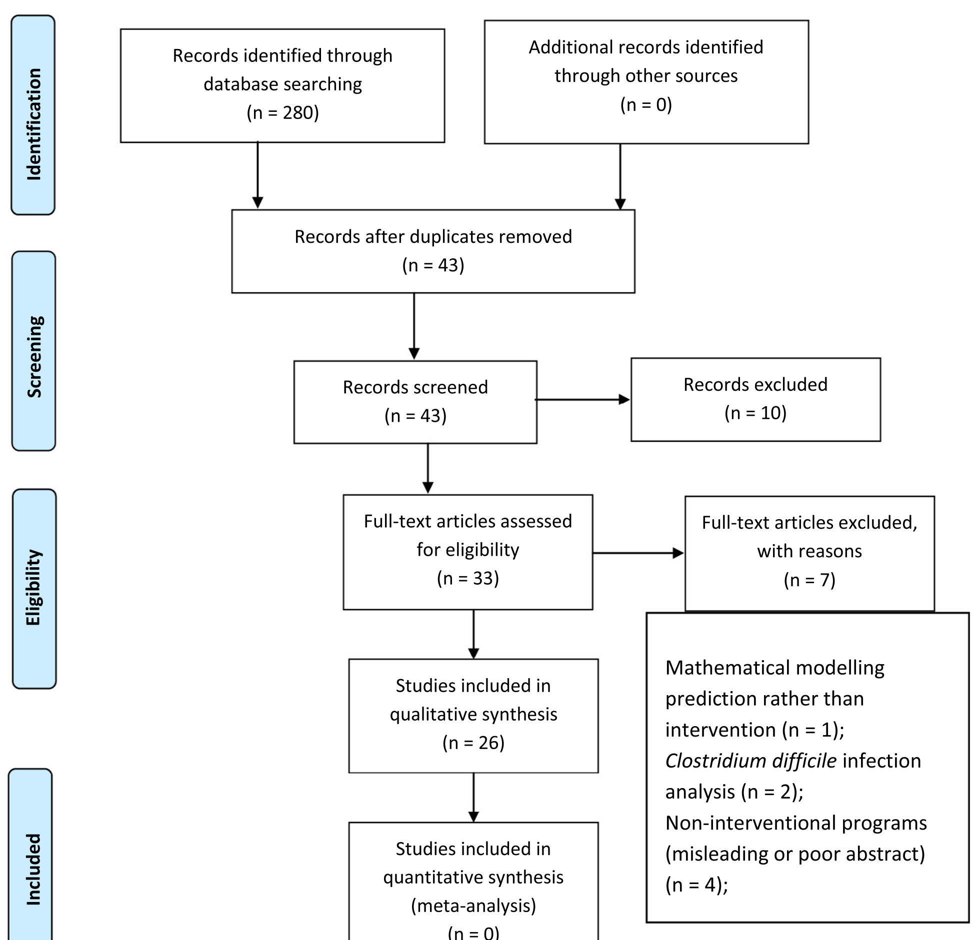

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flowchart of article selection for analysis.