Systematic review

Antimicrobial stewardship programs in emergency departments: how do we measure antimicrobial use? A systematic review

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ABSTRACT

Objectives. The implementation of antimicrobial stewardship programs (ASPs) has become a usual practice in hospital settings. However, the method for monitoring antimicrobial use in accident and emergency departments (ED) is not yet adequately defined. Thus, the objective of this review is to describe antimicrobial use indicators used by ASPs implemented in ED.

Material and methods. A systematic review was performed based on studies found in the following academic research databases: MEDLINE, EMBASE, Web of Science, and Scopus (Period: January 2000 to December 2019). Controlled clinical trials, before-and-after studies, interrupted time series, and repeated measures studies assessing the impact of ASPs on antimicrobial use in ED were included; studies published in languages other than English or Spanish were excluded from this review.

Results. Twenty-six studies met the inclusion criteria and were included in this systematic review. In total, 15 (62.5%) studies described the ASP team members who collaborated with the ED staff. Most (21; 80.8%) studies used the percentage of patients with an antibiotic prescription as an indicator. Four (15.4%) studies included defined daily dose data. The antibiotic treatment duration was reported in four (15.4%) studies. Only two studies assessed the impact of the ASP using microbiological indicators, both of which used the incidence of infection with Clostridioides difficile as the indicator.

Conclusions. The reports of experiences in implementing ASPs in ED show heterogeneous antimicrobial use indicators, which makes it difficult to compare results. Therefore, antimicrobial use indicators for ASPs must be standardised between hospital units.

Key words: Antimicrobial stewardship; antibiotic, emergency care, infection

Programas de optimización de uso de antimicrobianos en los servicios de urgencias: ¿cómo medimos el uso de antimicrobianos?
Una revisión sistemática

RESUMEN

Objetivos. La implementación de programas de optimización de antimicrobianos (PROA) se ha convertido en una práctica asistencial habitual en el medio hospitalario. No obstante, la metodología para monitorear el uso de antimicrobianos en los servicios de urgencias no están aún adecuadamente definidas. El objetivo de esta revisión es describir los indicadores de uso de antimicrobianos utilizados por los programas PROA implantados en los servicios de Urgencias.

Material y métodos. Se realizó una revisión sistemática en base a los resultados obtenidos en las siguientes bases bibliográficas: MEDLINE, EMBASE, Web of Science y Scopus. El periodo de búsqueda abarcó desde Enero de 2000 a Diciembre de 2019. Se incluyeron ensayos clínicos controlados, estudios antes-después, estudios de series de tiempo interrumpida y los estudios de medidas repetidas que evaluaron las intervenciones de los programas PROA en los servicios de urgencias sobre el impacto del consumo de antimicrobianos. Se excluyeron los estudios publicados en otros idiomas además del inglés o español.

Resultados. 26 estudios cumplieron los criterios y se incluyeron en la revisión sistemática. En 15 (62,5%) de los estudios incluyeron en su descripción los componentes del equipo PROA que colaboraron junto con el del equipo de urgencias.

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INTRODUCTION

The increase in antibiotic resistance observed in recent decades has had a significant effect on healthcare systems worldwide [1]. Infections caused by multiresistant microorganisms are associated with higher mortality and longer hospital stay, as well as with a significant increase in healthcare costs [2]. Excessive or inappropriate antimicrobial use is known to have helped generate and perpetuate these multi-resistant strains [3]. Therefore, in recent decades, antimicrobial stewardship programs (ASP) have become a priority for health authorities to minimise the expansion and number of infections caused by multi-resistant bacteria [4,5].

The application of ASPs in hospital settings has reduced antimicrobial consumption and improved the clinical outcomes of patients [6], albeit with a still unknown impact on resistance reduction [7,8] and the implementation of these programs is strongly recommended by various scientific societies [9-13].

Most experiences of such programs described in the literature thus far have focused on hospitalised patients, particularly critically ill patients, and more recently on primary care settings [6]. Emergency departments (ED) are one of the most important services where these programs can be implemented as they are the site of prescription of the first doses of antibiotics in hospitals and of a large number of antibiotics for patients discharged directly to their homes or other healthcare centres. Although the guidelines for the implementation of ASPs recognise that ED are the preferred sites for these programs, the participation of multidisciplinary teams in these hospital units is still low [14]. In turn, the indicators used to monitor antibiotic use lack uniformity. On the other hand, clinical outcomes related to an appropriate antibiotic use, such as mortality or length of hospital stay, are difficult to relate directly to the actions carried out in these units. The primary objective of this review is to identify antimicrobial use indicators used by ASPs in ED, and the secondary objectives are to describe the methods, healthcare professionals involved in these programs, and clinical and microbiological indicators that are used with consumption indicators in these hospital units.

MATERIAL AND METHODS

A systematic review was conducted based on published articles. Due to the variability in the methods, design, and results of the studies found in the literature, the indicators of both antimicrobial consumption and clinical and microbiological results, as well as the methods used in these studies, are summarised descriptively.

Data source and search strategy. Searches were performed in the following databases from January 2000 to December 2019 MEDLINE, Web of Science, Scopus and EMBASE. The following search terms were used in those databases: antibiotic AND (stewardship OR audit OR restriction OR decision support OR education OR guideline OR policy OR control OR de-escalation) AND (emergency department OR emergency service). Full-text, brief communications, and letters to the editor on randomised and non-randomised and controlled clinical trials, non-controlled before-and-after studies, interrupted time series, and repeated measures studies were included in this review. The exclusion criteria were studies outside the scope of the ED and studies without antimicrobial use measures. Studies published in languages other than English or Spanish were also excluded from this review.

The following variables were collected from each manuscript: country and year of publication; study design; group of patients or antimicrobials targeted by the ASP team; and clinical, microbiological, and antimicrobial consumption indicators. When requiring additional information regarding the manuscripts, the original authors of the corresponding articles were contacted to gather necessary data.

All indicators that reflected the variation in antimicrobial consumption before and after intervention were considered antimicrobial use indicators. The rates of infection with Clostridioides difficile, as well as variations in the rates of antimicrobial resistance and infection or colonisation with multidrug-resistant bacteria, were considered microbiological indicators. The following clinical outcomes were analysed: mortality, mean length of stay (both in the ED and in hospital), revisits, and adverse events; whether the studies assessed the effect of ASPs on health costs was also recorded.

Similarly, the work method was analysed, including prospective audit and feedback systems, formulary restrictions, application and compliance with internal clinical guidelines, treatment-shortening regimens, interventions in specific infections, dose-optimisation programmes, switch therapy from intravenous to oral route, computer support systems, review of microbiological records on discharge, pharmacokinetic monitoring, rapid diagnostic tests, training programmes, and specific interventions for allergies [9,11,15,16].

Study selection and data extraction. Two clinical pharmacists with training and experience in the implementation
Antimicrobial stewardship programs in emergency departments: how do we measure antimicrobial use? A systematic review

J. Ruiz-Ramos, et al.

A total of 8,451 references were found in the initial search. After applying the inclusion and exclusion criteria, 26 articles were included in the systematic review (Figure 1). Among the selected studies, four (15.4%) were controlled clinical trials, with 10 (38.5%) time series and 12 (45.1%) before-and-after studies. The median intervention period was 12 months (Range: 3 months–5 years). Table 1 outlines the characteristics of the studies selected for analysis, which are detailed in Table 1S-Supplementary material.

Team members. In total, 15 (62.5%) studies described the ASP team members who collaborated with the ED staff. The ASP team included an infectologist in eight (30.8%), a pharmacist in 11 (42.5%), the microbiology department in four (15.4%), the informatic department team in two (7.7%), and other staff in two (7.7%) studies. Nursing staff participation was described in five (19.2%) studies.

Method and performance targets. Most studies (21; 80.8%) reported training sessions as one of the strategies of the programmes, and these training sessions were the only measure described in three (11.5%) studies. The implementation of local and national guidelines/protocols was reported in 16 (61.5%) studies. In 10 (38.4%) studies, prospective audit and feedback systems were established for the prescribers. Other measures included the establishment of a consulting system (2; 7.7%), implementation of a computer support system (3; 11.5%), review of microbiological records on discharge (1; 3.8%), and formulary restrictions (1; 3.8%).

Respiratory tract infections were the main target of ASP teams, being their objective in 13 (50.0%) studies, of which six (23.1%) exclusively included a paediatric population. Urinary tract infections were the second most common infection targeted by ASPs, being present in five (19.2%) studies. Five (19.2%) studies targeted all patients on antibiotic treatment.

Consumption indicators. The different indicators used in the studies are outlined in Table 2. The percentage of patients with an antibiotic prescription was the most widely used indicator, being used in 21 (80.8%) of the published studies. Four (15.4%) studies included defined daily dose (DDD) data, adjusted for the number of stays in three (11.5%) studies and for the number of admissions in one. The duration of the antibiotic treatment was recorded in four (15.4%) studies, being adjusted for the number of stays in two (7.7%) and expressed as days of treatment (DOT) in one of the studies. Four (15.4%) studies evaluated antimicrobial spending after the implementation of the programmes.
Clinical outcome indicators. Among the clinical outcome results that accompanied the results of antimicrobial consumption, the number of readmissions or re-visits to the ED was the most frequently used, occurring in nine (37.5%) of the studies. The effect of the ASPs on mortality was evaluated in four (57.4%) studies, on mean stay in the ED in two (7.7%) studies, and on total hospital stay in five (19.2%) studies. Only two (7.7%) studies assessed the effect of ASPs using microbiological indicators; in both cases, the incidence of infection with *C. difficile* was the indicator used. One study (3.5%) collected the incidence of adverse events associated with antibiotic treatment. Evaluation of cost of antibiotic use was evaluated in two (7.7%) studies, observing a reduction in antimicrobials cost after the implementation of ASP in both cases.

**DISCUSSION**

According to the results from the present review, ASPs are applied in ED using different indicators to monitor antimicrobial consumption, and the percentage of patients with antibiotic prescription is the most widely used indicator. Most programmes described in the studies lack microbiological indicators. The experiences published in these studies highlight that multidisciplinary training in these units and prospective audit and feedback systems remain limited.

Although ED are an essential contributor to antimicrobial use as the starting point for many antibiotic prescriptions [17], our study has shown that few experiences described in the literature analyse the antibiotic use in these departments. A review on the clinical effect of implementing ASPs in ED has concluded that applying this type of programme has favourable clinical outcomes in most studies [14]. Our review is focused on the indicators used in these types of programmes and on the structure of the ASP team, beyond clinical outcomes. For this reason, a large number of studies on ASP-like interventions in these departments were excluded from this review because these interventions failed to include antimicrobial use monitoring in their activities. This element is essential to monitor the activity of such programmes, since the reduction in antimicrobial use is a primary objective of them and one of the tools that can predict the development of resistance [9,18-22].

According to our review, the percentage of patients prescribed antibiotics is the most frequently used indicator in these units. However, indicators based on daily doses of antibiotics have gradually been used in the last decade [23,24]. DDD, the main indicator used by ASP in hospitalized adults [25], is disadvantageous because it is not applicable to the paediatric population or to patients with impaired renal function. On the other hand, first dose of antibiotic administered in EDs in patients with serious infections may be higher than the maintenance dose, which makes it difficult to compare it with other services at the same center. DOT is widely accepted and applicable to the paediatric population. However, it requires an electronic administration record system for its calculation, in contrast to the DDD, and focuses on the duration of the antibiotic treatment, which is generally poorly controlled in ED [26]. Other indicators, such as prescribed daily dose, which makes it possible to adapt to the specific dosages of each unit, can be a suitable alternative, although it was not described in any of the studies included in this review. Another important point to note is the importance of monitoring hospital consumption of all groups of antimicrobials in ED, since reductions in the consumption of certain antibiotics are usually accompanied by increased consumption of others, which may even have a greater ecological impact or lead to changes. Regarding the denominator, the short stay of patients in these units makes it difficult to apply weighting based on the number of stays. For this reason, several authors have used the number of visits to the ED as an indicator, which is a more accepted denominator. The selection of indicators that include groups of antibiotics at a higher risk of generating resistance, such as quinolones or carbapenems, should also be part of the indicators used in ASPs in these units but were described in only two of the studies analysed [27,28]. Other mixed indicators have been proposed for other units even though their use in ED remains undescribed [29].

It should be noted that the difficulties inherent to these units derived from the short stay and the empirical manage-
ment of infectious pathology make it necessary to complement these consumption indicators with other indicators related to clinical processes and results related to the optimization of the activity carried out by these programs, such as the percentage of prescriptions that meet the accepted guidelines or used as references in the centre. However, these indicators have some limitations because they require a high workload to assess them and are partly affected by the subjectivity of the evaluator [30]. Using clinical outcome variables, such as mortality or number of re-visits, as indicators is also highly recommended [29], although these variables were poorly represented in the studies included in our review.

Another finding of our review is the limited evaluation of the ecological impact of these programmes. _C. difficile_ infection rate was used in two studies [26,31], being its value of doubtful applicability for ED intervention, as most of patients are already affected before ED admission. The selection of microbiologic indicators for these units remains a challenge because interventions such as antibiotic treatment shortening or antibiotic de-escalation, associated with reductions in the number of nosocomial infections due to multiresistant strains mostly match other levels of care. In turn, although these indicators are necessary, they are often difficult to interpret because their number depend, to a large extent, on other factors that are not directly associated with the adequate use of antibiotics, such as cross-contamination.

The methods used in this type of unit are highly heterogeneous. All these interventions have been designed with strategies for optimising antimicrobial use in these units [16] and have demonstrated, in all cases, benefits by reducing antibiotic prescription in these units [32]. The optimal strategy for ASPs in ED has not yet been established because no study has compared the different interventions proposed for such purposes. Regarding the ASP team members, the participation of an infectologist and pharmacist, together with the head of the ED and with the support of microbiology services, is the basis for implementing such programmes [33-35]. The success of these programmes requires adjusting the interventions to the local needs and to the available resources [9]. However, our review shows that most experiences described in the literature do not include this type of the ASP team composition, with infectologists being represented in only 30.7% and pharmacists in 42.3% of ASP teams.

In this review we have included studies of ASPs in adult and paediatric population. Although the objectives and indicators proposed for ASP in hospitalized patients and primary care are different from each other’s, the high care burden, the lack of diagnostic results for the initiation of antibiotic therapy

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Adult patients (n=19)</th>
<th>Pediatric patients (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients with antibiotic prescription</td>
<td>15 (78.9%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>DDD / 100 stays</td>
<td>3 (15.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>RDD / 100 stays</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DDD / 100 income</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DOT / 100 admissions</td>
<td>1 (5.3%)</td>
<td>1 (14.8%)</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Intravenous treatment duration</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Adjusted prescription ratio</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Antimicrobial costs</td>
<td>0 (0.0%)</td>
<td>2 (28.5%)</td>
</tr>
<tr>
<td>Length of stay in the emergency room</td>
<td>1 (5.3%)</td>
<td>1 (14.8%)</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>4 (21.0%)</td>
<td>1 (14.8%)</td>
</tr>
<tr>
<td>Readmissions / Revisits</td>
<td>7 (37.5%)</td>
<td>2 (28.5%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (21.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>No. <em>C. difficile</em> infections / 100 patients</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>No. <em>C. difficile</em> infections / 10,000 stays</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

DDD: Defined daily dose; RDD: Doses adjusted to guidelines; DOT: Days of treatment
and the pressures from patients or their caregivers are common elements in paediatrics and adults ED. These facts make necessary to form multidisciplinary teams in both cases, with common general objectives in terms of reducing the consumption of antibiotics and rate of clinical response and resistance profile analysis.

Among the limitations of our review, the inclusion criteria stand out. Only manuscripts written in English and Spanish were selected, thereby excluding experiences described in non-English or Spanish-speaking centres. Moreover, conference proceedings have also not been included, and experiences of the implementation of this type of programme may be presented in these conferences. Regarding the methods and ASP team members, the exclusion of studies that did not include antibiotic use monitoring may affect the proportion of programmes with multidisciplinary teams. However, the review published by Losier et al [14] reported conclusions similar to those described here. As previous revisions related to ASP [36,37], we have included studies published from 2000, as these programmes have undergone significant development during the last two decades. The inclusion of studies published prior to the chosen date possibly would have contributed to a smaller number of multidisciplinary teams involved, a greater disparity of actions and poorly defined consumption indicators.

The data on the consumption of antibiotics and resistance, which is the main objective of this review, are only one part of the panel of indicators that should be part of this type of program, especially in ED. Obtaining certain relatively accessible indicators has often been confused with the program objectives themselves. Consistent with the stated mission, ASPs must first select clinical objectives and indicators of both processes and results, which can be related to the antimicrobial consumption profile and the generation of resistance.

In conclusion, the indicators used to monitor antimicrobial use in ASPs implemented in ED are heterogeneous, making it difficult to compare these interventions, with poorly described clinical and microbiological indicators. Given the difficulty in selecting adequate indicators in these units, a consensus must be reached to guide the programs implemented in these units.

FUNDING

None to declare

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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J. Ruiz-Ramos, et al.


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