Official journal of the Spanish Society of Chemotherapy

Systematic review

Revista Española de Quimioterapia
doi:10.37201/req/028.2021

Jesus Ruiz-Ramos[1]
Emili Vallvé Alcón[2]
Francisco Moreno Ramos[3]
Rosario Santolaya-Perrín[4]
Jose María Guardiola Tey[5]

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

[1]Pharmacy Department, Hospital Santa Creu i Sant Pau, Barcelona, Spain.
[2]Pharmacy Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[3]Pharmacy Department, Hospital Universitario La Paz, Madrid, Spain
[4]Pharmacy Department, Hospital Universitario Príncipe de Asturias. Alcalá de Henares, Spain.
[5]Emergency Department, Hospital Santa Creu i Sant Pau, Barcelona, Spain.

Article history
Received: 4 February 2021; Revision Requested: 25 March 2021; Revision Received: 10 May 2021; Accepted: 26 July 2021; Published: 15 September 2021

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

Correspondence:
Jesus Ruiz
Pharmacy Department, Hospital Santa Creu i Sant Pau. C/San Quintín 89, 08041 Barcelona, Spain.. Phone: +34-932919000 (Ext: 1887)
E-mail: Jruizr@santpau.cat j

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

RESUMEN

Objetivos. La implantación de programas de optimización de antimicrobianos (PROA) se ha convertido en una práctica asistencial habitual en el medio hospitalario. No obstante, la metodología para monitorizar 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 interrumpido 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.

La mayor parte de los estudios utilizaron el porcentaje de pacientes con prescripción de antibióticos como indicador, estando presente en 21 (80,8%) de los estudios publicados. Cuatro (15,4%) de los estudios incluyeron datos en Dosis Diarias Definidas (DDD). La duración del tratamiento antibiótico fue recogida en cuatro (15,4%) de los estudios. Únicamente dos estudios evaluaron el impacto del programa con indicadores microbiológicos, siendo en ambos casos la incidencia de infección por *Clostridioides difficile* el indicador utilizado.

Conclusiones. Las experiencias descritas de implantación de programas PROA en los servicios de urgencia presenta indicadores de uso de antimicrobianos heterogéneos, que dificultan la comparación de resultados. Es necesario estandarizar los indicadores de optimización de uso de antimicrobianos en estas unidades.

Palabras clave: optimización de uso de antimicrobianos, Antibióticos, urgencias, infección

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 (ASPs) 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

of ASPs and ED care independently examined all titles and abstracts retrieved during the literature search. In texts over which the two specialists disagreed, a third specialist was included to reach a consensus decision after discussion the study with the other researchers.

RESULTS

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 deparment 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.

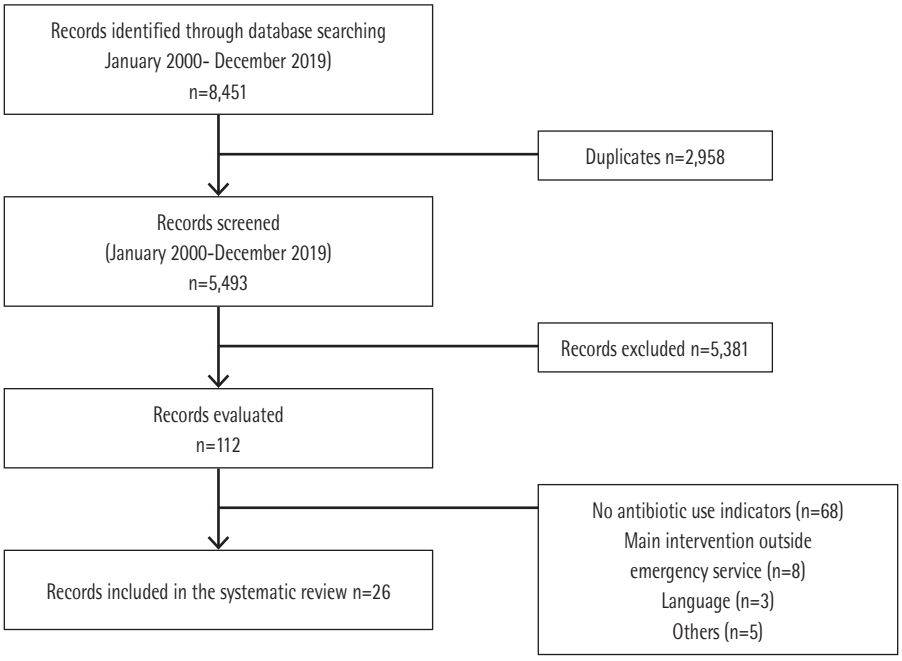

Figure 1 Study selection flow-chart

Table 1 Characteristics of the studies included in the analysis.

Design	
Randomized trial with control group	4 (15.4%)
Time series study	10 (38.5%)
Retrospective before-after study	12 (46.1%)
Studies in paediatric patients	8 (30.7%)
Target of intervention	
All patients with antibiotics	5 (19.2%)
Respiratory infections	13 (50.0%)
Urinary-tract infections	4 (15.4%)
Otitis	1 (3.8%)
Quinolones	1 (3.8%)
Vancomycin	1 (3.8%)
Sepsis	1 (3.8%)
Participants	
Without description	11 (42.3%)
Infectologists	8 (30.7%)
Pharmacists	11 (42.3%)
Microbiologist	4 (15.4%)
Informatic	2 (7.7%)
Nursing	5 (19.2%)
Others	3 (11.5%)

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 theses 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 general 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-

Table 2 Indicators used in the studies included (n = 26)

Indicator	Adult patients (n=19)	Peadiatric patients (n=7)
Antibiotic use indicators		
% Patients with antibiotic prescription	15 (78.9%)	7 (100%)
DDD / 100 stays	3 (15.7%)	0 (0%)
RDD / 100 stays	1 (5.3%)	0 (0%)
DDD / 100 income	1 (5.3%)	0 (0%)
DOT / 100 admissions	1 (5.3%)	1 (14.8%)
Treatment duration	1 (5.3%)	0 (0%)
Intravenous treatment duration	1 (5.3%)	0 (0%)
Adjusted prescription ratio	1 (5.3%)	0 (0%)
Antimicrobial costs	0 (0.0%)	2 (28.5%)
Outcome indicators		
Length of stay in the emergency room	1 (5.3%)	1 (14.8%)
Length of hospital stay	4 (21.0%)	1 (14.8%)
Readmissions / Revisits	7 (37.5%)	2 (28.5%)
Mortality	4 (21.0%)	0 (0%)
Treatment failure	1 (5.3%)	0 (0%)
Microbiological indicators		
No. *C difficile* infections / 100 patients	1 (5.3%)	0 (0%)
No. *C difficile* infections / 10,000 stays	1 (5.3%)	0 (0%)

DDD: Defined daily dose; RDD: Doses adjusted to guidelines; DOT: Days of treatment

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

and the pressures from patients or they 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 those 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.

REFERENCES

1. Eliopoulos GM, Cosgrove SE, Carmeli Y. The Impact of Antimicrobial Resistance on Health and Economic Outcomes. Clin Infect Dis. 2003;36(11):1433-7. Doi: 10.1086/375081.
2. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. Clin Microbiol Infect. 2016;22(5):416-22. Doi: 10.1016/j.cmi.2015.12.002.
3. Barbosa TM, Levy SB. The impact of antibiotic use on resistance development and persistence. Drug Resist Updat. 2000;3(5):303-11. Doi: 10.1054/drup.2000.0167.
4. Trivedi KK, Pollack LA. The Role of Public Health in Antimicrobial Stewardship in Healthcare. Clin Infect Dis. 2014;59(Suppl 3):S101-3. Doi: 10.1093/cid/ciu544.
5. Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012;33(4):322-7. Doi: 10.1086/665010.
6. Mas-Morey P, Valle M. A systematic review of inpatient antimicrobial stewardship programmes involving clinical pharmacists in small-to-medium-sized hospitals. Eur J Hosp Pharm. 2018;25(e1):e69-73. Doi: 10.1136/ejhpharm-2017-001381.
7. Schweitzer VA, van Heijl I, van Werkhoven CH, Islam J, Hendriks-Spoor KD, Bielicki J, et al. The quality of studies evaluating antimicrobial stewardship interventions: a systematic review. Clin Microbiol Infect. 2019;25(5):555-61. Doi: 10.1016/j.cmi.2018.11.002.
8. Rice LB. Antimicrobial Stewardship and Antimicrobial Resistance. Med Clin North Am. 2018;102(5):805-18. Doi: 10.1016/j.mcna.2018.04.004
9. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clinical Infectious Diseases. Clin Infect Dis. 2016;62(10):e51-77. Doi: 10.1093/cid/ciw118.
10. Overview | Antimicrobial stewardship: changing risk-related behaviours in the general population | Guidance | NICE [Internet]. NICE; [citado 11 de mayo de 2020]. Available at: https://www.nice.org.uk/guidance/ng63 (accessed on 15 March 2020).
11. Rodríguez-Baño J, Paño-Pardo JR, Alvarez-Rocha L, Asensio A, Calbo E, Cercenado E, et al. [Programs for optimizing the use of antibiotics (PROA) in Spanish hospitals: GEIH-SEIMC, SEFH and SEMPSPH consensus document]. Enferm Infecc Microbiol Clin. 2012;30(1):22.e1-22.e23. Doi: 10.1016/j.eimc.2011.09.018.
12. Centers for Disease Control and Prevention. National Hospital Ambulatory Medical Care Survey: 2011 Emergency Department Summary Tables. Available online: https://www.cdc.gov/nchs/data/ahcd/nhamcs_ emergency/2011_ed_web_tables.pdf (accessed on 18 March 2020).
13. Joint Commission on Hospital Accreditation. APPROVED: new antimicrobial stewardship standard. Jt Comm Perspect 2016;36(7):1, 3–4, 8. PMID: 27548932
14. Losier M, Ramsey TD, Wilby KJ, Black EK. A Systematic Review of Antimicrobial Stewardship Interventions in the Emergen-

cy Department. Ann Pharmacother. 2017;51(9):774-90. Doi: 10.1177/1060028017709820.

15. Dellit TH, Owens RC, McGowan JE, 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(2):159-77. Doi: 10.1086/510393.
16. May L, Cosgrove S, L'Archeveque M, Talan DA, Payne P, Jordan J, et al. A call to action for antimicrobial stewardship in the emergency department: approaches and strategies. Ann Emerg Med. 2013;62(1):69-77.e2. Doi: 10.1016/j.annemergmed.2012.09.002.
17. Pulcini C. Antimicrobial stewardship in emergency departments: a neglected topic. Emerg Med J. 2015;32(7):506. Doi: 10.1136/emermed-2014-204220.
18. 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(7):847-56. Doi: 10.1016/S1473-3099(16)00065-7.
19. Ryu S, Klein EY, Chun BC. Temporal association between antibiotic use and resistance in Klebsiella pneumoniae at a tertiary care hospital. Antimicrob Resist Infect Control. 2018;7(1):83. Doi: 10.1186/s13756-018-0373-6.
20. Antibiotic consumption and resistance of gram-negative pathogens (collateral damage). - Abstract - Europe PMC [Internet]. [cited 16 May 2020]. Available at: https://europepmc.org/article/med/30671336
21. Gutiérrez-Urbón JM, Gil-Navarro MV, Moreno-Ramos F, Núñez-Núñez M, Paño-Pardo JR, Periáñez-Párraga L. Indicators of the hospital use of antimicrobial agents based on consumption. Farm Hosp. 2019;43(3):94-100. Doi: 10.7399/fh.11163.
22. Brotherton AL. Metrics of Antimicrobial Stewardship Programs. Med Clin North Am. 2018;102(5):965-76.
23. Kaufman AJ, McCready J, Powis J. Impact of a multifaceted antimicrobial stewardship program: A front-line ownership driven quality improvement project in a large urban emergency department. CJEM. 2017;19(6):441-9. Doi: 10.1017/cem.2017.11.
24. Cunney R, Kirrane-Scott M, Rafferty A, Stapleton P, Okafor I, McNamara R. «Start smart»: using front-line ownership to improve the quality of empiric antibiotic prescribing in a paediatric hospital. BMJ Open Qual. 2019;8(3):e000445. Doi: 10.1136/bmjoq-2018-000445.
25. World Health Organization Collaborating Centre forDrug Statistics Methodology Web site. Available at: http://www.whocc.no [accessed on 7 February 2019].
26. Townsend J, Adams V, Galiatsatos P, Pearse D, Pantle H, Masterson M, et al. Procalcitonin-Guided Antibiotic Therapy Reduces Antibiotic Use for Lower Respiratory Tract Infections in a United States Medical Center: Results of a Clinical Trial. Open Forum Infect Dis. 2018;5(12):ofy327. Doi: 10.1093/ofid/ofy327.
27. Fagan M, Lindbæk M, Reiso H, Berild D. A simple intervention to reduce inappropriate ciprofloxacin prescribing in the emergency department. Scand J Infect Dis. 2014;46(7):481-5. Doi: 10.3109/00365548.2014.880187.
28. Hecker MT, Fox CJ, Son AH, Cydulka RK, Siff JE, Emerman CL, Sethi AK, et al. Effect of a Stewardship Intervention on Adherence to Uncomplicated Cystitis and Pyelonephritis Guidelines in an Emergency Department Setting. PLoS One. 2014; 9(2):e87899. Doi: 10.1371/journal.pone.0087899.
29. Gutiérrez-Urbón JM, Gil-Navarro MV, Moreno-Ramos F, Núñez-Núñez M, Paño-Pardo JR, Periáñez-Párraga L. Indicators of the hospital use of antimicrobial agents based on consumption. Farm Hosp. 2019;43(3):94-100. Doi: 10.7399/fh.11163.
30. DePestel DD, Eiland EH, Lusardi K, Destache CJ, Mercier R-C, McDaneld PM, et al. Assessing appropriateness of antimicrobial therapy: in the eye of the interpreter. Clin Infect Dis. 2014;59 Suppl 3:S154-161. Doi: 10.1093/cid/ciu548.
31. LaFave J, Levy D, Gekle R, Bramante R. Incidence of Clostridium difficile Infection After Sepsis Protocol Antibiotics. West J Emerg Med. 2019;20(6):977-81. Doi: 10.5811/westjem.2019.10.42070.
32. Santarossa M, Kilber EN, Wenzler E, Albarillo FS, Sterk EJ. BundlED Up: A Narrative Review of Antimicrobial Stewardship Initiatives and Bundles in the Emergency Department. Pharmacy (Basel). 2019;7(4). Doi: 10.3390/pharmacy7040145.
33. Pulia M, Redwood R, May L. Antimicrobial Stewardship in the Emergency Department. Emerg Med Clin North Am. 2018;36(4):853-72. Doi: 10.1016/j.emc.2018.06.012.
34. Randolph TC, Parker A, Meyer L, Zeina R. Effect of a pharmacist-managed culture review process on antimicrobial therapy in an emergency department. Am J Health Syst Pharm. 2011;68(10):916-9. Doi: 10.2146/ajhp090552.
35. Kiyatkin DE, Wright S, Zenilman J, Kisuule F. Improving utilization of antimicrobial drugs among physician assistants in the ED. JAAPA. 2011;24(10):44, 47-8, 50-1. Doi: 10.1097/01720610-201110000-00007.
36. Nathwani D, Varghese D, Stephens J, Ansari W, Martin S, Charbonneau C. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. Antimicrob Resist Infect Control. 2019; 8:35. Doi: 10.1186/s13756-019-0471-0.
37. Dik J-WH, Vemer P, Friedrich AW, Hendrix R, Lo-Ten-Foe JR, Sinha B, et al. Financial evaluations of antibiotic stewardship programs—a systematic review. Front Microbiol. 2015;6:317. Doi: 10.3389/fmicb.2015.00317
36. Småbrekke L, Berild D, Giaever A, Myrbakk T, Fuskevåg A, Ericson JU, et al. Educational intervention for parents and healthcare providers leads to reduced antibiotic use in acute otitis media. Scand J Infect Dis. 2002;34(9):657-9. Doi: 10.1080/00365540210147651.
37. Metlay JP, Camargo CA Jr, MacKenzie T, McCulloch C, Maselli J, Levin SK, et al. Cluster-randomized trial to improve antibiotic use for adults with acute respiratory infections treated in emergency departments. Ann Emerg Med. 2007;50(3):221-30. Doi: 10.1016/j.annemergmed.2007.03.022.
38. McIntosh KA, Maxwell DJ, Pulver LK, Horn F, Robertson M, Kaye KI, et al. A quality improvement initiative to improve adherence to national guidelines for empiric management of community-acquired pneumonia in emergency departments. Int J Qual Health

Care. 2011;23(2):142-50. Doi: 10.1093/intqhc/mzq077.

39. Buising KL, Thursky KA, Black JF, MacGregor L, Street AC, Kennedy MP, et al. Improving antibiotic prescribing for adults with community acquired pneumonia: Does a computerised decision support system achieve more than academic detailing alone?--A time series analysis. BMC Med Inform Decis Mak. 2008;8:35. Doi: 10.1186/1472-6947-8-35.
40. Johnson LW, Robles J, Hudgins A, Osburn S, Martin D, Thompson A. Management of Bronchiolitis in the Emergency Department: Impact of Evidence-Based Guidelines? Pediatrics. 2013. 131 Suppl 1:S103-9. Doi: 10.1542/peds.2012-1427m.
41. Akenroye AT, Baskin MN, Samnaliev M, Stack AM. Impact of a bronchiolitis guideline on ED resource use and cost: a segmented time-series analysis. Pediatrics . 2014;133(1):e227-34. Doi: 10.1542/peds.2013-1991.
42. Julián-Jiménez A, Palomo de los Reyes MJ, Laín-Terés N. [Is it possible to improve the management of community acquired pneumonia in hospital emergency departments?]. Arch Bronconeumol. 2010;46(8):448-9. Doi: 10.1016/j.arbres.2010.03.001.
43. Angoulvant F, Skurnik D, Bellanger H, Abdoul H, Bellettre X, Morin L, et al. Impact of implementing French antibiotic guidelines for acute respiratory-tract infections in a paediatric emergency department, 2005-2009. Eur J Clin Microbiol Infect Dis. 2012;31(7):1295-303. Doi: 10.1007/s10096-011-1442-4.
44. Landry E, Sulz L, Bell A, Rathgeber L, Balogh H. Urinary Tract Infections: Leading Initiatives in Selecting Empiric Outpatient Treatment (UTILISE). Can J Hosp Pharm. 2014;67(2):116-25. Doi: 10.4212/cjhp.v67i2.1339.
45. Borde JP, Kern WV, Hug M, Steib-Bauert M, de With K, Busch HJ, et al. Implementation of an intensified antibiotic stewardship programme targeting third-generation cephalosporin and fluoroquinolone use in an emergency medicine department . Emerg Med J. 2015;32(7):509-15. Doi: 10.1136/emermed-2014-204067.
46. Percival KM, Valenti KM, Schmittling SE, Strader BD, Lopez RR, Bergman SJ. Impact of an antimicrobial stewardship intervention on urinary tract infection treatment in the ED. Am J Emerg Med. 2015;33(9):1129-33. Doi: 10.1016/j.ajem.2015.04.067.
47. Quintos-Alagheband ML, Noyola E, Makvana S, El-Chaar G, Wang S, Calixte R, et al. Reducing Antibiotic Use in Respiratory Syncytial Virus—A Quality Improvement Approach to Antimicrobial Stewardship. Pediatr Qual Saf. 2017;2(6):e046. Doi: 10.1097/pq9.0000000000000046.
48. Ouldali N, Bellêttre X, Milcent K, Guedj R, de Pontual L, Cojocaru B, et al. Impact of implementing national guidelines on antibiotic prescriptions for acute respiratory tract infections in pediatric emergency departments: an interrupted time series analysis. Clin Infect Dis. 2017;65(9):1469-1476. Doi: 10.1093/cid/cix590.
49. Wathne JS, Kleppe LKS, Harthug S, Blix HS, Nilsen RM, Charani E, et al. The effect of antibiotic stewardship interventions with stakeholder involvement in hospital settings: a multicentre, cluster randomized controlled intervention study. Antimicrob Resist Infect Control. 2018;7:109. Doi: 10.1186/s13756-018-0400-7.
50. Powell SL, Liebert E. BSN, CPEN, Appropriate Use of Vancomycin in a Pediatric Emergency Department Through the Use of a Standardized Electronic Guideline. J Pediatr Nurs. 2015; 30, 494–497. Doi: 10.1016/j.pedn.2014.12.014
51. Dinh A, Duran C, Davido B, Bouchand F, Deconinck L, Matt M, ET AL. Impact of an antimicrobial stewardship program to optimize antimicrobial use for outpatients at emergency department. J Hosp Infect. 2017;97(3):288-293. Doi: 10.1016/j.jhin.2017.07.005.
52. Dorzin SE, Halaby C, Quintos ML, Noor A, El-Chaar G.. Antimicrobial Stewardship Program Using Plan-Do-Study-Act Cycles to Reduce Unjustified Antibiotic Prescribing in Children Admitted With an Asthma Exacerbation. J Pediatr Pharmacol Ther. 2017;22(6):436-443. Doi: 10.5863/1551-6776-22.6.436.
53. Yadav K, Meeker D, Mistry RD, Doctor JN, Fleming-Dutra KE, Fleischman RJ, et al. A Multifaceted Intervention Improves Prescribing for Acute Respiratory Infection for Adults and Children in Emergency Department and Urgent Care Settings. Acad Emerg Med. 2019;26(7):719-731. Doi: 10.1111/acem.13690
54. Jorgensen SC, Yeung SL, Zurayk M, Terry J, Dunn M, Nieberg P, et al. Leveraging Antimicrobial Stewardship in the Emergency Department to Improve the Quality of Urinary Tract Infection Management and Outcomes. Open Forum Infect Dis. 2018;5(6):ofy101. Doi: 10.1093/ofid/ofy101.