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Narrative review

Antimicrobial stewardship in the emergency department: characteristics and evidence for effectiveness of interventions

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ABSTRACT

Background: Emergency departments (EDs) are the entrance gates for patients presenting with infectious diseases into the hospital, yet most antimicrobial stewardship programmes are primarily focused on inpatient management. With equally high rates of inappropriate antibiotic use, the ED is a frequently overlooked yet important unit for targeted antimicrobial stewardship (AMS) interventions.
Objectives: We aimed to (a) describe the specific aspects of antimicrobial stewardship in the ED and (b) summarize the findings from improvement studies that have investigated the effectiveness of antimicrobial stewardship interventions in the ED setting.
Sources: : (a) a PubMed search for 'antimicrobial stewardship' and 'emergency department', and (b) published reviews on effectiveness combined with publications from the first source.
Content: : (a) An in depth analysis of selected publications provided four key antimicrobial use processes typically performed by front-line healthcare professionals in the ED: making a (tentative) clinical diagnosis, starting empirical therapy based on that diagnosis, performing microbiological tests before starting that therapy and following up patients who are discharged from the ED. (b) Further, we discuss the literature on improvement strategies in the ED focusing on guidelines and clinical pathways and multifaceted improvement strategies. We also summarize the evidence of microbiologic culture review.
Implications: : Based on our review of the literature, we describe four essential elements of antimicrobial use in the ED. Studying the various interventions targeting these care processes, we have found them to be of a variable degree of success. Nonetheless, while there is a paucity of AS studies specifically targeting the ED, there is a growing body of evidence that AS programmes in the ED are effective with modifications to the ED setting. We present key questions for future research. **Larissa May, Clin Microbiol Infect 2021;27:204**

Introduction

Emergency departments (EDs) are usually the first place where patients with infectious diseases come into contact with the hospital. Antimicrobial treatment is typically empiric in the ED setting and clinical decision making must occur quickly, generally in the absence of microbiological results or feedback regarding patient course and outcomes. Rates of inappropriate antimicrobial treatment in the ED are similar to the inpatient context: around 40–60% [1,2]. This is unacceptably high, all the more so because complete guideline adherence for all aspects of antimicrobial prescription is associated with reduced mortality [3].

The main goal of antimicrobial stewardship programmes (ASPs) is to optimize antimicrobial treatment in order to maximize clinical outcomes for patients presenting with infection,

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reducing morbidity and mortality and adverse events as well as preserving the clinical effectiveness of antimicrobials by slowing down the development of antimicrobial resistance [4]. However, most of these programmes are frequently focused on hospitalized patients and do not include ED or they lack the specificity required by these departments [5].

To develop an ED-specific ASP, insight is needed into what exactly distinguishes ED antimicrobial use from other hospital departments. For example, in many EDs discharged patients account for the majority of patients seen and treated. Arguably, given the rates of inappropriate prescribing for viral respiratory tract and other infections treated in the outpatient setting, this might be an important area that should be targeted.

In addition, it needs to be determined which of multiple antimicrobial stewardship programme strategies are most appropriate for the ED. It is important to know which interventions are commonly used to achieve ASP goals in the ED and what their effectiveness is, as improvement strategies might work differently in the ED. To be effective, such interventions should take into account the unique ED workflow and healthcare system context—e.g. the clinical decision making in an environment with limited access to rapid diagnostic tools and follow-up—making use of implementation science and other behaviourally oriented techniques [6–8].

This narrative review aims to describe the specific aspects of antimicrobial stewardship (AMS) in the ED and to summarize the results of improvement studies that have investigated the effect of ASP in the ED setting.

Literature base

To characterize key aspects of AMS that are specific for the ED, we performed a search on PubMed (Table S1) for articles that described characteristics of AMS in the ED. Of the 183 publications identified, two investigators (T.S. and J.S.) independently screened all titles and abstracts to select potentially eligible articles for full text screening. Any disagreement between these two investigators was resolved by discussion. As a result, full texts of 18 papers were retrieved (Table S2) from which information was extracted that differentiate AMS in the ED from general AMS.

Four reviews (Losier et al. [9], May et al. [6], Schuetz et al. [10] and Mathioudakis et al. [11]) formed the starting point of our analysis of the effect of stewardship interventions in the ED setting. We added relevant references regarding effectiveness based on the 18 articles from our primary search described above. Finally we used more recent references from one of the authors (May et al. [12], Yadav et al. [13] and Yadav et al. 2020 [14]) and 'snowballed' all of these articles for relevant references. The articles that were taken up in our review are described in Table 1.

Key aspects of antimicrobial stewardship in the ED

Notably, the intrinsic fast-paced setting of the ED with high patient and staff turnover makes AMS challenging [9,15–23]. Based on in-depth analysis of the 18 selected papers (Table S2), we suggest that the following characteristics differentiate AMS in the ED from a general AMS approach.

First, AMS in the ED is concentrated around the clinical diagnosis [8]. The (tentative) diagnosis is made by the front-line doctors at the ED. The most important AMS questions that they need to answer at this stage are: Is there a rationale for starting antimicrobials for this diagnosis? Should I treat now? Or can I wait? AMS in the ED is increasingly facilitated by the application of rapid diagnostics, which include molecular techniques to diagnose viral infections and biomarkers to differentiate bacterial from viral infections. Incorporating these results in the process of making a clinical diagnosis in the ED has the potential to significantly reduce unnecessary antibiotic use [8,15,24].

Second, as a result, AMS in the ED is strongly focused on empirical therapy. This includes timing, choice of spectrum, route, dose and dosing interval. The empirical therapy started in the ED has a major impact on therapy further downstream (either in-hospital or outpatient care settings), since it is most often continued by other health professionals in the first days after admission to the hospital [5,6,23,25]. Restricted antibiotics (often broad spectrum) once started as empirical therapy in the ED are often continued until culture results become available. The need for quick decision making increases the risk of 'quick-win' administration of a broad spectrum antibiotic. Implementation of the Surviving Sepsis Campaign, promoting quick administration of broad spectrum antibiotics, has had a major impact on antibiotic use in the ED. Thus, critical appraisal of the choice of empirical therapy provides an important opportunity for AMS in the ED [17,19,26,27].

Third, AMS in the ED emphasizes the relevance of appropriate culture taking and other microbiological tests before starting antimicrobial therapy. This allows for identification of the causative pathogen and its sensitivity, leading to reasoned de-escalation of antimicrobial therapy in the days following start of therapy [6,8]. The need for quick decision making, again, increases the risk of omission of culture orders.

Fourth, AMS in the ED needs to address follow-up for outpatients who are discharged from the ED either with or without antimicrobials and/or culture taking [8,25]. The follow-up should evaluate both clinical response to antimicrobial therapy and culture result assessment. This is often a logistically challenging process [28].

Effect of AMS interventions targeting the ED setting

The number of ED focused AMS interventions are to date limited in the literature [6,9]. To our knowledge, there has been only one systematic review published for the ED setting [9]. Common strategies to achieve AMS goals include the implementation of guidelines or clinical pathways, multifaceted approaches, and culture review.

Evidence-based guidelines and clinical pathways for single infection types

Implementation of guidelines and clinical pathways in the ED frequently focuses on single infection types, for example respiratory or urinary tract infections, and are centred on appropriate management of hospitalized patients. In paediatric ED settings, study outcomes include reducing rates of antibiotic prescriptions for non-bacterial conditions along with avoiding ordering unnecessary tests. Mixed results have been obtained in avoiding inappropriate antibiotics for antibiotic non-responsive conditions. For example, Akenroye et al. [29] conducted a study during a 7-year period comparing results before and after implementation of a guideline for bronchiolitis in which they analysed almost 3000 episode of care. After guideline implementation, the authors showed that chest imaging, testing for respiratory syncytial virus, and albuterol use decreased significantly; however, there were no significant differences in antibiotic use.

For studies of community-acquired pneumonia, results have been more promising. The impact of interventions on improvement in prescribing appears to depend on the intensity of the interventions that are implemented. Angoulvant et al. [30] demonstrated a significant change in antibiotic prescription trends in seven paediatric emergency departments in France after implementation of national French empiric antibiotic guidelines for acute

Table 1
Studies included in the effectiveness review

Reference	Type of studio	Patients—setting	Intervention	Main outcomes
May 2013	Narrative review	—	—	—
Losier 2017	Systematic review	—	—	Different AMS initiatives can have success in the ED
Schuetz 2017	Systematic review	Patients with acute respiratory tract infections	Procalcitonin guidance to initiate or not antibiotics	Procalcitonin guidance was not associated with increased mortality or treatment failure. Antibiotic exposure and days of antibiotic were reduced
Mathioudakis 2017	Meta-analysis	Patients with COPD exacerbation	Procalcitonin guidance to initiate antibiotics	Antibiotic prescriptions decreased with use of procalcitonin: relative risk: 0.56 (95% CI 0.43-0.73) Total antibiotic exposure: mean difference: −3.83 (95% CI: 4.32−3.35). No differences in failure rates
Akenroye 2014	Unicentre interrupted time series study	Paediatrics Emergency Department	Bronchiolitis Guidelines implementation	No significant differences in antibiotic use Absolute reduction of: - Chest X Ray of 23% (95% CI: 11−34%) - Albuterol use of 7% (95% CI: 0.2−13%) - Length of stay: 41 minutes (95% CI: 16−65)
Angoulvant 2014	Multicentre interrupted time series study	Paediatrics Emergency Department	Acute respiratory tract infections Antibiotic guidelines	Increase of amoxicillin prescriptions: 34.0 to 84.7% Reduction of: - Amoxicillin clavulanate: 43.0 to 10.2% - Cefpodoxime: 16.6 to 2.5% - Outpatient antibiotics: 26% to 24.2%
Buising 2008	Unicentre interrupted time series study	Patients with community acquired pneumonia at ED	Three periods: - Baseline. - Academic period: Training in antibiotic prescriptions for ED physicians. - Computerized decision support	Concordant therapy compared with baseline period: - Academic period: OR: 2.79 (1.88−4.14, p < 0.01) - Computerized period: 1.99 (1.07−3.69, p 0.02)
May 2019	Unicentre randomized clinical trial	Patients with upper respiratory infection	Rapid multiplex respiratory pathogen testing	Antibiotic prescriptions was lower in intervention group: 22% vs 34% (95% CI: −25% to 0.4%, p 0.06)
Hecker 2014	Unicentre interrupted time series study	Patients with UTI at ED	Electronic order set and 2 months period of audit and feedback	Increase of adherence to guidelines: 44% to 82% (p < 0.015). Prescription of fluroquinolones decreased for uncomplicated cystitis: 44% to 13% (p < 0.001) Unnecessary antibiotic days decreased from 250 to 52 days (p < 0.001)
Percival 2015	Unicentre interrupted time series study	Patients discharged from ED with uncomplicated UTI	Educational intervention	Increase in guidelines adherence from 44.8% to 83% (CI 33 −43% p < 0.001) with increase in nitrofurantoin use for cystitis In cystitis, concordance between empiric antibiotic and isolated pathogen increased from 74% to 89% (p 0.05)
Metlay 2007	Multicentre cluster randomized trial	Patients with acute respiratory tract infections in the ED	Educational intervention	Antibiotic prescriptions decreased in the intervention group by 10% while increased in the control group (0.5%) without differences in rates of readmissions
McIntosh 2011	Multicentre interrupted time series study	Patients diagnosed of community-acquired pneumonia in the ED	Educational intervention.	Antibiotics concordance with guidelines improved: 20% to 29% (p < 0.0001) at the end of the study
Borde 2015	Unicentre interrupted time series study	Hospitalized patients on treatment with third generation cephalosporin and fluoroquinolone	Local guidelines and ASP	Antibiotic use density declined, especially in third-generation cephalosporin (68%). Fluoroquinolones density was lower after intervention but do not reach statistical significance
Marrie 2000	Multicentre controlled clinical trial	Patients diagnosed of community-acquired pneumonia	Implementation of critical pathway	Intervention group was associated with less days of hospitalization, days of intravenous therapy and rate of admission at hospital Intervention group received more frequently a single class of antibiotic (64% vs 27%, p < 0.001)
Yadav 2019	Pragmatic cluster-randomized clinical trial	Patients with acute respiratory infection	- Educational intervention (provider and patient) - Physician champion - Feedback - Peer comparison	Reduction in inappropriate antibiotic prescribing from 2.2% (95% CI = 1.0% to 3.4%) to 1.5% (95% CI = 0.7% to 2.3%) with an OR of 0.67 (95% CI = 0.54 to 0.82)
Randolph 2011	Unicentre interrupted time series study	Discharged patients from ED with cultures	Addition of a Pharmacist to review of antimicrobial	Improvement in: - Rates of readmissions related with antimicrobial treatment
Baker 2012	Unicentre interrupted time series study	Discharged patients from ED with positive cultures requiring antimicrobial revision	Addition of a Pharmacist to review of antimicrobial	Improvement in: - Median time to culture review (3 to 2 days, p 0.0001).

Table 1 (*continued*)

Reference	Type of studio	Patients—setting	Intervention	Main outcomes
Miller 2014	Unicentre interrupted time series study	Discharged patients from ED with positive cultures requiring antimicrobial revision	Addition of a Pharmacist to review of antimicrobial	Improvement in: - Revised antimicrobial agent for culture (19.2% to 1.3%, $p < 0.0003$) - Incorrect revised antimicrobial duration (27.4% to 12%, $p < 0.02$) - Adjustment of dosing to renal or liver altered function (5.5% to 0%, p 0.04)

ASP = antimicrobial stewardship programme; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ED = Emergency Department; OR = odds ratio.

respiratory tract infection. Implementation was supplemented with educational activities. After review of 36 413 episodes after guideline implementation, amoxicillin–clavulanate and cefpodoxime prescriptions decreased from 43.0% to 10.2% and from 16.6% to 2.5%, respectively, with an increase in single agent amoxicillin from 34.0% to 84.7%. A study showing how antibiotic prescribing improves according to the intensity of intervention was published by Buising et al. [31]. The authors compared three different strategies during three different time periods: first, they delivered copies of clinical guidelines to physicians in the ED without any other intervention; in the second period, they added educational activities in the ED, and, finally, a computerized algorithm based on guidelines was deployed via the hospital intranet. The odds ratio (OR) of receiving guideline concordant or the second period (education alone) compared with the baseline was 2.58, and the OR for the computerized decision support period compared with the educational period was 2.03.

Other strategies include the implementation of clinical pathways incorporating biomarkers, with procalcitonin (PCT) as the main actor. A recent Cochrane database review and meta-analysis published by Schuetz et al. [10] showed a reduction of total antibiotic exposure of 8.1 versus 5.7 days when comparing usual care with a PCT-based algorithm and a reduction of side effects (16.3 vs. 22.1%, respectively), with lower mortality in the PCT group (8.6 vs. 10.0%). The meta-analysis included 32 studies in primary care, ED and ICU settings. Arguably, the inclusion of multiple settings increase heterogeneity in the systematic review, which is one limitation.

Mathioudakis et al. [11] published a review and meta-analysis evaluating PCT-based protocols for acute exacerbations of chronic obstructive pulmonary disease. The main result was a decrease in antibiotic prescriptions and total antibiotic exposure (RR of receiving antibiotic of 0.56, compared with standard treatment) without differences in safety (rate of treatment failures, length of hospitalization, recurrence rates or mortality). However, other studies evaluating PCT to effect changes on empiric antibiotic use or clinical outcomes have not yielded positive results. Thus, interventions employing diagnostic tests should take into account clinical workflow and barriers to practice change, such as lack of access to follow-up care outside the ED, diagnostic uncertainty and a busy shift-based environment, as simply introducing a test without also considering ASP is not likely to succeed in changing prescriber behaviour [12,32].

Multifaceted interventions

Multifaceted interventions are the most frequent type of approach found in the literature. Multidimensional strategies offer a deeper solution in order to achieve ASP goals and usually include an educational intervention, the implementation of a pathway or guidelines to treat the infection and an audit before and after the application of the ASP with or without feedback in order to address the need for behaviour change. Most frequently, studies are focused on one condition, such as urinary tract infections (UTIs) [33,34] and respiratory tract infections [31,35,36]. A few studies have been focused on the goal of reducing specific antibiotics, mainly cephalosporins and quinolones [26].

In the case of ASPs for UTIs, the main objectives are to avoid treatment of non-UTI conditions including asymptomatic pyuria and asymptomatic bacteriuria by facilitating the appropriate diagnosis and selection of the appropriate antimicrobial therapy, more specifically with the reduction of quinolones for uncomplicated cystitis. Studies have implemented an educational intervention to prescribers, with specific recommendations regarding microbiological work-up and local guidelines based on institutional antibiograms. Hecker et al. [33] published a quasi-experimental study that employed multifaceted interventions. The interventions included the development of specific UTI guidelines based on the resistance patterns of the institution, recommendations regarding microbiological work-up and feedback to clinicians after the patients visit via messaging through the electronic health record. During the study period, adherence to UTI guidelines improved from 44% to 82%, with a decrease in fluoroquinolones of 30% for uncomplicated cystitis (from 44% to 14%). Percival et al. [34] showed an increase from 44.8% to 83% in adherence to guidelines in UTI after implementation of a specific ASP. The investigators adapted antibiotic guidelines to the ED specific antibiogram and developed a teaching programme: an institution-specific educational programme by a pharmacist and educational material delivered by e-mail. In addition, the authors conducted a retrospective audit for 2 months during the post-educational period with an e-mail to the ED physician as feedback.

Respiratory tract infection interventions have yielded similar results, with reduced rates of antimicrobial prescribing after multifaceted interventions. Several have focused on conditions where antimicrobials are not indicated, such as non-specific upper respiratory tract infections or acute bronchitis. For example, Metlay et al. [35] conducted a clinical trial in 16 hospitals. In the eight intervention sites they implemented clinician feedback and clinical and patient educational materials. The global aim was to highlight the principles of judicious antibiotic use in respiratory tract infections. They included a patient centred approach, with posters and brochures and an educational video displayed in the waiting room of the ED. After the intervention, antibiotic prescriptions for acute respiratory infections decreased by 10% at intervention sites and increased by 0.5% in control sites. There were no differences in returned patients to ED with upper respiratory tract infections. A study focused on pneumonia improved antibiotic prescribing in 10% with a multifaceted approach [36]: the authors developed a standard of care guide with retrospective audit of prescriptions. Buising et al. [31] designed a multifaceted study in two steps. First, an academic training programme developed by a multidisciplinary team including an ED physician, nurse and a pharmacist along with informative posters regarding pneumonia recommendations. In the second phase, the first phase activities. They found clear improvement in antibiotics prescribing in both periods, being

better after the second period. Compared with the baseline, the OR for the academic teaching period was 2.79 (1.88–4.14) and for this period compared with the second one the OR was 1.99 (1.07–3.69). Finally, a second clinical trial in ASP in the ED [37] in which Marrie et al. assigned hospital to conventional management versus an interventional pathway for pneumonia consisting of clinical practice guidelines, prediction rules to admit the patient and levofloxacin use. The intervention group showed a decrease in length of stay, fewer admissions of patients with low-risk pneumonia and a shortened duration of intravenous antibiotic therapy.

Borde et al. [26] implemented an ASP with the aim to reduce cephalosporin and fluoroquinolone prescriptions in the ED. To that end, they reviewed and updated local guidelines for the most frequent infections, informed and provided education about antimicrobial use and tried to emphasize the need for infectious diseases specialist consultation in specific cases. They obtained a reduction of daily doses of antibiotics, with the highest rates for cephalosporins (68%) with corresponding high rates of prescription for aminopenicillin/beta lactamase inhibitors.

More recently interventions geared towards reducing antibiotic prescribing for viral respiratory tract infections borrowed from the primary care literature [38] have demonstrated success using behavioural nudges such as peer comparisons and public commitment to reduce inappropriate prescribing. An evidence-based toolkit for implementation of such programmes in EDs and urgent care centres based on the Centers for Disease Control and Prevention core elements for outpatient antibiotic stewardship is available publicly online and the authors found a multifaceted intervention that adapted the strategies of Meeker et al. to the ED setting reduced inappropriate prescribing for acute respiratory infections in the ED although the authors where not able to show a difference between education alone and a more behaviourally oriented approach likely due to lack of power in academic settings where prescribing was already low [13,39].

Culture review

Programmes designed to review microbiological positive culture after patient discharge have been studied previously [40–42]. Most of these culture call-back programmes are made possible by pharmacist staff dedicated to this during the study. Reduction of duration of inappropriate antibiotic prescriptions are demonstrated in all of them. The Randolph et al. study [40] compared 12 months of review of cultures after patient discharge by ED physicians with the same work by a pharmacist. Interestingly, the results were better for the pharmacists, with a greater rate of antibiotic modification and fewer readmissions.

What are the strengths and weaknesses of the ASP in the ED?

Most studies we reviewed here led to improved rates of appropriate antimicrobial prescribing. As noted by Losier et al. [9], it is difficult to determine the best option in order to select and implement an ED based ASP. Depending on the characteristics of the institution, the volume and setting of the ED and previous implementation of an institutional hospital-based ASP-specific intervention for ED ASP could be adapted from existing models. Each stewardship intervention indeed requires a tailored approach: apart from choosing the right intervention for the right care setting, an inventory of potential barriers and facilitators to that intervention should ideally be carried out prior to its execution [7]. Multidisciplinary collaboration and pharmacist participation is critical to success as our resources dedicated to the ED ASP [43].

Heterogeneity of studies is a limitation and may be dependent on the specific characteristics of the ED environment and context. Nonetheless, this is a limitation of the conception of the ASP approach due to the need to adapt the programme to the local institutional context in order to obtain success.

Previous studies have focused on measuring the appropriateness of antibiotic prescribing. However, published outcomes have been limited by the use of intermediate or process endpoints. The ultimate goal of any ASP must be to improve patient outcomes including clinical cure, and a decrease in adverse events as well as to maintain adequate (or to decrease) rates of antimicrobial resistance using the minimum antibiotic spectrum as possible [4]. The need for process measures to start hinges on two realities: (a) if patient is discharged after ED admission, it is difficult to measure the impact of the ASP distant from the direct patient outcomes particularly due to lack of follow up; and (b) if admitted in another department, impact of the ED ASP is diluted by hospital-based interventions, inpatient prescribing decisions, the rate of invasive procedures (surgery, diagnostics tests) and other drugs related to ASP outcomes (for instance prescription of proton pump inhibitor related with *Clostridioides difficile*).

Finally, we note that there continues to be a paucity of ED specific ASP studies, and many do not take into account evidence-based behavioural approaches to changing practice. Most are non-randomized clinical trials save for a few studies [14,35,37], and most studies are based in cohorts without control groups (before–after, interrupted time series, bundle studies).

Key questions for future research

Taking into account the strengths and limitations of ED ASP interventions to date, future research should include rigorous study design with the measurement of clinical outcomes, including high-quality RCT, with outcomes focused not just on rates of antimicrobial use but other meaningful clinical and public health outcomes such as adverse events, patient mortality and community rates of antimicrobial resistance. Furthermore, identifying which components of multifaceted interventions are most effective and adapting ASP to the local site and setting using implementation science approaches is critically needed.

Conclusion

In summary, we found that although there is a paucity of high quality AMS studies in the ED setting, there is growing evidence that multifaceted interventions, clinical guidelines, and behavioural approaches targeting prescriber behaviour have moderate impact on antimicrobial prescribing in the ED. Further research should facilitate publication of high quality designs such as RCT and meta-analyses evaluating both antimicrobial prescribing and clinical outcomes for ED patients presenting with suspected infection.

Transparency declaration

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Author contributions

L.M. performed literature review, drafted key portions of the manuscript; A.M.Q. performed literature review, drafted key portions of the manuscript; J.t.O. critically revised the manuscript; J.H. critically revised the manuscript; T.S. performed literature review, drafted key portions of the manuscript; J.S. initiated the literature selection process (part 1), drafted key portions of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.10.028.

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