A systematic review of inpatient antimicrobial stewardship programmes involving clinical pharmacists in small-to-medium-sized hospitals

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ABSTRACT

Objective Antimicrobial stewardship programmes (ASPs) have been widely implemented in large hospitals but little is known regarding small-to-medium-sized hospitals. This literature review evaluates outcomes described for ASPs participated in by clinical pharmacists and implemented in small-to-medium-sized hospitals (<500 beds).

Methods Following PRISMA principles, PubMed and Cochrane Library databases were searched in early 2016 for English language articles describing implementation and outcomes for inpatient ASPs participated in by clinical pharmacists in small-to-medium-sized hospitals. Each included study was required to include at least one of the following outcomes: microbiological outcomes, quality of care and clinical outcomes or antimicrobial use and cost outcomes.

Results We included 28 studies from 26 hospitals, mostly American or Canadian. Most cases (23 studies) consisted of time-series comparisons of pre- and post-intervention periods. Of the 28 studies analysed, 8 reported microbiological outcomes, 21 reported quality of care and clinical outcomes, and 27 reported antimicrobial use and cost outcomes. Interventions were not generally associated with significant changes in mortality or readmission rates but were associated with substantial cost savings, mainly due to reduced use of antibiotics or the use of cheaper antibiotics.

Conclusion As far as we are aware, ours is the first systematic review that evaluates ASPs participated in by clinical pharmacists in small-to-medium-sized hospitals. ASPs appear to be an effective strategy for reducing antimicrobial use and cost. However, the limited association with better microbiological, care quality and clinical outcomes would highlight the need for further studies and for standardised methods for evaluating ASP outcomes.

INTRODUCTION

Antimicrobial resistance is a growing health problem worldwide that urgently needs to be tackled. Several studies have demonstrated that up to 50% of antimicrobial prescriptions in Europe and the USA are considered inappropriate.¹ Infections involving multidrug-resistant microorganisms and *Clostridium difficile* have been shown to increase hospital stays, healthcare costs and mortality,² and to be associated with misuse and overuse of certain antibiotics.^{3–5} Additionally, the decreased use of restricted agents is associated with a parallel increase in the prescription of other antimicrobials that may facilitate the development of yet other

types of resistant microorganisms, a phenomenon known as ‘squeezing the balloon’.^{6,7}

A tool for rationalising antibiotic use in health-care facilities is an antimicrobial stewardship programme (ASP), defined as an ongoing effort by a hospital to optimise antimicrobial use in order to improve patient outcomes, reduce adverse events associated with antimicrobial use (including antimicrobial resistance) and ensure cost-effective therapy.⁸ ASPs, implemented through multidisciplinary teams, monitor all aspects of antibiotic use – from selection and indication to factors related with time – but focus especially on four main measures: antibiotic use, clinical parameters, antibiotic resistance and cost.⁹ Guidelines published by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) indicate that ASP teams should include, as core members, an infectious disease physician and a clinical pharmacist with training in infectious diseases.¹⁰ Two types of interventions have been described for an ASP: in formulary restriction with prior authorisation, antibiotics are administered according to a certain set of patient- or antibiotic-specific criteria, whereas in prospective auditing with feedback, ASP team members interact directly with prescribers to optimally tailor antimicrobial therapy to each patient after initial drug prescription and dispensation.¹¹ A Cochrane systematic review states that it remains unclear which of the interventions is better since no direct comparison has been made between them.¹²

ASPs to date have typically been implemented in large teaching hospitals with substantial financial and human resources. However, for two time periods (2000–2004 vs 1990–1994), it has been shown that the greatest increase in multidrug-resistant microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and ceftazidime-resistant *Pseudomonas aeruginosa* was in hospitals with fewer than 200 beds.¹³ Community hospitals thus need to develop strategies adapted to their size, staffing and infrastructure as well as to specific and localised patterns of resistance.¹⁴

Clinical pharmacists are likely to play a greater role in community hospitals since they may personally review all antimicrobial prescriptions and hold face-to-face discussions with medical and nursing staff and so reinforce the message.¹⁵ Although infectious-disease clinical pharmacists may have several antimicrobial-related tasks (eg, producing evidence-based prescribing guidelines, educating prescribers in the prudent use of antimicrobials, supporting prescribers in optimising antimicrobial therapy for

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individual patients, advising on therapeutic drug monitoring and managing new antimicrobials in hospital formularies), the lack of good-quality evidence of their impact on optimising antimicrobial therapy and patient outcomes would indicate an urgent need for research in this area.¹⁶

The objective of this systematic review was to evaluate the implementation and outcomes of ASPs participated in by clinical pharmacists in small-to-medium-sized hospitals (fewer than 500 beds).

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) principles for systematic reviews were applied. The PubMed and Cochrane Library databases were searched in April 2016 for English language articles describing pharmacist-participated inpatient ASPs and their outcomes for small-to-medium-sized hospitals (fewer than 500 beds) and further relevant articles were identified from cross-references. Hospitals with fewer than 500 beds were defined as small-to-medium-sized hospitals since they accounted for 94% of American Hospital Association-defined community hospitals in 2013 and 78% of acute care facilities reporting to the National Healthcare Safety Network in 2015.^{17 18}

Articles selected for initial review had the following terms in their titles or abstracts: 'antimicrobial stewardship programmes'; 'antimicrobial stewardship program'; 'antimicrobial stewardship programmes'; 'antimicrobial stewardship programme'; 'antimicrobial stewardship community hospital'; 'antimicrobial control'; 'antibiotic control' or 'antibiotic stewardship'. Selection was further limited to those studies that also contained the following terms in the titles or abstracts: 'clinical pharmacist'; 'pharmacists'; 'clinical pharmacy'; 'pharmacy'; 'pharmacist'; 'pharmacist interventions'; 'community hospital'; 'community hospitals'; or 'pharmaceutical care'.

Selected for review from the studies meeting the above initial selection criteria were articles reporting ASP evaluations and outcomes in inpatient settings with the participation of at least one clinical pharmacist, provided the full text was accessible via PubMed, the Cochrane Library, the library of the Autonomous University of Barcelona or could be obtained directly from the authors. Multicentre studies were excluded because it is difficult to guarantee similarity in the characteristics of hospitals, patients and methodologies.

From each of the above studies, two reviewers independently extracted the following information:

- ▶ General characteristics. City and country, hospital size (number of beds), patient exclusion criteria, number of patients, mean/median age of patients, whether the ASP was run for a specific department or the entire hospital, study design, study duration, inclusion of antivirals and antifungals, ASP team members and ASP strategies.
- ▶ Microbiological outcomes. Changes in antibiotic susceptibility, incidence of antimicrobial-resistant microorganisms and *C. difficile* infection, and proportion of sterile/non-sterile site cultures treated.
- ▶ Care quality and clinical outcomes. Length of stay, improvement in patient chart documentation details, mortality rates, readmission rates, number of pharmacotherapeutic interventions and acceptance rates, adverse events and physician satisfaction regarding ASP interventions.
- ▶ Antimicrobial use and cost. Antimicrobial costs, personnel costs, implementation costs and total cost savings.

Figure 1 Flow chart showing screening process.

Risk-of-bias assessment

We applied the 2016 Cochrane Effective Practice and Organisation of Care (EPoC) risk-of-bias criteria to all papers included in this review.¹⁹ Studies were scored for risk of bias as follows: low, if all criteria were scored as 'low'; medium, if one or two criteria were scored as 'unclear' or 'high'; and high if three or more criteria were scored as 'unclear' or 'high'.²⁰

RESULTS

Our search identified 644 titles and abstracts and five additional articles identified through cross-referencing (total 649 studies), of which only 28 studies met eligibility criteria for inclusion in this systematic review. Reasons for excluding other studies are explained in the screening flow chart in figure 1. Letters to the editor and abstracts from conferences were excluded since they frequently lack the data necessary to evaluate methodological quality.

General characteristics

Online supplementary table 1 summarises setting, ASP team compositions, study designs, study durations and stewardship intervention types for the 28 included studies. The 28 studies described formal ASPs in 26 hospitals of different sizes: fewer than 100 beds (n=1); 100–200 beds (n=6); 201–300 beds (n=5); 301–400 beds (n=6); and 401–500 beds (n=8). Most of the studies referred to the USA or Canada (n=21). ASP strategies implemented were as follows: prospective auditing with feedback (n=17); preauthorised formulary restriction (n=4); and both strategies (n=7). ASP teams comprised at least one physician and one pharmacist and, in most cases (22 studies), the ASP was rolled out across the entire hospital. Most cases (23 studies) consisted of a time-series comparison of the pre- and post-intervention periods, and the remaining five studies were randomised controlled trials (n=3), a prospective interventional study (n=1) and a quasi-experimental stepped-wedge controlled study (n=1). In most cases (21 studies) the intervention period ranged between 1 and 3 years. Regarding antimicrobial classes, only 5 and 11 studies reported including antiviral drugs and antifungal drugs, respectively, in their analysis. Finally, the number of patients reviewed by the ASP team was only clearly specified in 17 of the 28 studies: these reported numbers of 14 to 8765 patients for the intervention group/period (age range: 56–78.3 years for adult studies and 2.5–8.5 years for paediatric studies).

In the nine studies that clearly highlighted exclusion criteria, the most frequently applied criteria were paediatric patients (four studies) and patients with cystic fibrosis (two studies).

Microbiological outcomes

Most studies did not report statistically significant results for microbiological outcomes (online supplementary table 2). One study reported cumulative susceptibilities to specific organism-antibiotic combinations such as *Enterobacter aerogenes*, *Proteus mirabilis* and *Pseudomonas aeruginosa*.²¹ Another study highlighted a drop in the rate of carbapenem-resistant *Pseudomonas spp.* from 6% to 1% despite rates for ceftazidime-resistant *Klebsiella spp.* and ceftazidime-resistant *Pseudomonas spp.* increasing from 12% to 42% and from 4% to 14%, respectively.²² Another study reported a higher proportion of sterile-site cultures and a lower proportion of non-sterile site cultures being treated after ASP implementation.²³ Two studies reported a significant decrease in the annual *C. difficile* rate: from 0.11 to 0.07 per 1000 patient-days²¹ and from 5.5 to 1.6 cases per 10 000 patient-days.²⁴ Finally, contradictory results were reported for MRSA infections, with two studies reporting a decrease in monthly rates from 2.9 to 1.5 cases per 1000 patient-days²⁵ and a decrease from 50% to 34% of all clinical isolates,²⁶ but with two other studies reporting higher rates of MRSA infections in the post-intervention period^{27 28} and a decrease in the number of patients with vancomycin-resistant *Enterococcus* infection (from 10 to 2 cases annually), while the number of patients with vancomycin-susceptible *Enterococcus* infection increased.²⁸

Quality of care and clinical outcomes

The number of ASP-proposed pharmacotherapeutic interventions implemented by physicians was not reported by 13 studies, and the remaining 15 studies reported 10 to 2457 interventions (obviously dependent on study length). Interventions differed between studies and not all were described in detail. Intervention acceptance rates ranged from 50.5% to 94%, with 4 of the 28 studies reporting acceptance rates of more than 90%. None of the studies reported significant drops in readmission rates after ASP implementation, but one study reported reduced hospital stays for the intervention group²⁹ and another study reported reduced mortality and reduced stays (of around 2.4 days) for patients with infections.²⁶ Contradictory results were reported, however, for length of stay for patients with community-acquired pneumonia.^{30 31} One study reported chart documentation improvements for intensive-care unit (ICU) patients in terms of antimicrobial indication, dosage, stop dates and de-escalation after the ASP was initiated.²³ Only six of the studies collected data on possible adverse outcomes associated with ASP-related pharmacotherapeutic interventions, but no study recorded any actual adverse event. Four studies reported increased physician satisfaction with ASP interventions most notably, an increase from 22% to 68% after implementation of an online ASP.³² A further three studies reported greater physician confidence in pharmaceutical and antimicrobial recommendations after implementing an ASP.^{24 29 33}

Antimicrobial use and cost outcomes

Twenty-two and 19 studies reported outcomes for antimicrobial use and cost, respectively (online supplementary table 2). The 22 studies reporting data on use indicated decreased antimicrobial use after ASP rollout, although the specific metrics differed between studies. Some studies reported decreases in general antimicrobial use^{22 23 31–37} or decreases in certain targeted antibiotics such as the carbapenems,^{30 35 38–40} linezolid³⁵ and daptomycin.³⁰ Despite curtailment of general or targeted antimicrobials, increased use was

reported for specific antibiotics such as the beta-lactams,^{21 30 35 37 40} quinolones^{21 38} and clindamycin.^{28 37} As for the 19 studies with data on cost, all reported decreased antimicrobial spending after ASP rollout: nine reported pre- and post-ASP implementation comparisons between antibiotic cost per inpatient-days;^{23–25 33–35 39 41 42} and 11 reported reductions in antimicrobial purchase costs of between 17% and 69%.^{22 23 26 29 30 32 33 37–39 43} Finally, only three studies reported annual personnel costs, at \$22,092,²⁹ \$47,220⁴¹ and \$121,300.³⁸ None of the 19 studies reporting cost data included information regarding the actual ASP cost.

Risk-of-bias assessment

Risk of bias was low for eight studies,^{22 23 27 28 30 37 40 42} medium for 12 studies^{25 26 31 32 34–36 38 39 41 45 46} and high for eight studies.^{21 24 29 33 43 44 47 48}

DISCUSSION

No clear conclusions can be drawn from the results of our review of inpatient ASPs rolled out in small-to-medium-sized hospitals, other than regarding benefits in terms of reduced antimicrobial use and cost.

The importance of ASPs as national strategies to improve antibiotic prescribing is widely recognised, to the point where ASPs are now included in regulatory frameworks, some of which include provisions for healthcare providers to put an ASP in place.⁴⁹ We evaluated 28 studies referring to small-to-medium-sized hospitals a similar number of studies to reviews referring to larger hospitals.^{50–52} As with the larger hospitals, for small-to-medium-sized hospitals there is still limited evidence for the impact of ASPs on patient outcomes, mainly because many of the studies have methodological limitations, include few patients or have short follow-up periods.

Although optimising clinical outcomes is the primary goal of ASPs, results for mortality, hospital readmission and length of stay were rarely reported, and if reported, were mostly non-significant. Only one study in our review found an association between ASP implementation and a drop in mortality rates.²⁶ For larger hospitals, ASP implementation was not associated with reductions in mortality or readmission rates, and contradictory results have been reported for length of stay.^{50–52} However, both small-to-medium-sized and large hospitals seem to obtain positive results in terms of antimicrobial use and cost savings, and ASP implementation appears not to be associated with adverse outcomes.^{50 51} We suggest that the fact that ASPs are not associated with increases in mortality rates or hospital readmissions is of paramount importance, since it demonstrates that ASPs are not harmful for patients but are likely to produce important cost savings for the hospital.

Individual strategies should be taken into account if a full ASP cannot be implemented. For instance, an infection team could focus on sequential therapy (a systematic plan to switch from parenteral to oral antimicrobials with excellent bioavailability) and so achieve shorter stays, fewer nosocomial infections and lower healthcare costs.⁵³ If an ASP cannot be rolled out in the entire hospital, it could be targeted in especially appropriate areas such as the emergency or surgical departments,^{54 55} or, as happened in three studies in our review, the ICU.^{23 34 39}

Results regarding microbiological outcomes would appear to depend on the pathogen. Although two studies in our review found a significant decrease in the annual *C. difficile* rate,^{21 24} contradictory results were found for MRSA^{27 28} and for ceftazidime-resistant *Klebsiella spp.* and ceftazidime-resistant *Pseudomonas spp.*²² Regarding MRSA, the two studies reporting higher MRSA rates

during the ASP rollout period may not be truly representative, as they were focused on reducing vancomycin use in a paediatric setting.^{27,28} As for the increases reported for ceftazidime-resistant *Klebsiella spp.* and ceftazidime-resistant *Pseudomonas spp.*,²² these were attributed to decreased carbapenem and increased cephalosporin prescriptions, a phenomenon widely recognised as 'squeezing the balloon'.⁶

The benefits of ASPs were especially evident in antimicrobial use and cost outcomes. Leaving aside a study that did not evaluate these parameters⁴⁴ and another study that found limited efficacy for these outcomes,⁴⁸ all the remaining 26 studies described significant decreases in antimicrobial use or cost. The fact that some studies provided no information regarding reasons for switching antimicrobials or reducing antimicrobial use limits the usefulness of those results when it comes to evaluating whether or not guidelines were followed. Note that none of the studies included accurate information on the cost of the ASP itself and each study used different metrics for ASP results — both issues that have been widely discussed. A recent systematic review has indicated, for instance, that without such information it is impossible to compare studies or draw general conclusions regarding the financial benefits of ASPs.⁵⁶ All this would suggest that much more work remains to be done, both to improve this kind of study and to conduct formal financial studies that calculate the real impact of ASP implementation.

As far as we are aware, ours is the first systematic review that evaluates ASPs involving clinical pharmacists in small-to-medium-sized hospitals — a setting where it is recognised that most work is needed.^{13,14} Our review, however, confirms the important role played by clinical pharmacists and infectious disease physicians in ASP implementation in the 28 evaluated studies. A European cross-sectional study of 263 hospitals (with a median of 669 beds) showed that antibiotic consumption was lower when a pharmacist worked with the prescriber.⁵⁷ There is also evidence that availing of a pharmacist specialising in infectious diseases, as opposed to a ward pharmacist, may ensure greater adherence to antimicrobial therapy recommendations.⁵⁸ Interestingly, the British National Health Service reported a significant increase in absolute numbers of antimicrobial-specialist pharmacy staff between 2005 and 2011.⁵⁹

Our systematic review has a number of limitations. First, although we tried to mine the maximum number of relevant studies using a wide range of specific search terms, we may have missed out on some studies depending on how authors described their paper, wrote their title and abstract, or chose their key words. Furthermore, the full text was unavailable for one study that appeared to meet with all the inclusion criteria (although we could not be sure that the hospital had under 500 beds), but it is unlikely that this single paper could change the conclusions of our review.⁶⁰

Second, we could not consult Embase since we did not have access to this database. Nonetheless, we suggest that articles found in PubMed and the Cochrane Library are sufficiently representative of published evidence on this topic. Third, although it is likely that more than 26 small-to-medium-sized hospitals have implemented ASPs in recent decades, we cannot rule out the possibility that many of them found negative results — and it is well known that negative results are less likely to be published than positive results.⁶¹ Fourth, since around two-thirds of the included studies had medium or high risk-of-bias scores, additional clinical trials in small-to-medium-sized hospitals that compare antibiotic stewardship with no intervention could well change our conclusions. Fifth, 21 of the 28 studies were performed in the USA (n=17) or Canada (n=4), so their results cannot be extrapolated to hospitals located in other countries. What is remarkable is the lack of studies for European hospitals (we identified only one study for Europe), as

such studies would, naturally, be useful for comparison with results for the USA and Canada. Finally, the objectives and conclusions of the individual studies were variable, which makes it difficult to draw any clear conclusion regarding the clinical benefits of ASP implementation involving clinical pharmacists in small-to-medium-sized hospitals.

CONCLUSION

Our review of ASPs involving clinical pharmacists rolled out in small-to-medium-sized hospitals would indicate that ASPs are effective in decreasing both antimicrobial use and cost. What remains unclear, however, is the association with better clinical, care quality and microbiological outcomes. This highlights the need for more studies and for standardised methods for evaluating ASP outcomes.

Key messages

What is already known on this subject?

- ▶ Antimicrobial stewardship programmes are widely implemented in large hospitals but evidence about their usefulness in small-to-medium-sized hospitals is lacking.
- ▶ The clinical pharmacist as an expert in pharmacotherapy can play a crucial role in this setting.

What this study adds?

- ▶ Implementing an antimicrobial stewardship programme that involves clinical pharmacists in a small-to-medium-sized hospital is an effective approach in decreasing antimicrobial use and cost.
- ▶ More studies are urgently needed to demonstrate ASP correlation with better microbiological, care quality and clinical outcomes.

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