Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis

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Summary

Background Antimicrobial stewardship is advocated to improve the quality of antimicrobial use. We did a systematic review and meta-analysis to assess whether antimicrobial stewardship objectives had any effects in hospitals and long-term care facilities on four predefined patients' outcomes: clinical outcomes, adverse events, costs, and bacterial resistance rates.

Methods We identified 14 stewardship objectives and did a separate systematic search for articles relating to each one in Embase, Ovid MEDLINE, and PubMed. Studies were included if they reported data on any of the four predefined outcomes in patients in whom the specific antimicrobial stewardship objective was assessed and compared the findings in patients in whom the objective was or was not met. We used a random-effects model to calculate relative risk reductions with relative risks and 95% CIs.

Findings We identified 145 unique studies with data on nine stewardship objectives. Overall, the quality of evidence was generally low and heterogeneity between studies was mostly moderate to high. For the objectives empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral treatment, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation the overall evidence showed significant benefits for one or more of the four outcomes. Guideline-adherent empirical therapy was associated with a relative risk reduction for mortality of 35% (relative risk 0·65, 95% CI 0·54–0·80, p<0·0001) and for de-escalation of 66% (0·44, 0·30–0·66, p<0·0001). Evidence of effects was less clear for adjusting therapy according to renal function, discontinuing therapy based on lack of clinical or microbiological evidence of infection, and having a local antibiotic guide. We found no reports for the remaining five stewardship objectives or for long-term care facilities.

Interpretation Our findings of beneficial effects on outcomes with nine antimicrobial stewardship objectives suggest they can guide stewardship teams in their efforts to improve the quality of antibiotic use in hospitals.

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Introduction

Although the benefits of antibiotic use are indisputable, misuse and overuse of antibiotics have contributed to antibiotic resistance, which has become a serious and growing threat to public health.[1,2] Patients with infections caused by resistant bacteria generally have an increased risk of poor clinical outcomes and death and use more health-care resources than patients infected with non-resistant bacteria of the same species.[2]

Of all antibiotics prescribed in acute-care hospitals, 20–50% are either unnecessary or inappropriate.[3–6] Hospitals worldwide have been incorporating antimicrobial stewardship into hospital policy, with the goal of improving the quality of antimicrobial use. The primary goal of antimicrobial stewardship is to achieve optimum clinical outcomes and ensure cost-effectiveness of therapy while keeping to a minimum unintended consequences of antimicrobial use, including toxic effects, selection of pathogenic organisms, and the emergence of resistance.[7] The characteristics of antimicrobial stewardship programmes vary[8] but generally consist of a range of interventions that can be selected and adapted to fit the infrastructure of any hospital.[9]

In stewardship programmes, two sets of interventions should be distinguished. The first relates to recommended care at the patient level (stewardship objectives), such as treating patients according to the guidelines or taking cultures of blood and from the site of infection. The second set relates to recommended strategies for achieving the stewardship objectives, such as restrictive (eg, formulary restriction) and persuasive (eg, education and feedback) strategies, to improve appropriate antimicrobial use. The evidence for the second set of interventions has been systematically reviewed,[5] but the yields of individual stewardship objectives do not seem to have been assessed.

We did a systematic review and meta-analysis to summarise the current state of evidence of the effects of antimicrobial stewardship objectives on patients' clinical outcomes (eg, mortality and length of stay [LOS] in

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Research in context

Evidence before this study

We searched for all relevant studies published up to April 11, 2014, in Embase, Ovid MEDLINE, and PubMed. Each search addressed one of 14 antimicrobial stewardship objectives, and every search included terms for four predefined outcomes (clinical outcome, adverse events, costs, and resistance). An initial broad search strategy was used as the basis for all searches, to which specified strings were added that defined the 14 objectives being reviewed. Eligible study types were randomised controlled trials, non-randomised controlled trials, interrupted time series, and observational studies published in English, German, Spanish, French, or Dutch. We have found no systematic reviews published on this topic since our search.

Added value of this study

This systematic review revealed that the use of empirical therapy according to guidelines, de-escalation of therapy, switching from intravenous to oral treatment, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation (especially in case of *Staphylococcus aureus* bacteraemia) are the most important objectives of the antimicrobial stewardship programme. The overall evidence for these objectives shows significant benefits for clinical outcomes, adverse events, costs, resistance rates, or combinations of these. However, the included studies were generally of low quality.

Implications of all the available evidence

For several antimicrobial stewardship objectives there is abundant, although low-quality, evidence on clinical outcomes, adverse events, costs, and resistance rates in hospitals. High-quality studies are now needed to provide better information on the effects of these objectives. We found no studies done in long-term care facilities, and research is needed in this setting. Our results combined with the previous critical appraisal of restrictive and persuasive strategies to improve appropriate antimicrobial use in patient care could guide hospital stewardship teams in improving the quality of antibiotic use.

hospital), adverse events, costs, and bacterial resistance rates in hospitals and long-term care facilities.

Methods

Review topics

International experts had previously used a RAND-modified Delphi procedure to create a set of 11 quality indicators for appropriateness of antibiotic use in the treatment of all bacterial infections in adults while in hospital.[10] Because these quality indicators were designed to be used in antimicrobial stewardship programmes to determine features of antibiotic use that need improvement, we used them as our set of stewardship objectives to study. Three additional objectives were mentioned in the 2007 Infectious Diseases Society of America guidelines on antimicrobial stewardship[7] or identified during a consensus meeting with an antimicrobial stewardship guideline development group representing the professional societies most involved in establishing antimicrobial stewardship programmes in the Netherlands. We included these to create a final list of 14 antimicrobial stewardship objectives (table 1).

Search strategy

Together with a clinical librarian, we searched Embase, Ovid MEDLINE, and PubMed for all relevant studies published up to April 11, 2014, on the antimicrobial stewardship objectives and four predefined outcomes (clinical outcomes, adverse events, cost, and resistance rates; appendix). Each objective was reviewed separately. The same broad search strategy was used as the basis for all 14 searches, and individual search strings were added according to the specific antimicrobial stewardship objective that was being reviewed (appendix). The primary search results were imported into a database (EndNote, Thomson Reuters, Philadelphia, PA, USA) and duplicate studies were removed.

See Online for appendix

All titles and abstracts were screened by one author (ECS) to identify studies that potentially met the inclusion criteria, and 10% (minimum 100 papers per search) were independently screened by another author JMP. We allowed up to 2·5% of papers per search identified by JMP as being eligible to have been missed by ECS. Differences in opinion were resolved by discussion. If after discussion the difference remained more than 2·5%, all titles and abstracts within the specific search were reviewed by JMP. Next, the full texts of all potentially relevant articles were retrieved and assessed by both authors for eligibility. Any disagreement on inclusion or exclusion of studies was resolved through discussion with a third author (MEJLH). We searched the reference list of each article for additional suitable studies.

Inclusion and exclusion criteria

To assess the evidence for each separate stewardship objective, we looked for studies that reported data on any of the four predefined outcomes in patients in whom the targeted antimicrobial stewardship objective was met compared with patients in whom the targeted objective was not met (eg, patients in whom empirical treatment was prescribed in accordance with guidelines *vs* patients in whom it was not). Ineligible papers were those that primarily studied strategies for how to achieve the stewardship objectives or that reported group data instead of comparisons of patients. Eligible study types were randomised controlled trials (RCTs), non-RCTs, interrupted time series, and observational studies, and

	Definitions
Empirical therapy according to the guidelines	Empirical systemic antibiotic therapy prescribed according to local guide or national guidelines*
Blood cultures	Take at least two sets of blood cultures before starting systemic antibiotic therapy
Cultures from the site of infection	Take cultures from suspected sites of infection, preferably before starting systemic antibiotic therapy
De-escalation of therapy	Change to narrow-spectrum antibiotic or stop antibiotics as soon as culture results are available[10–13]
Adjustment of therapy to renal function	Adjustment of dose and dosing interval of systemic antibiotics
Switch from intravenous to oral therapy	Switch after 48–72 h, when the clinical condition of the patient is stable, oral intake and gastrointestinal absorption are adequate, and when sufficiently high concentrations in blood with a suitable oral antibiotic can be achieved[10,14,15]
Documented antibiotic plan	Documented antibiotic plan should include indication, drug name and dose, and administration route and interval, and should be included in the case notes at the start of systemic antibiotic treatment
Therapeutic drug monitoring	NA
Discontinuation of antibiotic therapy if infection is not confirmed	Discontinuation of empirical treatment based on lack of clinical or microbiological evidence of infection†
Presence of a local antibiotic guide	Local antibiotic guide present in the hospital and assessed for update every 3 years
Local antibiotic guide in agreement with national antibiotic guidelines	Corresponds for all features but can deviate on the basis of local resistance patterns
List of restricted antibiotics	Removal of specific antibiotics from the formulary or restriction of use by requiring preauthorisation by a specialist (infectious diseases or medical microbiology) or allowing use for only 72 h with mandatory approval for further use; studies in outbreak settings excluded
Bedside consultation	Formal consultation by an infectious disease specialist leading to written comments and advice on treatment based on physical examination and review of medical records (informal consultation, for example by telephone, does not count as bedside consultation)
Assessment of patients' adherence	NA

NA=not applicable. *All results extracted if both reported. †Studies only reporting on differences between discontinuing and continuing treatment were included, whereas those including more general reports on de-escalation of therapy (broad to narrower spectrum or stopping treatment based on culture results) were included in the review of de-escalation of therapy.

***Table 1*: Antimicrobial stewardship objectives included in systematic review**

could be published in English, German, Spanish, French, or Dutch. Studies meeting the inclusion criteria were also retrieved from systematic reviews. Study outcomes had to be related to antibiotic treatment, although we did not restrict our search to any specific infections, and had to be assessed in hospital or long-term care facilities. Papers could be included in more than one search if the effects of the separate objectives could be distinguished.

We excluded case reports, narrative reviews, discussion papers, conference papers, letters to the editor, and editorials, any studies published after April, 2014. We also excluded studies done in resource-limited settings and those that included outpatients or patients treated by general practitioners. Finally, we excluded studies in which all patients were younger than 18 years and those that assessed outbreak settings, prophylactic and peri-operative treatment, and *Helicobacter pylori*, malaria, HIV, and mycobacterial disease.

Data extraction and statistical analysis

We used a standard form to extract data from included studies to enable evidence synthesis and assessment of study quality. We extracted title, year, authors, study setting, disorder studied, details of the intervention and control conditions, data on the four predefined outcomes, and information necessary to assess risk of bias. To prevent double counting, where possible we report aggregated data (eg, total hospital costs instead of costs of antibiotics by class), median rather than mean values, and data for 1 year rather than data per day. If available, we used data from multivariate analyses and those represented as standardised measures, such as defined daily dose. Since cost is a variable dependent on setting and time, we did not transform data into standardised measures, and we report the unit of costs as reported in the selected studies.

All information was extracted by one author (ECS) and was fully checked for accuracy by a second author (JWM, PDvdL, JAS, or JMP). Discrepancies were identified and resolved through discussion (with a third author if necessary).

If the data on the predefined outcomes were not present or were incomplete, missing data were not requested from study authors and the study was excluded. We pooled data on outcomes, irrespective of study design or type of disorder, and analysed them with a random-effects model and, when relevant, displayed them in forest plots. We report relative risk reductions (RRRs) with risk reductions (RRs) and 95% CIs. We used the I^2 test to test for heterogeneity, with values greater than 65% representing major heterogeneity, those of 40–65% moderate heterogeneity, and those less than 40% low heterogeneity. If appropriate, we did sensitivity analyses by study design or the largest group of patients (eg, by disorder). We followed the PRISMA criteria for all systematic reviews (appendix).[11,12] The protocol is available online.

For the **protocol** see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014466

Quality assessment

The risk of bias of each included study was assessed by two independent authors (ECS, MEJLH, JWM, PDvdL, JAS, or JMP) with the Cochrane Risk of Bias tool for RCTs,[13] the Quality in Prognostic Studies tool for prognostic factors,[14] and an adapted version of the Newcastle-Ottawa Quality Assessment Scale for non-RCTs (appendix).[15] The final assessment on quality of evidence, for each predefined endpoint was done with the Grading of Recommendations Assessment, Development, and Evaluation approach. More information on the quality assessment of the studies can be found in the appendix.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Search results

In 14 searches we found 22 017 citations: 8330 in MEDLINE, 13 129 in Embase, and 558 in PubMed only. In addition to the primary search, we identified 87 papers by reviewing reference lists. After removing all duplicates, 16 387 papers remained. After screening of titles and abstracts, 669 potentially relevant studies were selected for full-text screening, including nine systematic reviews that were used to identify additional eligible studies. 146 papers (145 studies) met the inclusion criteria (figure 1, table 2, appendix). The main reasons for excluding studies were lack of data on any of the four predefined outcomes, the study design, or use of a language outside the search parameters. In all searches less than two (2·5%) papers screened by the second author were deemed to have been missed for eligibility by the first author.

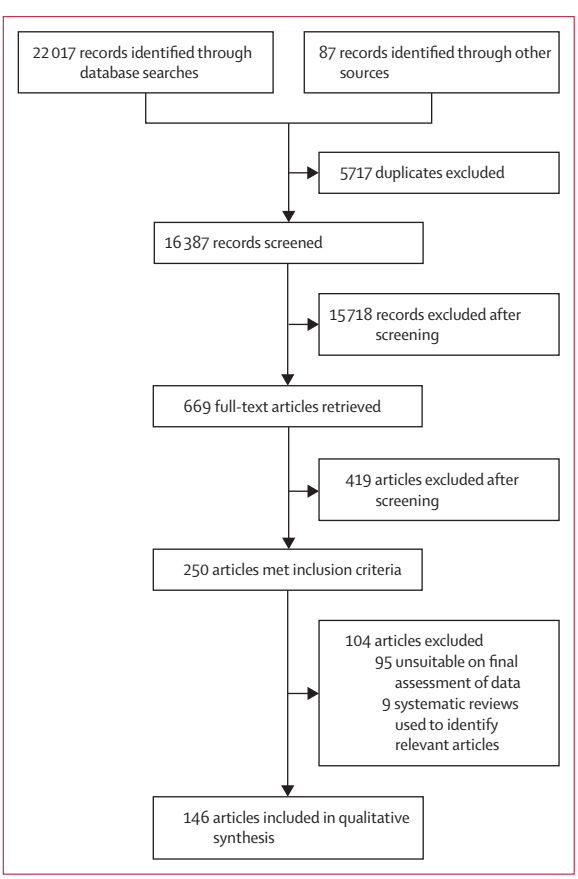

Figure 1: **Trial profile**

Most papers reported evidence on five of the stewardship objectives: adherence to guidelines, lists of restricted antibiotics, de-escalation of therapy (empirical therapy changed to pathogen-directed therapy as soon as culture results became available), switching from intravenous to oral treatment, and therapeutic drug monitoring. A few studies included data for bedside consultation, adaptation of dose or dosing interval according to renal function, criteria for discontinuing treatment, or the presence of a local antibiotic guide. No papers provided data on the five remaining objectives (table 2, appendix). We therefore present results for the nine objectives with data. Data, including those from sensitivity analyses, were pooled only for mortality and adverse events because SDs were seldom reported for LOS and costs (appendix).

Empirical therapy according to the guidelines

40 studies reporting data on empirical treatment according to guidelines were identified (appendix), all of which were observational and had a high risk of bias. Therefore, the quality of research on this objective was judged to be poor.

Of 37 studies reporting effects on mortality, 31 showed that prescribing according to guidelines was associated with reduced mortality, with 14 studies showing significant associations. One study reported no effect on mortality and five reported increased mortality (one significantly so). The RRR for mortality across all studies was 35% (RR 0·65, 95% CI 0·54–0·80, p<0·0001), with moderate heterogeneity (I^2 65%, figure 2). Most studies involved patients with pulmonary infections, mainly community-acquired pneumonia, and, therefore, we did a sensitivity analysis based on this disorder. The effect on mortality did not change (appendix). Four studies provided data on treatment failure and showed a significant benefit with adherence to guidelines.

Of 24 studies assessing the effects on hospital LOS, 17 showed decreased durations with adherence to guidelines, with significant effects in eight; whether there was a similar effect for intensive-care unit (ICU) LOS was less clear. Among the remaining seven studies, four showed non-significantly increased LOS with adherence to guidelines and three showed no effect.

The four studies reporting data on costs indicated that savings were made with adherence to guidelines. The cost reductions were highly significant in two of these studies.

De-escalation of therapy based on culture

Of 25 studies reporting on this objective (appendix), one was a good-quality RCT, but the others were observational studies and had high risk of bias, resulting in poor-quality evidence. The hypothesis of most of the studies was that de-escalating therapy would be non-inferior to unmodified therapy. Of the 19 observational studies reporting data on mortality, however, 17 showed benefits with de-escalation, with effects being significant in seven. The two remaining studies reported increased mortality, although the difference from patients without de-escalation of therapy was not significant. The RRR for mortality across studies was 66% (RR 0·44, 95% CI 0·30–0·66, p<0·0001) and heterogeneity was moderate (I^2 59%, appendix). A sensitivity analysis of the observational studies did not affect the mortality findings (appendix).

Ten studies assessed LOS, of which nine observational studies suggested decreased duration, although only two showed significant effects. The tenth study, the RCT, reported non-significantly increased LOS in hospital and ICU. Four observational studies that reported ICU LOS showed reduced durations, with significant effects seen in two.

Of the 13 studies reporting on costs, 11 showed savings when comparing de-escalation of therapy with unmodified therapy, and five reported significant differences. Two studies reported increased costs associated with de-escalation—one because of culturing of samples and one because of higher median daily antimicrobial costs.

Adjustment of therapy according to renal function

Five observational studies assessed adjustment of antibiotic treatment according to renal function (appendix). The risk of bias was high and the quality of studies was deemed poor.

Very few data on our predefined endpoints were reported in these studies. One study noted a non-significant positive effect on mortality and a significant shortening of ICU LOS. Three studies reported benefits for adverse effects, which were significant in two. Four studies showed cost savings by adjustment of therapy, but no significance levels were mentioned.

Switch from intravenous to oral therapy

18 studies assessed switching routes of therapy, of which 13 were RCTs and five were observational studies (appendix). Nevertheless, the quality of evidence was generally low because of small sample size and high risk of bias.

Most studies tested non-inferiority hypotheses. Five RCTs reported data on mortality, with four showing non-significant beneficial effects and one showing a non-significant negative effect. One observational study reported non-significantly reduced mortality in patients who switched to oral treatment. The overall effect on mortality was non-significant with low heterogeneity, and these findings were not altered by a sensitivity analysis of RCTs (appendix). 11 studies reported data on cure or resolution, none of which showed a significant result. Seven studies reported a positive effect on cure or resolution, three a negative effect, and one no effect. The two observational studies and five RCTs showed significant effects on reducing hospital LOS. Of the remaining three RCTs, two showed non-signficant increases in LOS and one a non-significant decrease. Costs were reduced in three observational studies and eight RCTs, with two and one, respectively, reporting significant differences.

	Number of records after duplicates removed	Number of full-text articles screened	Number of studies included in qualitative synthesis
Empirical therapy according to the guidelines	760	110	40
Blood cultures	1921	9	0
Cultures from site of infection	1352	14	0
De-escalation of therapy*	2726	121	25
Adjustment of therapy to renal function	1087	24	5
Switch from intravenous to oral therapy	1499	112	18
Documented antibiotic plan	234	2	0
Therapeutic drug monitoring	2250	64	17†
Discontinuation of antibiotic therapy if infection not confirmed	447	19	3
Presence of a local antibiotic guide	946	4	1
Local guide in agreement with national guidelines	295	8	0
List of restricted antibiotics	1231	140	30
Bedside consultation	684	24	7
Assessment of patients' adherence	868	18	0
Total	16 300‡	669	146

*From a broad-spectrum to narrower-spectrum antibiotic. †16 studies used for data analysis because two papers reported the same study. ‡Review of references led to identification of 87 additional records.

Table 2: **Results of database searches per antimicrobial stewardship objective**

Therapeutic drug monitoring

16 unique studies reported on drug monitoring activities, of which nine were observational studies and seven were RCTs or non-RCTs (appendix). Mortality data were presented in six of the RCTs and non-RCTs. None showed a significant effect, but mortality seemed to be decreased in four studies among patients who underwent monitoring, and to be increased in two. Three observational studies reported data on mortality, with one showing no effect and two studies reporting significant reductions. The overall effect on mortality was non-signficant and heterogeneity was moderate (appendix). The effect in observational studies became significant when we did a sensitivity analysis, but that in RCTs did not change (appendix).

Four of five RCTs and non-RCTs reported shorter LOS in hospital for patients in whom drugs were monitored

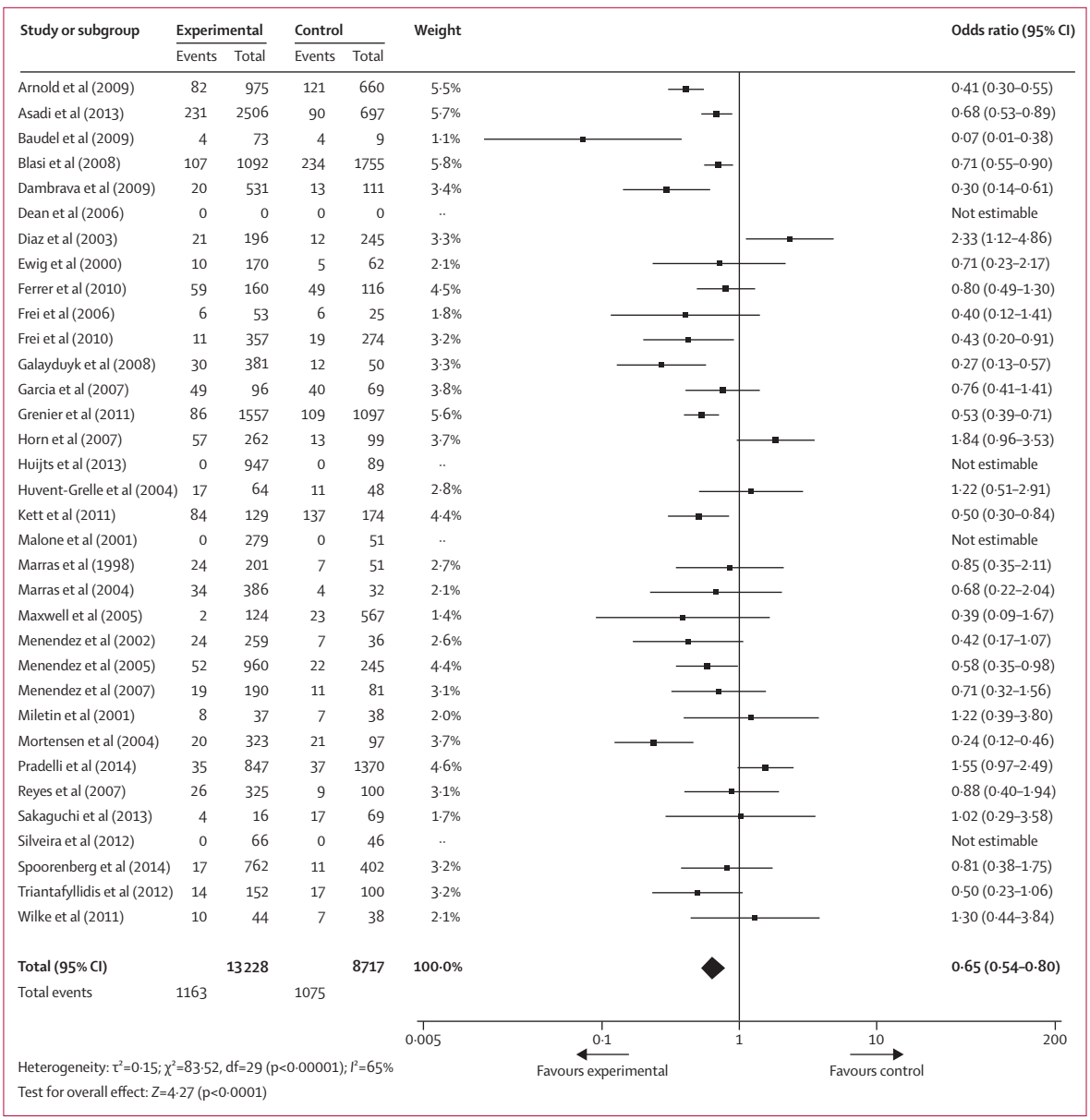

***Figure 2*: Effect on mortality of prescribing empirical antimicrobial therapy according to guidelines**

than for those in whom they were not, with two reporting significant differences. One RCT showed that therapeutic drug monitoring was associated with a non-significant increase in hospital LOS. In four of the six observational studies, LOS in hospital was shortened in the monitored patients, with significant differences seen in three studies. The remaining two observational studies reported non-significantly increased LOS.

13 studies—four non-RCTs and nine observational studies—reported on the rate of nephrotoxicicity. The RRR was significant at 50% (RR 0·50, 95% CI 0·29–0·88, p=0·02) across all studies, with moderate heterogeneity (I^2 45%, figure 3).

Data on costs showed wide variation when therapeutic drug monitoring was used, but overall there seemed to be a beneficial effect. Two RCTs and non-RCTs reported non-significant cost savings and one RCT reported a non-significant increase in costs. All five observational studies reported cost savings, which were significant in one.

Discontinuation of empirical treatment based on no evidence of infection

Only three studies reported on discontinuation of therapy due to no clinical or microbiological evidence of infection (appendix). Two of these studies were low-quality RCTs

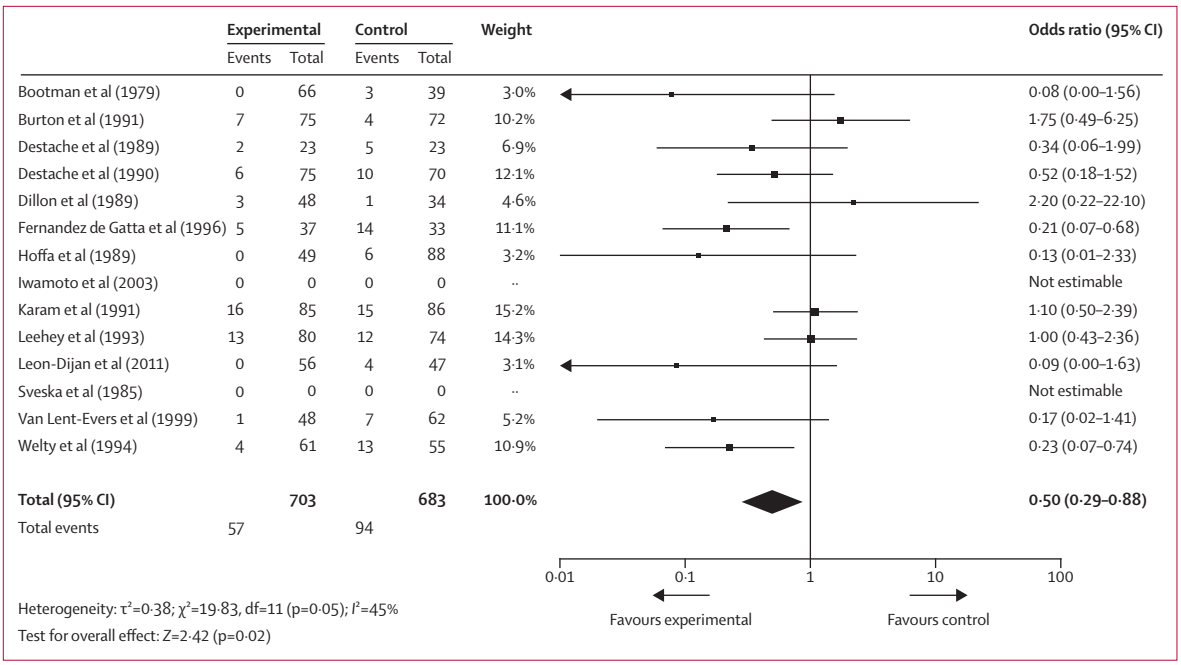

Figure 3: **Effect of therapeutic drug monitoring on the rate of nephrotoxicity**

and one was an observational study with a low risk of bias. Thus, the overall quality of the evidence was low to moderate.

Clinical endpoints were similar irrespective of whether treatment was discontinued. One observational study reported a positive effect on mortality and the two RCTs reported non-significant favourable effects on mortality in patients in whom therapy was stopped, but overall the effect was non-significant with low heterogeneity (appendix). Results did not differ after a sensitivity analysis of RCTs (appendix). A decrease was seen in ICU LOS in the two RCTs, with one study showing a significant effect. One RCT also reported that discontinuation of treatment was associated with reduced costs and a significant beneficial effect on resistance rates.

Presence of a local antibiotic guide

One (prospective) observational multicentre study on ICU patients done in France reported on the use of a local antibiotic guide (appendix). Of our predefined outcomes only mortality was assessed, which was decreased in patients with community-acquired infections, nosocomial infections, and postoperative intra-abdominal infections if a guide was available. However, the observational design meant that the quality of evidence was low.

List of restricted antibiotics

We identified 30 studies that investigated the use of restricted antibiotics lists (appendix). One was a non-blinded RCT and 29 were observational studies. Most studies were subject to a high risk of bias and, therefore, the general quality of evidence was low.

Effects on mortality were reported in nine observational studies and the RCT. Two observational studies reported non-significant increases in mortality and seven reported decreased mortality, with effects being significant in one. The RCT reported a non-significant increase in mortality. The overall effect on mortality was limited, non-significant, and did not change after a sensitivity analysis of observational studies (appendix).

LOS was reported in five observational studies and was associated with significantly shortened duration of hospital LOS in two studies, a non-significantly shortened duration in two other studies, and a non-significantly increased duration in one. The results were similar for ICU LOS.

Nosocomial infection rates were reported in five observational studies. Three studies reported decreased rates, with one showing a significant effect, and two studies reported an increase, also with one reporting a significant effect.

The effect on costs were reported in 11 observational studies and the RCT. All except one observational study showed reduced costs with a list of restricted antibiotics, with significant effects seen in four.

Resistance rates were assessed in 26 studies. Overall, restrictive measures were effective, with the amount of monthly prescribed defined daily doses of restricted antibiotics being significantly lower than without restriction, although this approach sometimes led to increased amounts of non-restricted antibiotics being

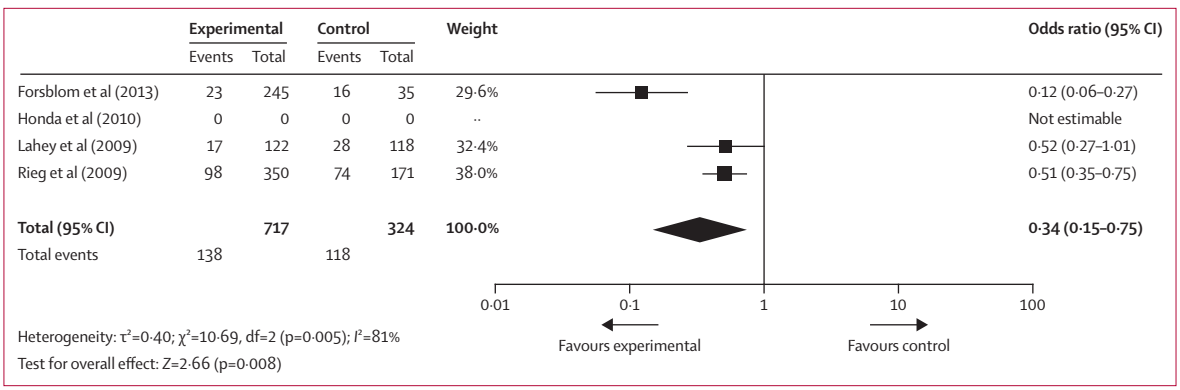

***Figure 4*: Effect of bedside consultation for *Staphylococcus aureus* bacteraemia on mortality**

prescribed. With only a few exceptions, resistance rates for restricted antibiotics were significantly decreased across a wide variety of infective agent and drug combinations. A few studies reported increased resistance rates for non-restricted antibiotics.

Bedside consultation

Seven observational studies discussed the effects of bedside consultation (appendix), most of which had high risk of bias, meaning the quality of research was poor for this objective. Studies with multiple interventions (eg, an infectious disease consultation combined with a PET scan) were not included.

Five studies showed decreased mortality with bedside consultation, with significant effects seen in three. Two studies reported non-significant increases in mortality. In one of these two studies the increase was 7%, although the possibility that infectious disease consultations were requested because of more severe illness than in patients who did not receive a consultation was cited as a potential source of bias. The overall effect on mortality was not significant (appendix), but a sensitivity analysis for patients with *Staphylococcus aureus* bacteraemia yielded a significant RRR of 66% (RR 0·34, 95% CI 0·15–0·75, p=0·008, figure 4). Heterogeneity was high.

Three studies reported the effect of bedside consultation on hospital LOS, with one showing a decrease and two showing increases (one significant). One study showed a significant increase in identification of deep infection foci, for instance mediastinitis, endocarditis, or deep-seated abscesses.

Only two of seven studies reported data on costs, one of which was the study that acknowledged bias. That study reported a non-significant increase in expenses, whereas the other reported significant cost savings with bedside consultations.

Discussion

Our systematic review revealed that use of empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral therapy, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation (especially for *S aureus* bacteraemia) can lead to significant benefits for clinical outcomes, adverse events, and costs, although the quality of evidence is generally low. Treatment according to guidelines and de-escalation of therapy had significant effects on mortality, although heterogeneity between studies was substantial. Most studies that assessed prescribing empirical therapy according to guidelines involved patients with community-acquired pneumonia, which makes it difficult to extrapolate the results to other infectious diseases. We assume, however, that effects would be similar where validated guidelines are available. Reduced mortality was also associated with switching from intravenous to oral therapy, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation, but these effects were not significant. When patients with *S aureus* bacteraemia received bedside consultations, mortality was lower and diagnosis of complicated disease were better than those in patients who did not. A study on the effects of infectious disease consultations, published after our literature search was completed, confirms these results.[16]

For some objectives, such as de-escalation of therapy and switch from intravenous to oral treatment, not showing harm is an important outcome. Some outcomes might also be more relevant for some objectives than for others. For example, a switch from intravenous to oral therapy could decrease the likelihood of catheter-related events, although we believe that this stewardship intervention would not affect mortality or bacterial resistance. Many studies included in this systematic review had retrospective designs, which carries an inherent risk of confounding. Without RCTs, no direct inference can be drawn on the causal relations between meeting stewardship objectives and outcomes.

Restrictive antibiotic policies were associated with reduced resistance rates in most of the studies we assessed, but inconsistent relations between antibiotic use and resistance rates were also found. In several

studies, increased prescriptions of non-restricted antibiotics were accompanied by concomitant increases in resistance rates. Additionally, settings and baseline resistance rates varied across the studies, and molecular typing to help clarify the mechanisms underlying the decreased resistance rates was generally not used. Of note, we did not assess the use of restricted antibiotics lists in outbreak settings because in this setting bundles of interventions are usually applied.

We were able to identify only five studies in which in all patients' antibiotic doses were adjusted to renal function by the study team, although some patients in the control groups might also have had doses adjusted by their treating physicians outside the study. Nevertheless, consistent adjustment of the dose seemed to decrease the risk of toxic effects. In clinical practice, adjustments are made in only 50% of cases where they are needed.[17] Very few studies were found on discontinuation of therapy based on lack of clinical or microbiological evidence of infection. These studies, which mainly assessed patients with ventilator-associated pneumonia, reported a beneficial effect on clinical outcomes, which suggests that discontinuation of therapy is a safe option.

We found no reports that assessed the effects of blood cultures or cultures from the site of infection, a documented antibiotic plan, whether local guides were in agreement with national guidelines, or patients' adherence to prescribed therapy, and we found only one that assessed the effect of having a local guide. Despite no direct evidence that culture, especially blood culture, is beneficial for patients, indirect evidence supports this approach: de-escalation of antibiotic therapy and switching from intravenous to oral therapy had positive effects on clinical outcomes, adverse events, and costs, and taking blood cultures is a prerequisite for these changes to therapy. Additionally, blood culture has been associated with reduced hospital LOS.[18]

No relevant studies on stewardship objectives in long-term care facilities were identified, and results obtained in the hospital setting cannot automatically be extrapolated because the populations of patients and amount of diagnostic resources differ. The lack of available evidence for the long-term care facilities is concerning, and this should be an area for urgent research.[19,20]

We did not include studies on the use of procalcitonin as a guide for antibiotic therapy because this marker is not captured by the definitions for adjusting therapy according to the pathogen or discontinuing therapy based on lack of clinical or microbiological evidence of infection. Nevertheless, as a stewardship intervention, the use of procalcitonin might play an important part in antimicrobial stewardship programmes.[21]

Our systematic review provides elaborate data on the evidence base for individual objectives of antimicrobial stewardship. The study has several strengths. First we did 14 systematic reviews, with a clinical librarian, and reviewed 16 387 titles. The initial search strategy was very broad and recovered a large amount of the available literature. Second, in every search we addressed the effect of a particular objective on multiple clinically relevant outcomes, which gives a clear view of the overall effect of each stewardship objective. The risk of bias was assessed for each study with a scale that was relevant to the study design, and the quality of the evidence for each outcome was summarised with the Grading of Recommendations Assessment, Development, and Evaluation method.[13,14,22,23] Finally, we used identical methods for all 14 systematic reviews, with every step being checked by a second author to ensure accuracy, and we followed the PRISMA reporting guidelines for systematic reviews and meta-analyses.[11]

The study also has limitations. We noted substantial heterogeneity between studies in relation to settings, methods, and reported outcomes, and the quality of evidence was generally low. These features make synthesis and interpretation of results difficult. Nevertheless, sensitivity analyses of the pooled mortality rates did not alter the findings. We did not do a grey literature search and we restricted our searches to Embase, Ovid MEDLINE, and PubMed, which introduces an inherent degree of publication bias. Also, as in any review, we might have missed some relevant studies. We chose to report only aggregated data when available. We did so to keep some overview of the results without being overwhelmed by data. We only report data on adults and inpatients because many objectives, such as de-escalation or switching from intravenous to oral therapy, are not applicable in the outpatient setting. We found only three studies that reported effects on rates of infection with *Clostridium difficile*, one each in three different searches. The final limitation is that we report data on studies published between 1979 and 2014. Treatment (eg, antibiotics used) and the environment (eg resistance rates) have changed substantially over this period and, therefore, not all the results of the included studies will be applicable to the current situation.

The goals of antimicrobial stewardship are to achieve optimum clinical outcomes and to ensure cost-effectiveness and minimum unintended consequences, including toxic effects, selection of pathogenic organisms, and resistance. For several stewardship objectives there is abundant, although low-quality, evidence on clinical outcomes, adverse events, costs, and resistance rates in hospital. Although we assessed objectives separately, in practice, interventions are generally bundled, and the combined effect of meeting several objectives could be greater than that of meeting one.[4] Thus, there is a clear need for high-quality studies to address these questions. We found no evidence on antimicrobial stewardship objectives in long-term care facilities, where more research is evidently needed. Our results, combined with the critical appraisal of restrictive and persuasive strategies to improve appropriate antimicrobial use,[5] might guide stewardship teams in their efforts to

improve the quality of antibiotic use in hospitals.

Contributors

MEJLH and JMP designed the study. ECS did the literature search. ECS, JWM, PDvdL, JAS, and JMP collected the data. ECS and JMP analysed the data. All authors were involved in interpretation of the data and the writing of the report. ECS designed figures.

Declaration of interests

We declare no competing interests.

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