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Impact of antimicrobial stewardship in critical care: a systematic review

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Objectives: To evaluate the current state of evidence for antimicrobial stewardship interventions in the critical care unit.

Methods: We performed a systematic search of OVID MEDLINE, Embase and Cochrane electronic databases from 1996–2010. Studies were included if they involved any experimental intervention to improve antimicrobial utilization in the critical care setting.

Results: Thirty-eight studies met the inclusion criteria, of which 24 met our quality inclusion criteria. The quality of research was poor, with only 3 randomized controlled trials, 3 interrupted time series and 18 (75%) uncontrolled before-and-after studies. We identified six intervention types: studies of antibiotic restriction or pre-approval (six studies); formal infectious diseases physician consultation (five); implementation of guidelines or protocols for de-escalation (two); guidelines for antibiotic prophylaxis or treatment in intensive care (two); formal reassessment of antibiotics on a pre-specified day of therapy (three); and implementation of computer-assisted decision support (six). Stewardship interventions were associated with reductions in antimicrobial utilization (11%–38% defined daily doses/1000 patient-days), lower total antimicrobial costs (US$ 5–10/patient-day), shorter average duration of antibiotic therapy, less inappropriate use and fewer antibiotic adverse events. Stewardship interventions beyond 6 months were associated with reductions in antimicrobial resistance rates, although this differed by drug–pathogen combination. Antibiotic stewardship was not associated with increases in nosocomial infection rates, length of stay or mortality.

Conclusions: More rigorous research is needed, but available evidence suggests that antimicrobial stewardship is associated with improved antimicrobial utilization in the intensive care unit, with corresponding improvements in antimicrobial resistance and adverse events, and without compromise of short-term clinical outcomes.

Keywords: antibacterial agents, drug resistance, microbial, critical care, intensive care, infection

Introduction

Dramatic increases in antibiotic utilization in hospitals continue to drive antibiotic resistance among hospital-acquired pathogens.[1–3] At the same time, the availability of new pharmaceutical agents is dwindling, leaving clinicians with limited effective antibiotic options for their patients.[4,5] Infections with antibiotic-resistant organisms have consistently been associated with increased attributable length of stay, mortality and costs.[6]

Recognizing that as much as 30%–50% of the antibiotic use in hospitals is unnecessary or inappropriate,[7] the Infectious Diseases Society of America recently published guidelines stating that all hospitals should develop an institutional programme to enhance antimicrobial stewardship.[6] Antimicrobial stewardship entails diverse interventions aimed at reducing inappropriate antimicrobial use while optimizing antimicrobial drug selection, dosing, route and duration of therapy in order to maximize clinical cure or prevention of infection and to limit unintended consequences, such as the emergence of resistance, adverse drug events and the selection of pathogenic organisms.[6]

Although these guidelines are intended to apply to all hospitalized patients, many have advocated that initial stewardship interventions be targeted at critical care patients.[8]

On the one hand, the critical care unit is the area of greatest antimicrobial use[9] and the epicentre of antimicrobial resistance in most hospitals.[10] On the other hand, the vulnerability of

critical care patients and the complexity of their clinical management may hinder reductions in antimicrobial use.[8]

Therefore, this systematic review was conducted to evaluate the current state of the evidence for antimicrobial stewardship interventions in critical care. The outcomes of interest included antibiotic drug utilization, antibiotic costs, antibiotic appropriateness, antibiotic duration, *Clostridium difficile* colitis, other antibiotic adverse effects, antibiotic resistance, nosocomial infection rates, length of stay and mortality.

Materials and methods

Search strategy

In order to identify all eligible studies we searched the OVID MEDLINE, Embase and Cochrane databases from January 1996 to December 2010 using the following broad search strategy: (antibiotic\$ OR antimicrobial\$ OR antibacterial\$).tw AND (stewardship OR restriction OR preauthorization OR pre-authorization OR audit OR feedback OR streamlining OR streamlining OR discontinuation OR de-escalation OR deescalation OR optimization OR step-down OR stepdown OR education OR program OR programme OR policy OR utilization OR control OR 'quality assurance' OR 'decision support').tw. The searches were narrowed by requiring a MeSH term to identify studies of intensive care patients (critical illness OR intensive care OR intensive care units OR critical care) (MeSH terms all exploded). The searches were limited to human studies. Citation titles and abstracts were scanned independently by two reviewers (R. K. and M. E.), and the full text was retrieved for all potentially relevant studies. Duplicate studies were identified and removed. The reference lists of all studies were reviewed to identify additional relevant studies. Conference abstracts were not searched because insufficient data would be available for quality assessment.

Study content inclusion criteria

Studies were then assessed by two reviewers (R. K. and M. E.) to determine whether they met the following broad content inclusion criteria: (i) application of any intervention; (ii) to improve antimicrobial utilization; and (iii) within an intensive care setting. Studies were excluded if no intervention was applied (e.g. observational studies of resistance trends), they were non-human or non-patient based (e.g. agricultural use of antibiotics), they were non-hospital based (e.g. outpatient clinic interventions) or they did not involve intensive care patients (e.g. hospital-wide interventions without a separate description of the intensive care subgroup). Additionally, antibiotic cycling references were excluded, as this topic has been recently reviewed elsewhere.[10]

Quality inclusion criteria

Pairs of reviewers then independently assessed each of the studies (R. K. and N. D., or M. E. and S. W.) to determine whether it met pre-specified quality criteria for inclusion. These criteria were based on the Cochrane Effective Practice and Organization of Care (EPOC) Review Group inclusion criteria for randomized controlled trials, interrupted time series and controlled before-and-after studies.[11] We anticipated that there would be few high-quality studies in this field, and modified the EPOC criteria to allow inclusion of uncontrolled before-and-after studies, as long as they met the following criteria: (i) measurement and reporting of potential confounding variables from the before-and-after periods; and (ii) either no statistically significant differences ($P < 0.05$) were identified among the measured confounders, or if significant differences were identified, they were adjusted for by multivariate regression. When the pair of reviewers disagreed as to whether a study met the quality

inclusion criteria, another study author from the other pair (M. E. or N. D.) resolved the disagreement. The quality of included studies was appraised using the Cochrane Risk of Bias tool for randomized controlled trials, and the Newcastle–Ottawa Quality Assessment Scale for non-randomized studies. The latter tool assigns a maximum of four points for patient selection, two points for comparability and three points for outcome assessment.[12]

Data extraction and statistical analysis

Three of the authors (R. K., M. E. and L. P.) abstracted study data into an Excel spreadsheet, including 42 variables related to study design, quality, interventions and outcomes. Author agreement in assessment of study quality was evaluated using the κ statistic. As expected, the heterogeneity of study design and outcome assessments precluded pooling of data, and so most analyses were descriptive and qualitative in nature. To facilitate comparisons across studies, where possible, units of drug utilization were converted to daily defined doses (DDD)/1000 patient-days and units of drug cost were converted to US\$/patient-day.

Results

Search results

Our search strategy identified 1187 citations in MEDLINE, of which 130 full-text studies were reviewed and 25 were determined to meet study content inclusion criteria (Figure 1). Similarly, 4059 citations were identified in Embase, of which 97 full-text studies were reviewed and 30 were determined to meet study criteria. Only 125 citations were identified in Cochrane, of which 5 full-text studies were reviewed and 5 were determined to meet study content criteria. After the removal of 26 duplicates between databases and the addition of 4 studies from reference list review, a total of 38 publications were available for assessment. Twenty-four of these studies met quality inclusion criteria and thus were included in the systematic review.

Quality of studies

The quality of research in this field was generally poor, with only three randomized controlled trials, three interrupted time series and no controlled before-and-after studies identified. Eighteen (75%) of the studies were uncontrolled before-and-after studies and thus would not have been included without our pre-specified modification of the Cochrane EPOC criteria (Table 1).[13–36] There was moderate agreement (κ=0.69) among our paired study authors regarding application of our modified criteria. A high risk of bias was evident for all three randomized controlled trials: only one study reported a clear randomization sequence, none reported on allocation concealment, and none employed blinding of study personnel and outcome assessors. The 21 non-randomized studies achieved moderate Newcastle–Ottawa scores (mean 6.5±0.7 out of a maximum score of 9). Patient selection subscores were high (3.5±0.5 out of a maximum score of 4), given the ease of definition of exposed and unexposed patients in a before-and-after intervention study, and outcome subscores were high (2.9±0.4 out of a maximum score of 3), given the ease of follow-up in a defined intensive care unit (ICU) cohort. However, comparability of intervention
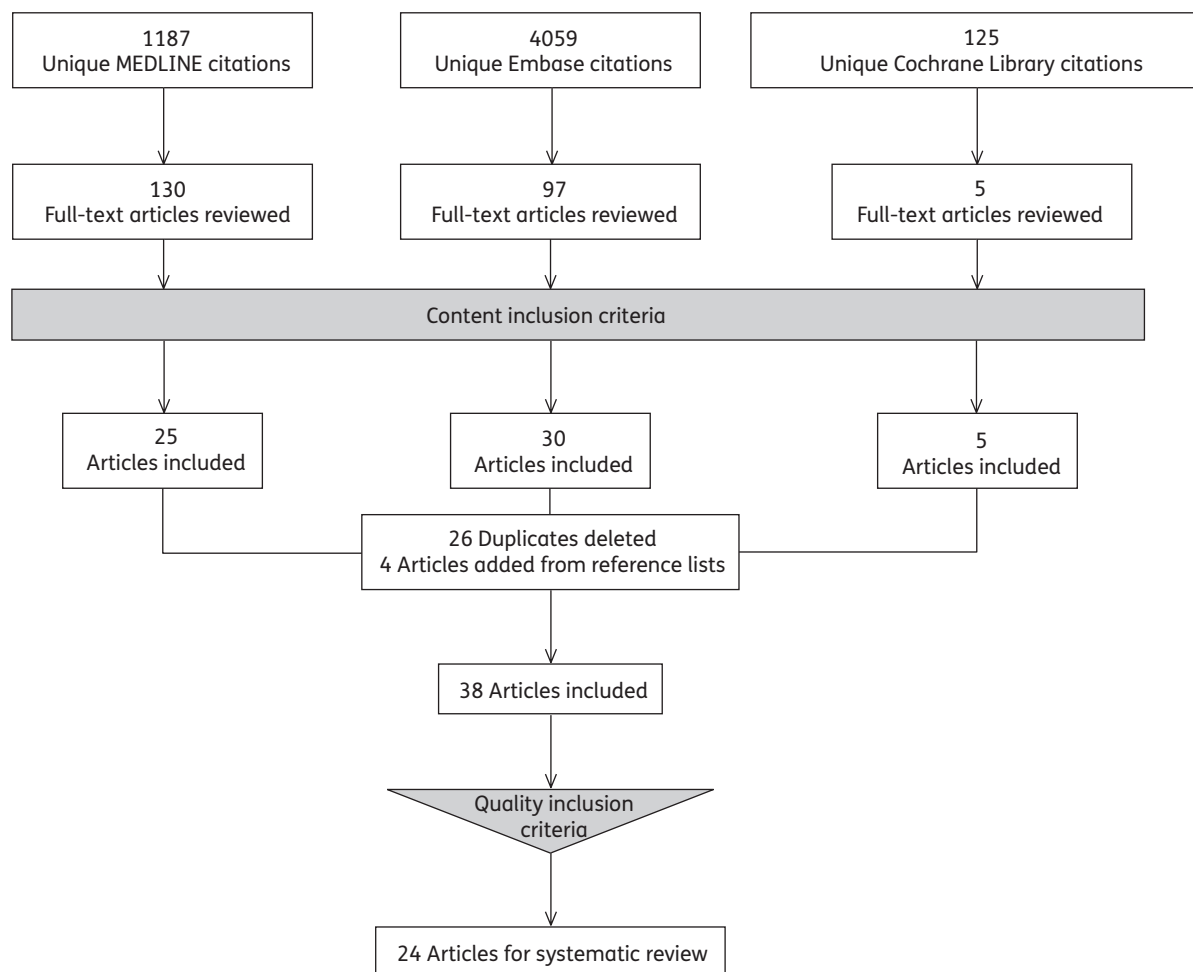
Figure 1. Flow chart of study extraction and selection.

and non-intervention cohorts was generally not clear $(0.05\pm0.22$ out of a maximum score of 2).[37]

Stewardship interventions identified

The studies originated from nine different countries spanning five continents, including the United States (7 studies), Brazil (3) Australia (3), China (2), France (4), Tunisia (2), Hungary (1), Greece (1) and Germany (1). All interventions were implemented within a single centre, but a range of medical and surgical ICUs were represented (Table 1). The variability in patient populations was also evident in baseline mortality rates ranging from 2% to 53%. We identified six major groups of interventions, including studies of antibiotic restriction or pre-approval,[13,15–17,19,26] formal infectious diseases physician consultation,[18,21,27,33,34] implementation of guidelines or protocols for de-escalation,[24,28] formal reassessment of antibiotics on a pre-specified day of therapy,[21,22,30] guidelines for antibiotic prophylaxis or treatment in the ICU[32,36] and implementation of computer-assisted decision support.[14,20,25,29,30,35] Given the expected heterogeneity in study interventions, as well as the differences in outcomes assessed (Table 1), a quantitative meta-analysis was not performed. Instead, we provide a qualitative review of the impact of ICU antibiotic stewardship on individual outcomes of interest.

Outcomes of antibiotic stewardship in ICUs

Amount of targeted or overall antibiotic use

Most studies (71%) assessed the impact of antimicrobial stewardship on antibiotic use.[13,15–17,19,20,22–35] The unit of measurement for drug use varied between studies, making it difficult to compare the impact of each intervention. Values for overall antibiotic use are summarized in Table 2. The denominator was converted to 1000 patient-days where applicable.

All studies of restriction[13–16,26] and pre-approval policies[19] reported a statistically significant reduction in the use of targeted antibiotics. However, all studies of restriction policies demonstrated a compensatory increase, by ~200%–300%, in the use of other agents with a similar spectrum of use.[13–16,26] For example, studies of fluoroquinolone restriction resulted in the increased use of cefepime[26] or aminoglycosides/macrolides,[13] while studies of ceftazidime[15] or cefepime[16] restriction resulted in the increased use of piperacillin/tazobactam. Studies of computer-assisted decision support, formal reassessment and the impact of an infectious diseases consultant all demonstrated decreases in antibiotic use among several classes of antibiotics without a pronounced compensatory increase in other agents with a similar spectrum.[22,23,27,29–31,34,35]

Table 1. Characteristics of studies of antimicrobial stewardship in intensive care

Author	Year	Type of ICU	Patients (patient-days)	Study design	Main intervention	Duration of intervention
Aubert[13]	2005	medical-surgical	781 (12070)	uncontrolled before-and-after study	antibiotic restriction/pre-approval	6 months
Bochicchio[14]	2006	trauma	not applicable[a]	randomized controlled trial	computer-assisted decision support	6 months
Brahmi[15]	2006	not described	321 (not available)	uncontrolled before-and-after study	antibiotic restriction/pre-approval	12 months
De Araujo[16]	2007	neonatal	995 (1373)	uncontrolled before-and-after study	antibiotic restriction/pre-approval	12 months
Ding[17]	2008	paediatric	900 (not available)	uncontrolled before-and-after study	antibiotic restriction/pre-approval	24 months
Dos Santos[18]	2003	medical-surgical	1473 (7478)	uncontrolled before-and-after study	infectious diseases consultant	12 months
Du[19]	2003	medical-surgical	1205 (7619)	uncontrolled before-and-after study	antibiotic restriction/pre-approval	12 months
Evans[20]	1998	shock-trauma-respiratory	1681 (not available)	uncontrolled before-and-after study	computer-assisted decision support.	12 months
Fox[21]	2001	trauma	295 (2134)	uncontrolled before-and-after study	infectious diseases consultant	6 months
Geissler[22]	2003	medical-surgical	1704 (19277)	uncontrolled before-and-after study	reassessment on pre-specified date	48 months
Marra[23]	2009	medical-surgical	not available	uncontrolled before-and-after study	reassessment on pre-specified date	10 months
Micek[24]	2004	medical	290 (2000)	randomized controlled trial	antibiotic de-escalation protocols	14 months
Mullett[25]	2001	paediatric	1758 (8639)	uncontrolled before-and-after study	computer-assisted decision support	6 months
Ntagiopoulos[26]	2007	not described	147 (3584)	uncontrolled before-and-after study	antibiotic restriction/pre-approval	24 months
Peto[27]	2008	surgical	3403 (8496)	interrupted time series	infectious diseases consultant	36 months
Singh[28]	2000	medical-surgical	81 (984)	randomized controlled trial	antibiotic de-escalation protocols	not available
Sintchenko[29]	2005	medical-surgical	762 (5014)	uncontrolled before-and-after study	computer-assisted decision support	6 months
Thursky[30]	2006	medical-surgical-trauma	1060 (4494)	uncontrolled before-and-after study	computer-assisted decision support	7 months
Brahmi[31]	2006	not described	318 (not available)	uncontrolled before-and-after study	reassessment on pre-specified date	24 months
Meyer[32]	2010	medical-surgical-trauma	11887 (34922)	interrupted time series	antibiotic prophylaxis guideline	24 months
Pavese[33]	2005	medical	190 (not available)	uncontrolled before-and-after study	infectious diseases consultant	3 months
Roger[34]	2000	medical	61 (not available)	uncontrolled before-and-after study	infectious diseases consultant	2 months
Yong[35]	2010	medical-surgical-trauma	13293 (55831)	interrupted time series	computer-assisted decision support	54 months
Price[36]	1999	surgical	321 (1097)	uncontrolled before-and-after study	antibiotic treatment guideline	1 month

[a]Unit of analysis was trauma and critical care fellows ($n=12$) rather than patients.

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Table 2. Reduction in overall antibiotic use associated with stewardship interventions in critical care

Study	Unit of measurement	Antibiotic use in non-intervention period or group	Antibiotic use in intervention period or group	Difference	P value
Aubert[13]	DDD/1000 pt-days	420[a]	370	−12%	NA
Marra[23]	DDD/1000 pt-days	1265	1112	−12%	0.61
Evans[20]	DDD/1000 pt-days	1852	1619	−13%	NS
Peto[27]	DDD/1000 pt-days	1629	1013	−38%	NA
Sintchenko[29]	DDD/1000 pt-days	1925	1606	−17%	0.04
Thursky[30]	DDD/1000 pt-days	1670	1490	−11%	NA
Meyer[32]	DDD/1000 pt-days	1059	888.6	−14%	0.05
Yong[35]	DDD/1000 pt-days	NA	NA	NA	NS
De Araujo[16]	DOT/1000 pt-days	6357[a]	6729	+6%	NA
Geissler[22]	DOT/1000 pt-days	940	610	−35%	<0.01
Roger[34]	DOT	596	455	−24%	NA
Du[19]	g/day	346.3[a]	310.9	−10%	0.25
Brahmi[15]	no. of prescriptions	318	295	−7%	NA
Ding[17]	no. of prescriptions	711	459	−35%	NA
Brahmi[31]	no. of prescriptions	1.8/pt	1.5/pt	−17%	0.02
Mullett[25]	doses/pt	19.8	22	+11%	NS
Ntagiopoulous[26]	NA	NA	NA	−55.4%	<0.05

DDD, defined daily dose; DOT, days of therapy; NA, not available; NS, not significant; pt, patient.
[a]For these three studies, overall antibiotic use was not reported but could be derived by summing the utilization of individual reported antibiotics (from at least three antibiotic classes).

Table 3. Antibiotic cost reductions associated with antibiotic stewardship in ICUs

Study	Antibiotic costs (US$/patient-day) non-intervention period or group	intervention period or group	Difference in cost (US$/patient-day)	P value
Ding[17]	17.3	12.7	4.6	<0.05
Dos Santos[18]	24.0	15.1	8.9	NA
Fox[21]	16.8	9.2	7.6	0.008
Geissler[22]	16.6	11.1	5.5	NA
Thursky[30]	NA	NA	6.3	NA
Price[36]	100.0	27.7	72.3	0.001

NA, not available.

Antibiotic costs

Eleven (46%) of the studies measured the impact of antibiotic stewardship on overall antibiotic acquisition costs in the ICU.[17,18,20–22,25,28,30,31,34,36] The unit of cost reporting varied, but for six studies sufficient denominator data were available to convert these costs to the units of US$/patient-day in the ICU (Table 3).[17,18,21,22,30] None of the studies summarized the impact of indirect savings of antibiotic stewardship (such as costs saved related to minimization of antibiotic adverse effects or selection of resistant pathogens). Similarly, none of the studies reported the full costs of implementation of their antibiotic stewardship interventions, although one did report the cost of infectious diseases consultation services.[21]

Appropriateness of antibiotics

Appropriateness of antibiotics was only examined in five studies,[14,20,25,30,31] most of which involved computer-assisted decision support systems.[14,20,25,30] In one such study, antibiotic decision accuracy (as adjudicated by two blinded infectious diseases specialists) improved among six trauma/critical care fellows randomized to use of a personal digital assistant antibiotic decision management guide (from 66% to 86% of decisions, $P=0.006$).[14] However, decision accuracy was not assessed in the control group of fellows who did not receive the intervention.[14] In another study, the use of antibiotic management support programmes resulted in fewer susceptibility-mismatch alerts (12 cases/year versus 103 cases/year, $P<0.01$), excessive drug-dosage alerts (87 cases/year versus 202 cases/year, $P<0.01$) and mean days of excessive anti-infective doses (2.7 versus 5.9 days/patient, $P<0.002$).[20] These results were reproduced when the programme was re-tooled for a paediatric ICU.[25] A reduction in antibiotic susceptibility mismatches [odds ratio (OR) 0.63, 95% confidence interval (CI) 0.39–0.98, $P=0.02$] was also documented with a different antibiotic management support programme.[30] No studies attempted broader analysis of antibiotic appropriateness according to pre-specified local or published clinical guidelines.

Duration of therapy or timing of discontinuation

Introduction of an infectious diseases consultation service was associated with an 18% decline in risk-adjusted mean days on

therapeutic antibiotics from 16.5 to 13.5 days, although this difference was not statistically significant ($P=0.27$).[21] The introduction of formal feedback on day 14 resulted in doctors discontinuing antibiotic therapy in 90% as compared with 48% of patients without such feedback ($P<0.001$).[22] A formal daily guideline for reassessment of ventilator-associated pneumonia (VAP) treatment led to a shorter duration of treatment (6.0 ± 4.9 days versus 8.0 ± 5.6 days, $P=0.001$),[24] while a re-evaluation guideline at day 3 for patients with pulmonary infiltrates led to far fewer patients being treated beyond this timepoint (28% versus 93%, $P=0.0001$) and a much shorter mean duration of antibiotic treatment (3 versus 9.8 days, $P=0.0001$).[28] Similarly, a broader day 3 reassessment protocol for all antibiotic recipients reduced average treatment durations in the ICU from 14.1 ± 2.9 days to 11.9 ± 1.2 days ($P<0.001$).[31]

Other antibiotic adverse effects

Antibiotic adverse effects were only evaluated in two studies of computer-assisted decision support system interventions that were also capable of tracking these events.[20,25] Use of a computer-assisted decision support system in an adult ICU was associated with a reduction in adverse events caused by anti-infective agents (4/545 versus 28/1136 patients, $P<0.05$) and fewer drug-allergy alerts (35/545 versus 146/1136, $P<0.01$).[20] However, when this system was adapted for use in a paediatric ICU study, these benefits on adverse events were not reproduced.[25] No studies evaluated the impact of antibiotic stewardship on rates of *C. difficile* colitis in the ICU.

Rates of antibiotic resistance

Only 13 of the 24 (54%) studies[13,15–17,19,22,23,26,28,31,32,35,36] assessed the impact of their antibiotic utilization intervention on bacterial resistance, including all 6 studies of antibiotic restriction or preauthorization,[13,15–17,19,26] 3 studies of formal antibiotic reassessment,[22,23,31] 1 study each of treatment guideline for de-escalation[28] or prophylaxis,[32] 1 study of computer-assisted decision support, but no studies of infectious disease consultation.

Of the studies that assessed the impact of restriction or preauthorization on resistance, two studies evaluated ciprofloxacin restriction.[13,26] Both of these studies observed a reduction in ciprofloxacin-resistant *Pseudomonas aeruginosa*.[13,26] One study[26] also observed a decrease in ciprofloxacin-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* over an 18 month period of ciprofloxacin restriction. In contrast, Aubert *et al.*[13] did not see a reduction in ciprofloxacin-resistant Enterobacteriaceae during a 6 month restriction of this antibiotic. Four studies[15,17,19,26] included an intervention of ceftazidime restriction and found reduced ceftazidime-resistant *A. baumanii*,[15] *P. aeruginosa*,[17,26] *Escherichia coli*,[19] *Klebsiella* spp.[19] and extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae*.[15] In addition to restricting ceftazidime, Du *et al.*[19] also restricted other third-generation cephalosporins (ceftriaxone and cefotaxime) and found a reduced risk of resistance to these agents among Gram-negative bacteria, particularly *E. coli* and *Klebsiella* spp. Fourth-generation cephalosporin (cefepime) restriction was associated with reduced resistance to cefepime among *E. coli*, *Klebsiella* spp. and multidrug-resistant Gram-negative

bacteria.[16,17,19] Ding *et al.*[17] observed a reduction in imipenem-resistant *P. aeruginosa* over a 2 year intervention period of broad antibiotic restriction and a requirement of preauthorization from a senior paediatrician.

Antibiotic utilization interventions that included either a formal antibiotic reassessment,[22,23,31] de-escalation protocol,[28] computer-assisted decision support[35] or antibiotic practice guidelines[32,36] demonstrated a beneficial effect on institutional antibiotic resistance. A day 3 reassessment protocol performed over 2 years was associated with reductions in ESBL *Klebsiella* (68% to 44%, $P<0.001$) and carbapenem-resistant *Pseudomonas* (61% to 41%, $P<0.05$);[31] a day 3, day 7 and day 10 antibiotic reassessment intervention performed over 3 years demonstrated an overall decrease in antimicrobial-resistant microorganisms (37% to 15% of nosocomial infections, $P<0.00001$), with a significant reduction in methicillin-resistant *Staphylococcus aureus* (MRSA; 61% to 13%, $P<0.001$) and ceftriaxone-resistant Enterobacteriaceae (37% to 13%, $P<0.0001$).[22] There was no impact on ceftazidime-resistant *P. aeruginosa* or ESBL-producing Enterobacteriaceae.[22] However, following a 10 month intervention period, Marra *et al.*[23] did observe a broad decline in resistance, including ceftazidime resistance among *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*; imipenem resistance among *A. baumannii* and *K. pneumoniae*; and ciprofloxacin resistance among *P. aeruginosa*, with their day 14 antibiotic reassessment protocol. A computer-assisted decision support system, implemented over 7 years, was associated with broad improvements in susceptibility of *Pseudomonas* and Enterobacteriaceae to carbapenems, aminoglycosides and fluroquinolones.[34] In an antibiotic de-escalation study of patients with presumed VAP, the intervention group was less likely to develop antimicrobial-resistant superinfections than those receiving standard therapy (14% versus 38%, $P=0.017$).[28] A focused guideline that reduced cefuroxime prophylaxis to a single dose for patients with external ventricular drains did not improve overall *E. coli* cephalosporin resistance in one ICU.[32] A much broader treatment guideline in the ICU was associated with trends of improved *Pseudomonas* susceptibility to gentamicin and ciprofloxacin, but these were not statistically significant over the short intervention period (1 month).[36]

Unanticipated positive[13,15,19] and negative[15,26] effects on non-intervention antibiotic resistance were also observed in studies that were included in this systematic review. Unanticipated beneficial effects included an observed reduction in MRSA with ciprofloxacin restriction[13] and a reduction in piperacillin/tazobactam- and imipenem-resistant *P. aeruginosa* with ceftazidime restriction.[15] Unanticipated negative effects included an increase in penicillinase-producing *K. pneumoniae* with ceftazidime restriction, favouring the use of piperacillin/tazobactam,[15] and an increase in carbapenem-resistant *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*,[26] along with an increase in *K. pneumoniae* resistant to piperacillin/tazobactam and cefepime in a study where ceftazidime and fluoroquinolones were restricted in favour of these other antibiotics.[26]

Clinical outcomes: nosocomial infection rates, length of stay and mortality

Most studies documented no significant difference in the frequency of hospital-acquired infections between periods with and without antimicrobial stewardship.[18–20,22–24,31]

The introduction of an infectious diseases consultation service was associated with an increase in 'diagnosed infection rates' in one study (4.1% versus 3.4%, relative risk 1.49, P=0.011), but this was attributed to improved detection of infection.[21]

Most studies measured ICU and/or hospital length of stay among groups receiving or not receiving antimicrobial stewardship.[16,18–21,24–35] Many studies documented no significant difference in the length of stay, none documented an increased length of stay in association with implementation of antimicrobial stewardship and, intriguingly, six studies documented a decrease in the length of stay associated with stewardship.[19,20,28,29,31,36]

Most studies measured mortality rates in the presence and absence of stewardship, but none addressed this as a primary outcome. No studies detected a significant increase in overall intensive care mortality. One study documented a lower crude mortality among patients who developed nosocomial infection in the stewardship intervention group, implying that these infections may be less drug resistant and hence easier to treat.[23]

Discussion

Our systematic review revealed that the current state of evidence for antimicrobial stewardship in critical care patients is mostly limited to uncontrolled before-and-after studies conducted in single ICUs. Studies have been heterogeneous with respect to outcomes assessed and the interventions attempted in the ICU (antibiotic restriction, formal infectious diseases physician consultation, protocols for de-escalation, guidelines for ICU antibiotic prophylaxis or treatment, formal reassessment of antibiotics on a pre-specified day of therapy and implementation of computer-assisted decision support). Nevertheless, some clear overall trends have emerged.

Most stewardship interventions are associated with a decrease in either targeted or overall antibiotic use in critical care patients. However, the approach of restricting the use of certain antibiotic classes is associated with a compensatory increase in unrestricted antibiotics, a phenomenon that has been previously termed 'squeezing the balloon'.[38] Similarly, after 6 months, most stewardship interventions have been associated with decreased resistance rates among key ICU pathogens, but restriction policies have been associated with some decreased susceptibility rates to unrestricted antibiotic agents. Therefore, active interventions (rather than passive restriction policies) may be associated with more favourable outcomes.

Decreases in overall drug acquisition costs have been achieved on the order of US$ 5–10/patient-day, although formal cost-effectiveness analyses incorporating other costs and savings of these programmes are needed to evaluate their net benefit. A variety of stewardship interventions have been associated with reduced antimicrobial durations of therapy, but impacts of antibiotic appropriateness have only been narrowly studied (and documented) in programmes based on computer-assisted decision support. Similarly, adverse events have only been evaluated with computer-assisted decision support programmes, and arguably the most important antimicrobial adverse event (*C. difficile* colitis) has yet to be assessed for any stewardship intervention in the ICU context. Importantly, the reductions in antimicrobial utilization associated with stewardship interventions have not been associated with any worsening in nosocomial infection rates, length of stay or mortality among intensive care patients.

Our systematic review is limited by the quality of studies available for analysis as well as limitations inherent in our own methods. Relaxation of Cochrane quality criteria led to the inclusion of many before-and-after analyses, which are prone to temporal confounding by other complex time-dependent interventions in intensive care, as well as false-positive results through the statistical phenomenon of regression to the mean (by chance alone, extreme values are more likely to be less extreme on repeat measurement).[39] We also chose not to include unpublished studies, and so our findings may reflect some degree of publication bias. Heterogeneity in study designs, durations and outcomes makes it difficult to reach firm conclusions about the impact of any particular antibiotic stewardship intervention. Finally, application of our modified quality inclusion criteria was only moderately consistent between our pairs of blinded reviewers.

Ideally, to minimize selection bias and confounding, future studies in this field should randomize allocation of the stewardship intervention to different ICUs.[11] Even if there is a lack of clinical equipoise (a prevailing belief that stewardship provides benefit without harm), randomization can be performed in a stepped-wedge design, in which all units eventually receive the intervention, but the timing of implementation is staggered.[37,40] When randomization is not possible, bias can be minimized through inclusion of control units and the use of time series analysis with multiple measurements in the intervention and non-intervention time periods. In the meantime, antimicrobial stewardship interventions appear to be safe, given that our review has not documented any significant harms such as worsening nosocomial infection rates, length of stay or mortality. Given that passive restriction policies are often associated with increased antibiotic utilization and resistance among unrestricted alternative agents, we would recommend more active and interactive stewardship interventions. These stewardship interventions appear to offer the prospect of reduced antibiotic utilization, costs, duration, inappropriate use, adverse effects and resistance in the ICU.

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None to declare.

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