

Antimicrobial stewardship in the intensive care setting – a review and critical appraisal of the literature

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Summary

BACKGROUND: Many antimicrobial stewardship programmes (ASPs) target the intensive care unit owing to high antimicrobial utilisation. In this review, we summarise and assess the quality of evidence supporting the implementation of various ASP strategies in the intensive care unit setting with a focus on publications between 2010 and 2015.

METHODS: We searched Medline up to April 2015 and screened publications of interest for additional relevant articles. We grouped the strategies into four categories: audit and feedback, formulary restrictions, guidelines/clinical pathways, and procalcitonin. We used GRADE terminology to describe the quality of evidence.

RESULTS AND CONCLUSIONS: We identified several studies reporting optimisation and reduction of antibiotic utilisation as well as cost reduction in all four strategies. Randomised controlled trials reviewing the role of procalcitonin demonstrate a moderate level of evidence. Given the lack of randomised controlled trials to support the role of guidelines, formulary restrictions, and audit and feedback, the level of evidence supporting these strategies is low. Importantly, there is no convincing evidence to support the main goal of ASP, namely to improve patient outcomes. Larger, rigorous long-term studies using a cluster randomised controlled trial or at least a controlled quasi-experimental design with time series are required to assess the impact of ASP on patient-important outcomes and on the emergence of resistance in the intensive care unit setting.

Key words: stewardship; review; summary; ICU; intensive care; critical care; antimicrobial; quality

Background

For over 50 years, experts have noted extensive inappropriate or unnecessary use of antimicrobials in the range of 30–50% [1–6]. Inappropriate use of antimicrobials is typically defined as wrong indication, spectrum, route, dose

or duration of therapy [1]. The emergence of resistance as a consequence of antibiotic use [7, 8] (see www.anresis.ch for current resistance patterns in Switzerland) is associated with poor clinical outcomes and increased healthcare costs [9, 10]. In fact, emergence of resistance continues to pose a challenge as demonstrated by the global spread of New Delhi β -lactamase producing Enterobacteriaceae resulting in strains that are resistant to virtually all currently available antibiotics [11]. Furthermore, despite worldwide efforts to promote development of new antibiotics, the pipeline remains dry [12]. In addition, antibiotic exposure is a trigger for *Clostridium difficile* infections and outbreaks [2, 3, 13]. Antimicrobial stewardship programmes (ASPs) continue to be implemented in hospitals and communities around the world as quality improvement and patient safety programmes aimed at curbing inappropriate use of antibiotics with the ultimate goal of optimising patient outcomes while minimising its unintended consequences [1].

Given the high density of antibiotic utilisation in the intensive care unit (ICU) setting and the importance of appropriate choice, particularly in septic patients [14], many programmes focus on this setting, assuming the greatest return on investment. A systematic review published in 2011 summarised the evidence on ASP in ICUs published up to 2010 and concluded that although more rigorous studies were required, available evidence did suggest antimicrobial stewardship was associated with improved utilisation of antimicrobials in the ICU setting, improvement in resistance and fewer adverse events [15].

In this review, we summarise and assess the quality of evidence supporting the implementation of various stewardship strategies in the ICU setting with a focus on the time period from 2010–2015.

Methods

We searched Medline on April 1 2015 using the search terms “(critical care) AND stewardship” and “(intensive care) AND stewardship”. We identified 133 and 193 art-

icles, respectively, and also screened review and systematic review articles for additional studies. In this review we summarise 28 of the most relevant articles. We grouped the studies into those assessing the use of audit and feedback, formulary restrictions, procalcitonin, and those with mixed interventions or guidelines and clinical pathways. We adapted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [16] terminology to assess the quality of evidence for each of the four ASP strategies. A systematic assessment of the risk of bias of each included study and a full GRADE assessment of the overall level of evidence was beyond the scope of this non-systematic review article.

Results

Audit and feedback

Prospective audit with intervention and feedback is generally regarded as the gold standard stewardship intervention and received an A-1 grading in the Infectious Diseases Society of America (IDSA) guidelines [1]. This was based on two randomised controlled trials [16, 17] and two observational studies [18, 19], none of which were conducted in the ICU setting.

We identified nine relevant studies utilising audit and feedback in an ICU environment (table 1). The highest quality study was an interrupted time-series with a control group conducted at a large tertiary care centre in Ontario, Canada, by Elligsen et al., and targeted ICU patients on broad-spectrum antibiotics with audit and feedback on day 3 and 10 of therapy over a 1 year period [20]. The ASP pharmacist reviewed patients, conferred with the infectious diseases

Table 1: Studies on prospective audit and feedback.

Author	Country	Year	Design	ASP model	Acceptance rate for interventions	Outcomes and results
Amer [23]	Saudi Arabia	2010–2011	Quasi-experimental No control	ICU/ID pharmacist and ICU/ID physician	96.3%	Appropriateness: higher CDI: unchanged
Bornard [22]	France	2009	Quasi-experimental No control Time-series	ID physician Three-weekly rounds	NA	Appropriateness around day 3: unchanged Abx utilisation: lower Abx costs: lower
Diaz Granados [24]	USA	2006–2009	Quasi-experimental No control	ID physician Targeted antibiotics	66.5%	Abx utilisation: lower Abx selection: improved Abx duration: shorter Resistance: lower LOS: lower
Elligsen [20]	Canada	2008–2010	Quasi-experimental Control Time-series	ID physician and pharmacist	82%	Abx utilisation (broad-spectrum): lower Abx costs: lower Resistance pattern: improved CDI: lower LOS: unchanged Mortality: unchanged
Ijo [28]	USA	2009–2010	Comparison to published literature	ICU pharmacists	NA	LOS: lower Mortality: unchanged Abx cost: higher
Katsios [25]	Canada	2008–2009	Quasi-experimental No control	ID physician and pharmacist Daily ASP rounds	NA	% sterile cultures treated: increased % nonsterile cultures treated: decreased % appropriate documentation: improved Abx utilisation: lower Abx costs: lower
Leung [26]	Canada	2009–2010	Quasi-experimental No control	ID physician and pharmacist Daily ASP rounds	94%	Abx utilisation: lower Abx costs: lower CDI rates: unchanged
Rinawi [27]	USA	2011–2012	Quasi-experimental No control	ID fellow and pharmacist	88%	Appropriateness: higher Abx utilisation: lower Mortality: unchanged (ICU) LOS: shorter Mechanical ventilation days: reduced
Wang [21]	Taiwan	2010–2012	Quasi-experimental No control Time-series	ID physician review of positive blood cultures	80.6%	Abx utilisation: lower Abx costs: lower Mortality: unchanged HAI rate: unchanged ICU re-admission: unchanged

Abx = antibiotics; ASP = antimicrobial stewardship programme; CDI = *C. difficile* infection; HAI = hospital-acquired infections; ICU = intensive care unit; ID = infectious diseases; LOS = length of stay

physician and provided feedback to the team. They reported a reduction in broad-spectrum antibiotic use with no changes in overall use or in their two controls, resulting in a 23% reduction in antimicrobial costs (\$95 000). Also, Gram-negative susceptibility to meropenem improved over time in the ICUs. There was no impact on ICU length of stay (LOS) and mortality. The design of this study had the lowest risk of bias; however, the control groups were not optimal (broad-spectrum antibiotics in medical and surgical wards, stress ulcer prophylaxis in the ICU) and it was a single-centre study.

A second time-series analysis was published by Wang et al. from Taiwan [21]. They assessed the impact of a blood culture-guided de-escalation of empirical antimicrobials as an add-on to an existing stewardship programme in their 16 adult ICUs. They extended their pre-existing computerised antimicrobial approval system by flagging patients with a positive blood culture for a second review within 48 hours. Antibiotic utilisation, primarily carbapenems, gentamicin and those with activity against vancomycin-resistant *Enterococcus*, showed a significant reduction. This was reflected by a 19% decrease in antimicrobial costs. However, patient outcomes remained unchanged. Notably, this was an extension of a robust pre-existing ASP, thus, the findings might not be generalisable to a setting where an ASP has not been established.

Finally, Bornard et al. published a time-series study from France [22]. The intervention included thrice-weekly ASP rounds by an infectious diseases specialist combined with teaching sessions and daily contact with a microbiologist. They found a nonsignificant improvement in appropriate courses of antimicrobials during the intervention (80% vs 73% at baseline), with a higher rate of modification on days 2–4. This study was small (37 and 44 patients, respectively), and the lack of improvement might have been due to a ceiling effect that was attributed to a higher than expected baseline appropriateness of antibiotics.

We also identified five uncontrolled quasi-experimental studies [23–27]. Amer et al. from Saudi Arabia targeted five antibiotics and compared the appropriateness of empirical treatment in patients receiving these antibiotics before and after programme implementation [23]. Appropriateness of treatment increased from 30.6% to 100%. Prior to the ASP review, 20.9% of patients were treated appropriately, but the acceptance rate for ASP recommendations was 96.3%. The intervention resulted in a 68% reduction in the targeted antibiotics from 1 177.8 to 376.2 defined daily doses / 1000 patient days (DDD/1 000PD). This study was small (n = 24 and n = 49 in the two groups, respectively), and the intervention team was also assessing the appropriateness; thus, it was to be expected that the appropriateness postimplementation was high. It is unclear what resulted in the large reduction in drug utilisation, as only 8% of interventions (i.e. two interventions) targeted de-escalation or discontinuation of antibiotics. Katsios et al. from Canada emphasised appropriate documentation and treatment of sterile versus nonsterile cultures [25]. The proportion of cultures treated increased for sterile sites and the ratio decreased for nonsterile sites. They noted a significant improvement in appropriate daily documentation for antibiotic courses including the medication, dose, route and

duration, as well as de-escalation, if applicable. They also reported a reduction in antimicrobial utilisation and acquisition costs. A strength of this study was the unique goal to improve documentation through education as a component of audit and feedback, and measurement of the proportion of cultures treated as a surrogate for appropriate antibiotic usage. Rimawi et al. reported a significant improvement in guideline-concordant treatment and a reduction in utilisation of extended-spectrum penicillins, carbapenems, vancomycin and metronidazole, and antibiotic costs, but an increase in narrow-spectrum penicillins in a medical ICU in the USA [27]. A significant improvement in patient outcomes was reported: reduced mechanical ventilation days, LOS, and hospital mortality. However, the mortality difference was only observed for overall hospital mortality, and not for ICU mortality; therefore, these differences in reported outcomes may not be directly attributable to the ASP intervention. Diaz Granados targeted imipenem and piperacillin/tazobactam in a USA community hospital [24]. The acceptance rates for recommendations were comparably low (66.5%); however, they found an improvement in appropriate antimicrobial selection and resistance rates. They also reported a shorter overall and ICU LOS as well as shorter courses of treatment with similar mortality rates. Limitations included different patient populations in their study periods as well as their approach to quantifying resistance rates, which has neither been validated nor represents standard of practice for measurement. Finally, Leung et al. found a reduction in costs (36.2%) and antibiotic utilisation (38.9%) for antipseudomonal broad-spectrum antibiotics in a Canadian hospital [26]. Their model included an ASP pharmacist and physician who conducted daily reviews of ICU patients. No significant differences in *C. difficile* infection rates or mortality rates were reported.

Finally, the study by Ijo et al. from the USA was the least rigorous from this group since the authors compared patient outcomes (LOS and mortality) during a 4-month ASP audit and feedback intervention with the published literature [28]. They found a shorter LOS and similar mortality rates in the 70 patients included compared to the published literature.

Formulary restrictions

Restriction and preauthorisation of specific anti-infectives is recommended by the IDSA guideline as an A-II recommendation to improve drug utilisation and reduce costs. All studies cited in the guidelines were single centre, non-ICU focused, and all but one study targeted parenteral antibiotics. Four of the studies required a verbal approval from an infectious diseases physician prior to release of the antibiotic [29–32] and three studies utilised clinical pharmacists to enforce restriction criteria [33–35].

We identified only three recent studies related to restriction and preauthorisation. Sistanizad et al. conducted a controlled quasi-experimental study in a teaching hospital in Iran [36]. They restricted carbapenems for the treatment of documented multidrug-resistant organisms when no other therapeutic options were available in a medical ICU using the general ICU as the control group. Consequently, carbapenem use decreased significantly by 60% (from 68.6 to 27.5 DDD/1 000PD) while the overall antibiotic util-

isation remained unchanged. Limitations of this study included potential for cross-contamination between the intervention and control unit since physicians were practicing in both settings and, subsequently, carbapenem utilisation also decreased in both units.

Guarascio et al. developed an “antifungal bundle” intervention that was implemented in a medical and surgical ICU at a university hospital in the USA in order to limit excessive use of echinocandins, with a clinical pharmacist providing daily reassessment of treatment [37]. Historic controls were used for comparison in a matched cohort study design. The reduction in the medical ICU was significant (median DOT 4.0 vs 2.0) with a potential for cost savings of \$1 013 per patient.

Finally, Sharma and Barman implemented and assessed the impact of an antibiotic restriction form that outlined appropriate indications for reserved antibiotics in a tertiary care hospital in India [38]. They showed a reduction in carbapenem use from 18.8 at the beginning to 10.6 DDD/100 bed days at the end of a 4-month intervention and the antifungal use decreased from 56.1 to 22.1 DDD/100 bed days.

Guidelines, clinical pathways and mixed interventions

A combination of strategies will likely maximise the success of an ASP within an institution. Education, clinical pathways, antimicrobial cycling and integration of health-care information technology are elements discussed in the IDSA guidelines [1].

Overall, we identified nine studies that evaluated guidelines, clinical pathways and/or mixed interventions in an ICU setting (table 2).

Evidenced-based guidelines and pathways

The IDSA guidelines highlighted that evidence-based guidelines developed by a multidisciplinary team incorporating local resistance patterns can improve antimicrobial utilisation as an A-III recommendation [1] based on two randomised controlled trials [39, 40] and three quasi-experimental studies [41–43].

We identified two recent uncontrolled quasi-experimental studies [44, 45]. Rodriguez et al. implemented a prophylactic antibiotic protocol precluding the use of aminoglycosides or glycopeptides for open fractures in a USA hospital [45]. Use of these antibiotics was significantly reduced from 53.5% to 16.4% with no change in rates of surgical site infections.

Chiu et al. implemented a guideline restricting the use of vancomycin for late-onset sepsis in two tertiary care neonatal ICUs in the USA [44]. Vancomycin start rates were significantly decreased from 6.9 and 17 to 4.5 and 6.4 per 1 000 patient-days, respectively. No statistical difference in the overall incidence of late-onset sepsis, meningitis, duration of bacteraemia and mortality were found.

Education

Education is considered to be an important element of any intervention and is graded as A-III evidence in the IDSA guidelines. However, education alone is deemed to be marginally effective in modifying prescribing behaviour [1]. This recommendation was based on two quasi-experimental studies [46, 47].

Meyer et al. provided teaching sessions on changing antibiotic prophylaxis to a single cefuroxime dose prior to central nervous system shunt insertion and found a significant reduction in cefuroxime use in a time-series analysis [48]. Unexpectedly, the proportion of third generation resistant *Escherichia coli* increased postintervention. Limitations included the absence of clinically meaningful data such as shunt-related infections, and the unexplained change in resistance rates. Chaves et al. provided quarterly education sessions, developed ICU-specific treatment guidelines and implemented a reminder on the medication record for proper documentation [49]. Compared with the historical control, adherence to documentation standards significantly improved across all items: start date (72% to 90%), stop date (16% to 63%), indication (58% to 83%). Furthermore, antibiotic use concordance with national guidelines significantly improved from 74% to 89%.

Computerised decision support system

The recommendation of a computerised decision support system (CDSS) received a B-II grading in the IDSA guidelines [1]. The majority of the studies discussed in the IDSA guidelines were single centre experiences in the USA [50–53]. In these quasi-experimental studies, the authors demonstrated that CDSS significantly reduced the number of pharmacy interventions and adverse drug reactions, decreased antimicrobial consumption and associated drug costs. The only randomised controlled trial was from Shojanian et al., in which national guidelines advocating appropriate vancomycin use were incorporated into the hospital’s computerised physician order entry (CPOE) system [54], resulting in an overall reduction in vancomycin use and duration with no impact on patient-important outcomes reported.

More recently, Nachtigall et al. evaluated the impact of a CDSS that guided clinicians through a systematic, evidence-based approach in management of common infections in ICU, while addressing de-escalation strategies and targeted antibiotics following pathogen identification [55]. Guideline adherence and antibiotic-free days increased significantly compared with the historical control. Finally, the authors also found a lower mortality in patients where CDSS was adhered to (8% vs 12.3%). Overall, this study demonstrated the sustained effects of a CDSS over a 5-year period; however, the generalisability may be limited owing to the predominantly surgical patient population.

Ananda-Rajah et al. implemented a bundle consisting of CDSS, twice-weekly infectious diseases physician rounds and enhanced infection control practices in a mixed medical-surgical ICU in Australia [56]. Using time-series analysis, they reported a decrease in the *Staphylococcus aureus* incidence density by 83% (89% for methicillin-resistant *Staph. aureus* specifically) over the 8.5-year period and found a 26% decrease in broad-spectrum antibiotic utilisation. As a result of the bundle approach, however, the impact of individual interventions remained unknown.

Finally, Wilde et al implemented a computerised clinical pathway (CCP) to facilitate antimicrobial selection for ventilator-associated pneumonia treatment in the three ICUs of their tertiary care institution in USA [57]. They achieved 100% compliance and 70.8% of patients received

appropriate antibiotics within 24 hours of diagnosis of ventilator-associated pneumonia with mandatory use of CCP which was significantly better than voluntary use (44% and 56.3%, respectively). In addition, mandatory CCP shortened time to appropriate therapy and facilitated de-escalation in a greater proportion of patients.

Mixed interventions

In a mixed medical/surgical ICU in the USA, Slain et al. implemented prospective audit and feedback, formulary restriction and preauthorisation, education, pocket cards, and a ventilator-associated pneumonia antibiotic cycling protocol with streamlining and de-escalation in a step-wise fashion [58]. Ciprofloxacin and ceftazidime use declined from 148 and 62.5 to 40 and 24.5 DDD/1 000PD, respectively, as did the overall use of antibiotics, but no effect on *Pseudomonas aeruginosa* resistance patterns was noted. Similarly, Dortch et al. implemented routine bronchoscopy in cases of suspected pneumonia, surgical prophylaxis protocols, treatment guidelines and quarterly antibiotic cycling [59]. The proportion of healthcare-associated infections caused by multidrug resistant Gram-negative pathogens decreased from 37.4% to 8.5% over 8 years. Antibiotic cycling appeared to have a significant association with a reduction of multidrug resistant healthcare-associated infections, although this was not the primary endpoint. The potential benefits and risks of antibiotic cycling, which received a C-II grading due to insufficient data in the IDSA guidelines, are beyond the scope of this review [1].

Procalcitonin

Biomarkers, in particular procalcitonin, are emerging as potentially very useful laboratory tests to aid in the diagnosis of bacterial infections such as respiratory infections [57] and sepsis [55, 56]. Numerous studies have found procalcitonin to be useful in various settings, including the emergency department [60] and ICU (table 3).

In 2013, Prkno et al. conducted a meta-analysis to evaluate the use of procalcitonin in patients with severe sepsis [61]. They compared procalcitonin-guided therapy with standard of care, with mortality as the primary outcome. They included seven randomised controlled trials, four of which will be described in more detail [62–65]. Duration of antibiotics was reported in five studies and suggested a significant reduction in the median duration of antimicrobials in the procalcitonin guided group compared to the control group (hazard ratio 1.27, 95% confidence interval [CI] 1.01–1.53) while mortality and ICU LOS remained unchanged. The authors noted a moderate risk of bias across the studies. Although there was no statistical heterogeneity, there was clinical heterogeneity with the use of different procalcitonin algorithms, targeting escalation, de-escalation or a combination thereof, and differences in patient populations. Finally, duration of therapy in the control arms varied.

Hochreiter et al. conducted a single centre, open-label randomised controlled trial in a surgical ICU in Germany [64]. They included patients with confirmed or suspected bacterial infection and two or more systemic inflammatory response syndrome criteria comparing a procalcitonin-guided arm with an 8-day standard course. The authors found a

significant reduction in the duration of treatment (5.9 vs 7.9 days) and in the LOS in the ICU. The frequency of overriding the protocol was unclear as was the proportion of patients with infections requiring greater than 8 days of therapy. Of note, using an 8-day course as a comparator is questionable since shorter treatment courses can be used in the absence of procalcitonin [66, 67].

Using a noninferiority open-label randomised controlled design in seven ICUs in France, Bouadma et al. assessed a procalcitonin-guided protocol to initiate or discontinue antimicrobials [63]. The difference in mortality rates was within the 10% non-inferiority margin (21.2% vs 20.4%, risk difference 0.8 [95% CI –4.6 to 6.2] at 28 days). There was also a significant increase in antibiotic-free days from 11.6 to 14.3 days. There was no statistical difference in relapse, superinfection, number of days without mechanical ventilation, length of ICU or hospital stay. However, physicians overruled the procalcitonin algorithm 53% of the time. Furthermore, a 10% noninferiority margin for a mortality outcome is wide and the difference in mortality rates would not have met the noninferiority requirements with a smaller margin.

In another multicentre randomised controlled trial in nine ICUs in France reported by Annane et al., healthcare providers and investigators in the control arm were blinded to procalcitonin levels [62]. They included patients who presented with severe sepsis, no clear infection source and negative microbial cultures. The study was stopped early because of low patient enrolment; therefore, the two groups were not balanced and the study was underpowered. They did not find a significant difference between the procalcitonin arm and the control group in the proportion of patients receiving antibiotics on day 5. Furthermore, there was a high rate of protocol deviation, with up to 37% of patients being managed outside of the algorithm recommendations at day 5.

In Denmark, Jensen et al. conducted another multicentre, open-label, randomised controlled trial across nine ICUs [65]. In this escalation study, a procalcitonin level >1 mcg/l suggested expanding the antimicrobial coverage and searching for uncontrolled sources of infection. The primary outcome, 28-day survival, was similar. However, days of mechanical ventilation and median ICU LOS were significantly elevated in the procalcitonin arm. Antibiotic utilisation, particularly piperacillin-tazobactam and ciprofloxacin was increased in the procalcitonin arm. This may be explained by the large proportion of surgical patients in this study (41%), as surgical patients have elevated procalcitonin levels for other reasons, which may have prompted clinicians to continue antimicrobial therapy unnecessarily [68].

A more recent randomised controlled trial was published by Shehbabai et al. [69]. They evaluated the effect of procalcitonin on antimicrobial prescribing across 11 Australian ICUs in addition to twice-weekly antimicrobial stewardship rounds. Duration of antibiotic treatment was similar (9 days; interquartile range [IQR] 6–21 vs 11 days; IQR 6–22), as were antibiotic-free days (20 days; IQR 11–22 vs 17 days; IQR 7–22). However, there was a significant reduction in total antimicrobial consumption in DDDs. No difference was reported in ICU LOS, total LOS, and in the

90-day all-cause mortality. Of note, the cut-offs used for the procalcitonin algorithm were lower than those that have been applied in other randomised controlled trials, potentially leading to no difference in duration of therapy.

Finally, in a German surgical ICU, Hohn et al. conducted a quasi-experimental study evaluating the implementation of a procalcitonin protocol with ASP (antibiotic prescription restricted to senior ICU physician, daily ASP rounds, regular teaching, and local guidelines) [70]. There was a reduction in antimicrobial utilisation of 15.4% between 2010–2011 and 2011–2012, driven by a reduction of aminoglycosides, cephalosporins and fluoroquinolones, resulting in a reduction in antimicrobial costs by 43%. There was no difference in ICU LOS, and mortality rates. Owing to the bundle approach, it is unclear whether the effect is attributable to ASP, or to the use of procalcitonin.

A more extensive review of the literature for procalcitonin in the ICU setting was beyond the scope of this article, and we refer to the recently published review article by Albrich et al. [71].

Discussion

The evidence for ASPs in the ICU setting is based on quasi-experimental studies with or without times-series analysis

and/or control groups and – with the exception of studies on procalcitonin – no randomised controlled trials were identified. While individual-patient randomised controlled trials would not be feasible for the majority of interventions given the hospital-wide implementation of ASP and the risk of cross-contamination, cluster randomised controlled trials with or without a cross-over design would be feasible. The lack of randomisation increases vulnerability to both measured and unmeasured confounders. Also, in the absence of rigorous time-series analyses with an appropriate control group, these studies are at risk of bias as a result of temporal trends [72]. While the impact of ASP intervention on appropriateness of antibiotics, utilisation and costs is fairly consistent across the studies, there is currently no convincing evidence that there is an effect on patient-important outcomes or resistance rates. One unpublished and not yet fully analysed study on audit and feedback from 11 academic hospitals with 14 participating ICUs in Ontario, Canada was recently conducted using a quasi-experimental stepped wedge design. Although again a nonrandomised study, the sample size of this study may allow for the detection of changes in patient-important outcomes as well as an impact on the antimicrobial susceptibility patterns.

Prospective audit and feedback received an A-I grading in the IDSA guideline based on two non-ICU randomised

Table 2: Education, evidence-based guidelines and pathways, mixed interventions.

Author	Country	Year	Design	Patient population	ASP intervention(s)	Outcome and results
Ananda-Rajah [56]	Australia	2000–2008	Quasi-experimental No control	Adults; medical surgical ICU	CDSS, prospective audit and feedback, dedicated ICP	<i>S. aureus</i> incidence density: lower Rates of MRSA bacteraemia: lower Broad spectrum abx: lower
Chaves [49]	Australia	2010–2012	Quasi-experimental No control	Adults; medical & surgical ICU	Education, reminder stickers	Documentation (start/stop dates and indication): improved Abx concordant with guidelines: increased
Chiu [44]	USA	2005–2008	Quasi-experimental No control	Neonates	Guideline (restriction of vancomycin)	Vancomycin use: lower Duration of bacteraemia, incidence of complications or death in late-onset sepsis: unchanged
Dortch [59]	USA	2001–2008	Quasi-experimental No control	Adults; surgical and trauma ICU	Protocol and treatment guidelines + abx cycling + de-escalation (based on bronchoscopy results in suspected VAP)	% HAI due to MDR Gram-negative pathogens: lower % HAI due to pan-sensitive pathogens: higher Rate of HAI due to MDR: lower
Meyer [48]	Germany	2002–2006	Quasi-experimental Interrupted time series	Adults; surgical ICU	Comprehensive education on cerebrospinal shunt insertion prophylaxis	Abx use: lower Abx resistance: variable
Nachtigall [55]	Germany	2006–2010	Cohort study	Adults; primarily surgical ICU units	CDSS	Adherence to treatment guidelines: higher Abx-free days: increased
Rodriguez [45]	USA	2006–2008	Quasi-experimental No control	Level 1 trauma centre; adults with open extremity fractures	Evidence-based protocol for antibiotic prophylaxis	Abx utilisation (aminoglycosides and glycopeptides): lower SSTI: unchanged
Slain [58]	USA	2003–2010	Quasi-experimental No control	Adults; medical and surgical ICU	Prospective audit and feedback + formulary restriction + preauthorisation + education + VAP abx cycling protocol with streamlining/de-escalation	Abx utilisation (antipseudomonal agents): lower from 2004–2007, but increased 2008–10 <i>P. aeruginosa</i> resistance rate: variable
Wilde [57]	USA	2006–2010	Quasi-experimental No control	Adults; medical, surgical and neurotrauma ICU	CDSS (comparison was between mandatory versus voluntary use)	Appropriate Abx within 24 hours for VAP: unchanged Mortality: unchanged

Abx = antibiotics; CDSS = computerised decision support system; HAI = hospital-acquired infections; ICP = infection control practitioner; MRSA = methicillin-resistant *S. aureus*; ICU = intensive care unit; SSTI = skin and soft tissue infection; VAP = ventilator-associated pneumonia

controlled trials [1]. We identified several rigorously conducted quasi-experimental studies that used either time-series and/or a control group; thus, there is good evidence suggesting that audit and feedback has a positive impact on antibiotic utilisation in the ICU setting. However, given the lack of evidence from randomised controlled trials, our confidence in this finding is low when using GRADE terminology [73].

Formulary restrictions and preauthorisation is listed as an A-II recommendation in the IDSA guidelines [1]. Despite the high grading of the evidence in the guideline, we found a small number of recent studies on this topic. This might be related to the common concern of a “squeezing the balloon” phenomenon for this type of approach [74]: restriction of certain classes of antibiotics may result in a reduction in use and resistance rates, but without additional measures in place, it may also result in a shift to a higher usage of other antibiotics [32, 33, 35], thus negatively affecting the resistance rates for those alternative antibiotics. The previous evidence summarised in the IDSA guidelines [1] suggesting that restriction and preauthorisation impact antibiotic utilisation was corroborated by the more recent studies, but downstream effects due to increased use of other antibiotics was not assessed in these studies. Similar to other strategies, the lack of randomised controlled trials results in a low level of evidence for these strategies.

The use of education, evidence-based guidelines and pathways, CDSS and mixed interventions are all endorsed by

IDSA [1]. Our review of the literature found that the majority were uncontrolled quasi-experimental studies. Existing evidence appears to suggest that any of these interventions, alone or in combination, have a positive impact on process measures such as adherence rate or antimicrobial utilisation. Results on clinically relevant outcomes such as infection rates or resistant patterns were variable. The absence of randomised controlled trials and inclusion of multiple components in the intervention are two recurring challenges when reviewing this group of literature. Given these limitations, we can assign only a low grading.

The use of procalcitonin in the ICU setting has been well studied in numerous randomised controlled trials and the findings are promising in terms of reduction of antibiotic use without negatively affecting patient outcomes. While the majority of studies favoured the procalcitonin arm, one large procalcitonin-escalation study found a negative impact on antibiotic utilisation as well as on days on mechanical ventilation and LOS [65]. Several limitations were identified: there was significant heterogeneity in protocols, with some studies using procalcitonin to initiate, others to discontinue antibiotics or both. In addition, there is variability in the procalcitonin cut-offs that were used. The populations studied are heterogeneous, as some studies evaluated medical/surgical patients whereas others looked predominantly at surgical patients. Only two studies from our review explicitly stated there were ASPs present in the ICUs [69, 70]; thus, the added value of procalcitonin within

Table 3: Procalcitonin studies in the ICU setting.

Author	Country	Year	Design	Patient population	Procalcitonin protocol	Outcome and results
Annane [62]	France	2006–2009	Multicentre RCT	Medical/surgical ICU patients with sepsis (not microbiologically proven) n = 58	No Abx when PCT <0.25 mcg/l and abx discouraged when PCT ≥0.25 mcg/l to <0.5 mcg/l	Proportion of abx treated patients at day 5: no difference
Bouadma [63]	France	2007–2008	Multicentre, open-label noninferiority RCT	Medical/surgical ICU n = 621	Starting Abx if level >0.5 mcg/l Discontinuing Abx if PCT level <0.25 mcg/l, or decrease of >80% from peak concentration or PCT level ≥0.25 and <0.5 mcg/l	Mortality: noninferiority for the PCT group vs standard care Abx-free days: higher in the PCT arm
Hochreiter [64]	Germany	2006–2007	Single centre, open-label, RCT	Surgical ICU n = 110	Discontinuation of abx if PCT level <1 mcg/l, or if PCT > 1 mcg/l but decreased 25–35% over 3 days vs standard care	Duration of therapy: reduced in PCT arm Length of ICU stay: reduced in PCT arm
Hohn [70]	Germany	2010–2012	Single centre, retrospective quasi-experimental	Surgical ICU n = 2 422	Discontinuation of abx when PCT <0.25 mcg/l, or –with clinical improvement – when PCT ≥0.25 to <0.5 mcg/l or PCT decreases to 10% of peak level	Abx use density: decrease
Jensen [65]	Denmark	2006–2009	Multicentre, open-label, RCT	Medical/surgical ICU n = 1 200	Escalation study: PCT level ≥1.0 mcg/l suggested to expand antimicrobial coverage or search for uncontrolled sources of infection.	28-day mortality: no difference Days on mechanical ventilation: higher in the PCT arm ICU LOS: higher in the PCT arm
Prkno [61]	NA	NA	Systematic review and meta-analysis	7 studies n = 1 075 patients	Variable	Hospital mortality: no difference 28-day mortality: no difference Duration of Abx: reduced
Shehbab [69]	Australia	2011–2012	Multi-centre RCT	Medical/surgical ICU n = 394	Stop abx if PCT <0.1 mcg/l, if PCT is 0.1 to 0.25 mcg/l and infection was unlikely, or if PCT has decreased >90% from baseline	Time to Abx cessation: no difference Ab- free days: no difference At day 28 total DDD: reduced in PCT group Hospital LOS: no difference 90-day all-cause mortality: no difference

abx = antibiotic; DDD = defined daily dose; ICU = intensive care unit; LOS = length of stay; PCT = procalcitonin, DDD = defined daily dose; RCT = randomised controlled trial

a strong ASP remains unclear. Furthermore, there was significant deviation from the procalcitonin-protocol noted [62, 63]. Finally, costs remain a concern given the comparably high costs for testing, although a recent cost-minimisation and cost-utility study suggested improved patient quality of life with reduced costs in ICU patients with bacterial infections and sepsis [75]. Overall, there is a moderate level of evidence supporting the use of procalcitonin to reduce duration of antibiotics in the ICU setting.

While we found overall convincing data – within the limitations of nonrandomized studies- that most stewardship strategies are potentially effective in reducing and optimizing antibiotic utilisation, the impact on patient-important outcomes has been variable with no convincing evidence at this point. The absence of such evidence does not imply ASP strategies in the ICU setting are not beneficial to patient-important outcomes, but their detection is difficult given the small event rates of failures, and the lag time until effects may affect future patients, for example, due to reduction of the emergence of resistance. Future studies should be large, i.e. multi-centre studies, optimally using a cluster randomised control trial design or at least controlled quasi-experimental studies with time-series analysis over a prolonged period of time in order to be able to identify the impact of ASP on patient-important outcomes and on the emergence of resistance.

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