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REVIEW

# Antibiotic stewardship programmes in intensive care units: Why, how, and where are they leading us

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## Abstract

Antibiotic usage and increasing antimicrobial resistance (AMR) mount significant challenges to patient safety and management of the critically ill on intensive care units (ICU). Antibiotic stewardship programmes (ASPs) aim to optimise appropriate antibiotic treatment whilst minimising antibiotic resistance. Different models of ASP in intensive care setting, include "standard" control of antibiotic prescribing such as "de-escalation strategies" through to interventional approaches utilising biomarker-guided antibiotic prescribing. A systematic review of outcomes related studies for ASPs in an ICU setting was conducted. Forty three studies were identified from MEDLINE between 1996 and 2014. Of 34 non-protocolised studies, [1 randomised control trial (RCT), 22 observational and 11 case series], 29 (85%) were positive with respect to one or more outcome: These were the key outcome of reduced antibiotic use, or ICU length of stay, antibiotic resistance, or prescribing cost burden. Limitations of non-standard antibiotic initiation triggers, patient and antibiotic selection bias or baseline demographic variance were identified. All 9 protocolised studies were RCTs, of which 8 were procalcitonin (PCT) guided antibiotic stop/start interventions. Five studies addressed antibiotic escalation, 3 de-escalation and 1 addressed both. Six studies reported positive outcomes for reduced antibiotic use, ICU length of stay or antibiotic resistance. PCT based ASPs are effective as antibiotic-stop (de-escalation) triggers, but not as an escalation trigger alone. PCT has also been effective in reducing antibiotic usage without worsening morbidity or mortality in ventilator associated pulmonary infection. No study has demonstrated survival benefit of ASP. Ongoing challenges to infectious disease management, reported by the World Health Organisation global report 2014, are high AMR to newer antibiotics, and regional knowledge gaps in AMR surveillance. Improved AMR surveillance data, identifying core aspects of successful ASPs that are transferable, and further well-conducted trials will be necessary if ASPs are to be an effective platform for delivering desired patient outcomes and safety through best antibiotic policy.

**Key words:** Antibiotic stewardship programme; Intensive care; Antimicrobial resistance; Antibacterial resistance; Antibiotic resistance

**Core tip:** Antibiotic stewardship programmes (ASPs) aim to optimise appropriate antibiotic treatment and minimise antimicrobial resistance (AMR). Multistrategic approaches must address challenges to future management of infectious disease. Models of ASP in intensive care unit, include "standard" control of antibiotic prescribing (*e.g.,* "de-escalation strategies") through to interventional approaches utilising biomarker-guided decisions. Protocolised ASPs using procalcitonin guided antibiotic-stop but not antibiotic-start alone decisions demonstrate reduced antibiotic and AMR rates, but not survival benefit. Immediate research needs include better AMR surveillance, early microbial diagnostic tests, and core transferable elements of ASPs.

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## BURDEN OF INFECTION IN THE CRITICALLY ILL - MAJOR CHALLENGES TO PATIENT MANAGEMENT

The intensive care unit (ICU) is often regarded as an epicentre of infections, with sepsis being the second non-cardiac cause of mortality[1]. In two major cross-sectional studies of sepsis in the intensive care setting, Sepsis in European Intensive care units (EPIC Ⅱ)[2] and SOAP[3], 50% and 38% of all patients respectively had infections.

Mortality from Sepsis in the critically ill can approach 50%, with time to initiation of antibiotic treatment as the single strongest predictor of outcome. Each hour's delay increases mortality by 7.6%, over the first 6 h[4]. ICUs account for 5%-15% of total hospital beds but 10%-25% of total healthcare costs[5]. Sepsis increases patient-related costs six-fold[6]. In the United States, antibiotic-resistant infections are associated with 23000 deaths and 2 million illnesses per year, with estimated excess direct healthcare costs of $20 billion and $35 billion in lost productivity[7]. Resistant organisms can increase patient-related prescribing costs by $8000 to $30000[1]. Such empiric practice, deemed necessary at the point of care, due to uncertainty of causative organisms, is often ineffective and results in higher costs.

## ANTIBIOTIC RESISTANCE IN ICU, ITS CONTRIBUTORS AND IMPACT

Antimicrobial resistance (AMR) is an increasing global healthcare phenomenon, with apocalyptic predictions of a post-antibiotic era where common infections and minor injuries may not be treatable by conventional antibiotics[8]. A WHO global report describes the majority of world regions with over 50% resistance of *Escherichia coli* (*E. Coli)* and *Klebsiella Pneumoniae* to 3rd generation cephalosporins and fluoroquinolones. The increasing prevalence of carbapenem-resistant organisms, and other multi-resistant strains such as Methicillin resistant *Staphylococcus aureus* (MRSA) as well as extended-spectrum beta-lactamase (ESBL) producers justifies these concerns. Specifically, AMR has a number of proposed causes. Data from United States National Nosocomial Infection Surveillance programme (NNIS) demonstrated 20%-30% increase in resistant isolates of *Pseudomonas*, *Staphylococcus aureus* and *Enterococcus* across a 5-year period[9]. In particular, fluoroquinolone-resistant *Pseudomonas* showed more than 50% increase during the period.

Intensive care units represent the heaviest antibiotic burden within hospitals. They are described albeit provocatively, as a factory creating, disseminating and amplifying antibiotic resistance[1]. In a European multi-centre cross-sectional prevalence study of academic ICUs, there were 14% of *Klebsiella* ESBL-producers, and nearly 25% of *Pseudomonas aeruginosa* isolates were carbapenem-resistant[10].

ICUs in emerging economies report notably higher prevalence of ESBL-producers[11-13] and carbapenem-resistant organisms[11-14]. Of note, the majority of multi-resistant *Acinetobacter* (MRA) isolates in these studies also demonstrates reduced susceptibility towards carbapenems[11-13].

The dynamics of antibiotic resistance are multifarious. Firstly, antibiotic usage in the animal and plant industry, to improve growth and productivity, is a major contributor to AMR[15]. The increasing prevalence of ESBL producers in animal products has been suggested. Furthermore, a link between antibiotic resistance in human clinical microbiological isolates and those from poultry has been raised[16]. On the contrary, other studies rule out such associations between chicken meat and colonisation of ESBL-producing *E. coli* in humans[17].

Within the ICU setting itself, causes of AMR may conveniently be categorised by procedure-related, management-related, and antibiotic-related factors. Procedure-related factors include central venous catheters[18,19] and endotracheal intubation for mechanical ventilation[20]. Management-related factors include poor adherence to infection control policy[20], lack of microbiological surveillance with delayed/failed recognition of resistant isolates[21], patient overcrowding[22,23], understaffing and implicit spread of AMR through human vectors[24,25], prolonged ICU length of stay[20,26], and pre-infection with resistant organisms at the time of ICU admis-

sion[26]. Antibiotic-related factors are related to the appropriateness and duration of treatment. Non-controlled usage[27] is well documented. Ceftriaxone for example, was shown to cause a rise in rates of vancomycin resistant *Enterococci* (VRE) rates[28]. The use of broad-spectrum antibiotics, often as the first step in therapy for patients with suspected infections, has accumulated considerable evidence regarding its association with the development of antibiotic resistance[20,26,29-32]. Similarly, the ease of access to certain antibiotic classes, either through their availability over-the-counter in certain countries (*i.e.,* penicillins, fluoroquinolones) or through unfounded clinician concerns of missing unlikely bacterial infection, leads to documented AMR, although causation proves difficult at an individual patient level. As such, the evidence behind the duration of treatment and AMR is comparatively lacking. In the PneumA trial, patients with ventilator-associated pneumonia (VAP), who had prolonged antibiotic treatment (15 d *vs* 8 d) developed higher rates of multi-resistant Pseudomonas isolates[33]. Clearly, one must be circumspect about distinguishing natural selection of antibiotic resistant bacteria through necessary antibiotic usage and judgements of inappropriate antibiotic usage as causation of AMR.

Although only shown in hospital wards rather than ICU, failure to de-escalate or discontinue therapy[34,35] is also a likely contributory factor to antibiotic resistance in ICU.

The exact impact of multidrug resistance (MDR) microbial organisms is difficult to quantify, depend as it does on, the causative microbe and its pathogenicity, patient populations, severity of illness and the appropriateness of therapy[36]. The association of increased ICU mortality and hospital length of stay (LOS) with MRSA, VRE, *Acinetobacter*, *Pseudomonas* and *Klebsiella* are well documented[37]. These mirror poor outcomes associated with such organisms in general ward settings[38]. From a financial perspective for instance, bloodstream infections caused by MDR organisms are estimated to increase treatment costs by 50%[39]. What effect such local outbreaks of MDR bacteria have on process of care within a hospital setting and outwith is dependent on effective surveillance, and links between infection control, Public health, and health policy makers. This data is all too often insufficient or not translated into effective intervention.

## ANTIBIOTIC STEWARDSHIP PROGRAMMES IN ICU

Antibiotic stewardship programmes (ASP) are regarded as a keystone in tackling AMR in ICU. The intention is to reduce antibiotic resistance by minimising selection pressure, through optimising antibiotic therapy[40-44]. In Europe, the implementation of ASP follows a "top-down" model, with European council recommendations (*i.e.,* the Prague framework) and national-level guidance (*e.g.,* The Scottish Management of Antimicrobial Resistance Action Plan, ScotMARAP) informing delivery programmes at critical care network and individual unit levels[45,46]. In the context of these strategic initiatives, we have conducted the following systematic review of published ASPs in the ICU.

## SUCCESS AND SHORTFALLS OF ASP IN THE ICU SETTING

### *Search strategy*

To identify the eligible studies MEDLINE was searched from January 1996 to May 2014 using the following strategy: antibiotic and (stewardship programme or restriction or audit or decision support or education or guideline or policy or control or escalation or de-escalation) and (intensive care or critical care). The search was further refined by adding MeSH terms (intensive care unit or intensive care or critical care). Only human studies were included. The reference lists of all studies were reviewed to identify additional studies. Duplicate studies and conference abstracts were excluded.

### *Results*

Forty three studies of ASPs in the ICU were identified. Thirty four were non-protocolised ASPs, and 9 studies of protocol-based ASPs. Their major findings are summarised in Table 1 and Table 2, respectively.

Out of the 34 non-protocolised ASPs, only 1 (3%) was a randomised controlled trial, whilst 22 (65%) were retrospective observational studies. Twenty nine (84%) studies comprised a single strategy, and 10 (29%) studies had a follow-up period of longer than one year. Antibiotic usage was the most common primary outcome measure (28 studies, 82%), followed by ICU LOS (19, 56%), mortality (15, 44%), antibiotic resistance (14, 41%) and antibiotics' cost (11, 32%). Twenty nine (85%) studies were regarded as positive studies, defined as achieving favourably in least one of the five aforementioned outcomes. Thirteen (38%) studies were conducted in specialist ICUs (purely medical, surgical, neonatal, paediatric or trauma). With respect to limitations, 8 (24%) had missing patient characteristics, whilst 4 (12%) studies had inconsistencies in patient characteristics between pre- and post-intervention arms.

Limitations of many of the non-protocolised ASP studies, particularly in regard to lack of consistency between the ASP and standard care arms are evident. Therefore, interpretation of the findings from these studies can at best be hypothesis-generating only. For instance, lack of standardised

**Table 1 Non-protocolised antibiotic stewardship programmes**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Kollef *et al*[18] | 1997 | 9351601 | Prospective cohort study<br>Follow-up 6 mo | Incidence of VAP<br>Incidence of bloodstream infection and sepsis<br>Duration of mechanical ventilation<br>LOS<br>Mortality | 680 | Non-protocolised<br>Components<br>Rotating antibiotic schedule | 1 Positive study<br>2 ↓ in resistant Gram negative organisms<br>3 ↓ in VAP incidence<br>4 No change to mortality<br>5 No change to LOS | 1 No information on antibiotic usage<br>2 6 mo follow-up period only |
| Evans *et al*[91] | 1998 | 9435330 | Prospective observational study<br>Follow-up 1 yr | Antibiotic use<br>Antibiotic cost<br>Cost of hospitalisation<br>Number of adverse events caused by anti-infective agents<br>No. of days of excessive antibiotic dosage<br>LOS<br>Mortality | 1681 | Non-protocolised<br>Components<br>Computerised decision support tool | 1 Positive study<br>2 ↓ in total antibiotics cost<br>3 No change in DDD<br>4 ↓ in susceptibility-mismatch<br>5 ↓ in allergy-mismatch<br>6 ↓ of mortality<br>7 ↓ of LOS from 4.9 d to 2.7 d (4.9 to 8.3 d if overridden) | 1 Less patients in post-intervention group<br>2 Young patients (mean age < 50 yr) |
| Price *et al*[84] | 1999 | 10548192 | Retrospective observational study<br>Follow-up 1 mo | Antibiotic cost<br>Antibiotic resistance<br>LOS | 321 | Non-protocolised<br>Components<br>Antibiotic guideline | 1 Positive study<br>2 77% ↓ in antibiotic cost<br>3 No change to LOS<br>4 No change to mortality | 1 Surgical ICU only<br>2 1 mo FU follow-up<br>3 High compliance rate with guideline (95.6%)<br>4 High baseline APACHEII score (38.0-39.1) |
| Roger *et al*[64] | 2000 | 11089498 | Retrospective observational study<br>Follow-up 2 mo | Antibiotic use<br>Antibiotic cost | 61 | Non-protocolised<br>Components<br>ID specialist input | 1 Positive study<br>2 ↓ in duration of treatment from mean 23 d to 13 d<br>3 ↓ in total antibiotic days from 596 d to 455 d<br>4 19% ↓ in total antibiotic cost<br>5 No change to mortality<br>6 No change to LOS | 1 2 mo follow-up period |
| Fox *et al*[63] | 2001 | 11712090 | Retrospective observational study<br>Follow-up 1 yr | Antibiotic use<br>LOS<br>Days on mechanical ventilation<br>Days with fever<br>No. of cultures performed<br>Antibiotic resistance<br>Antibiotic cost | 295 | Non-protocolised<br>Components<br>ID specialist input | 1 Negative study<br>2 No change to antibiotic usage<br>3 57% ↓ in antibiotics cost<br>4 ↑ infection rate<br>5 No change in LOS | 1 Trauma ICU only<br>2 Young patients (age < 35 yr) |
| Mullett *et al*[90] | 2001 | 11581483 | Retrospective observational study<br>Follow-up 6 mo | Antibiotic cost<br>Rate of anti-infective sub-therapeutic and excessive-dose days | 1758 | Non-protocolised<br>Components<br>Computerised decision support tool | 1 Negative study<br>2 No change to total cost of antibiotics<br>3 ↓ of excessive dose days and sub-therapeutic days (*i.e.*, dose optimisation) | 1 Paediatric ICU only<br>2 Significantly younger patients in post-intervention group |
| Dos Santos *et al*[61] | 2003 | 14552737 | Retrospective observational study<br>Follow-up 1 yr | Antibiotic use<br>Antibiotic cost | 1473 | Non-protocolised<br>Components<br>ID specialist input | 1 Positive study<br>2 ↓ in cephalosporin, carbapenems and vancomycin usage<br>3 ↑ in penicillin usage<br>4 ↓ of cost by 37% | 1 Limited patient characteristics<br>2 No information on antibiotic resistance<br>3 No information on LOS and mortality |

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|---|---|---|---|---|---|---|---|---|
| Du *et al*[62] | 2003 | 12682477 | Prospective observational study<br>Follow-up<br>1 yr | Antibiotic use<br>Antibiotic resistance<br>LOS | 1205 | Non-protocolised<br>Components<br>Antibiotic restriction<br>Senior clinician input | 1 Positive study<br>2 ↓ in 3rd generation cephalosporin usage<br>3 ↑ in cefepime usage<br>4 No change to resistance pattern<br>5 ↓ in LOS from 13.1 d to 9.3 d | 1 Significant reduction in APACHEII scores and organ failure % in post-intervention group<br>2 High baseline Pseudomonas and *Acinetobacter* rate<br>3 No information on mortality |
| Geissler *et al*[82] | 2003 | 12528022 | Retrospective observational study<br>Follow-up<br>4 yr | Antibiotic use<br>Antibiotic resistance<br>Antibiotic cost | 1704 | Non-protocolised<br>Components<br>*Antibiotic guideline* | 1 Positive study<br>2 35% ↓ in antibiotic days<br>3 37% ↓ in antibiotics cost<br>4 Significant ↓ in total number of resistant isolates | 1 High baseline mortality<br>2 No data on LOS |
| Micek *et al*[81] | 2004 | 15136392 | RCT<br>Follow-up<br>14 mo | Antibiotic use<br>Incidence of VAP<br>LOS<br>Mortality | 290 | Non-protocolised<br>Components<br>Antibiotic discontinuation policy | 1 Positive study<br>2 ↓ of antibiotic treatment duration<br>3 No change to LOS<br>4 No change to mortality | 1 Medical ICU only<br>2 Limited microbiology data |
| Aubert *et al*[80] | 2005 | 15620440 | Retrospective observational study<br>Follow-up<br>1 yr | Antibiotic use<br>Microbiological profile and antibiotic resistance | 781 | Non-protocolised<br>Components<br>Antibiotic restriction | 1 Positive study<br>2 ↓ in fluoroquinolone usage by 75.8%<br>3 ↓ in usage of aminoglycosides and macrolides<br>4 ↓ of antibiotic resistance in *Pseudomonas*<br>5 No change to mortality<br>6 No change to LOS | 1 No information on antibiotic usage |
| Sintchenko *et al*[89] | 2005 | 15802478 | Prospective observational study<br>Follow-up<br>6 mo | Antibiotic use<br>LOS<br>Mortality | 5176 patient-days | Non-protocolised<br>Components<br>Computerised decision support tool | 1 Positive study<br>2 Significant ↓ in total DDD from 1925 to 1606, particularly vancomycin and beta-lactam resistant penicillins<br>3 ↓ of mean LOS from 7.15 to 6.22 d<br>4 No change to mortality | 1 6 mo follow-up period<br>2 No information on antibiotic resistance |
| Bochicchio *et al*[88] | 2006 | 16500251 | Randomised pilot study<br>Follow-up<br>6 mo | Antibiotic decision accuracy | 125 | Non-protocolised<br>Components<br>Computerised decision support tool | 1 Positive study<br>2 ↑ in decision accuracy (verified by ID specialists) | 1 No information on antibiotic usage<br>2 No information on antibiotic resistance |
| Brahmi *et al*[78] | 2006a | 16944257 | Retrospective observational study<br>Follow-up<br>2 yr | Antibiotic use | 727 | Non-protocolised<br>Components<br>Antibiotic restriction | 1 Positive study<br>2 Significant ↓ in ceftazidime usage<br>3 ↓ in tazocin and imipenem resistance<br>4 ↑ resistance to penicillins | 1 High baseline rate of VAP patients (63%-70%)<br>2 High baseline resistance rate among Pseudomonas (59% to tazocin, 58% to ciprofloxacin, 58% to imipenem, 47% to ceftazidime)<br>3 No info on mortality and LOS |
| Thursky *et al*[87] | 2006 | 16415039 | Prospective observational study<br>Follow-up<br>6 mo | Antibiotic use<br>Antibiotic susceptibility-mismatches<br>Mortality | 1060 | Non-protocolised<br>Components<br>Computerised decision support tool | 1 Positive study<br>2 ↓ of total DDD from 1670 to 1490<br>3 ↓ in usage of ceftriaxone, vancomycin and carbapenems<br>4 ↓ of susceptibility-mismatch<br>5 No change to mortality | 1 6 mo follow-up period<br>2 High baseline mortality (19%)<br>3 Fewer isolates in intervention group<br>4 No information on LOS |

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|---|---|---|---|---|---|---|---|---|
| Brahmi *et al*[79] | 2006b | 17027213 | Prospective cohort study<br>Follow-up<br>2 yr | Antibiotic use<br>Antibiotic resistance | 318 | Non-protocolised<br>Components<br>Antibiotic guideline | 1 Positive study<br>2 ↓ in duration of treatment from 14.1 to 11.9 d<br>3 ↓ in antibiotics cost<br>4 ↓ in LOS from 20.4 to 16.9 d<br>5 No change to mortality | |
| de Araujo *et al*[69] | 2007 | 17625777 | Retrospective observational study<br>Follow-up<br>1 yr | LOS<br>Days of parenteral nutrition<br>Requirement for mechanical ventilation<br>Antibiotic use | 995 | Non-protocolised<br>Components<br>Rotating antibiotic schedule | 1 Positive study<br>2 ↓ in cefepime usage<br>3 ↑ in tazocin usage<br>4 No change to LOS | 1 Neonatal ICU only<br>2 High baseline rates of *Pseudomonas* and *Klebsiella*<br>3 No information on mortality |
| Ntagiopoulos *et al*[77] | 2007 | 17629680 | Retrospective observational study<br>Follow-up<br>6 mo | Antibiotic use<br>Antibiotic resistance | 147 | Non-protocolised<br>Components<br>Antibiotic restriction | 1 Positive study<br>2 ↓ of overall antibiotic usage by 55%<br>3 ↓ in resistance in Pseudomonas<br>4 ↑ in resistant strains of *Klebsiell*a and *Acinetobacter*<br>5 No change to mortality<br>6 No change to LOS | 1 Male predominance<br>2 High baseline mortality<br>3 6 mo follow-up period<br>4 High baseline ceftazidime and fluoroquinolone resistance<br>5 90% policy compliance among clinicians |
| Ding *et al*[76] | 2008 | 18493864 | Retrospective observational study<br>Follow-up<br>2 yr | Antibiotic use<br>Rate of bacterial resistance | 900 | Non-protocolised<br>Components<br>Antibiotic guideline<br>Staff education | 1 Positive study<br>2 ↓ in usage of 3rd generation cephalosporin<br>3 ↑ in usage of beta-lactams<br>4 ↓ in antibiotics cost<br>5 No change to LOS | 1 Paediatric ICU only<br>2 High baseline antibiotic utilisation (98.7% patients were on antibiotics)<br>3 High baseline resistance rate (> 60% to cefepime, for E coli and Klebsiella; > 20% to cefepime and imipenem, for *Pseudomonas*)<br>4 No information on mortality |
| Peto *et al*[60] | 2008 | 19011742 | Retrospective observational study<br>Follow-up<br>2 yr | Antibiotic use<br>Incidence of sepsis<br>LOS<br>Mortality | 3403 | Non-protocolised<br>Components<br>Senior clinician input | 1 Positive study<br>2 ↓ of mean DDD from 162.9 to 101.3.<br>3 No change to LOS<br>4 No change to mortality | 1 Surgical ICU only with > 60% neurological patients<br>2 Low baseline resistance rate<br>3 Increased patient turnover since intervention |
| Marra *et al*[59] | 2009 | 18986735 | Retrospective observational study<br>Follow-up<br>10 mo | Antibiotic resistance | 360 | Non-protocolised<br>Components<br>ID specialist input | 1 Positive study<br>2 ↓ of total DDD by 12.1%<br>3 ↓ of resistant strains of *Pseudomonas*, *Klebsiella* and *Acinetobacter* | 1 High baseline resistance rate<br>2 Limited patient characteristics<br>3 Unknown sample size<br>4 No information on mortality and LOS |
| Meyer *et al*[74] | 2010 | 19904488 | Retrospective observational study<br>Follow-up<br>3 yr | Mortality<br>Antibiotic use | 11887 | Non-protocolised<br>Components<br>Antibiotic prophylaxis | 1 Positive study<br>2 15% ↓ in total antibiotic usage primarily cefuroxime and co-trimoxazole<br>3 Sustained ↓ to antibiotic usage<br>4 No change to LOS<br>5 No change to mortality | 1 Surgical ICU only<br>2 Limited resistance data |

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|---|---|---|---|---|---|---|---|---|
| Yong *et al*[86] | 2010 | 20215130 | Retrospective observational study<br>Follow-up 4.5 yr | Antibiotic susceptibilities of *Pseudomonas*, *Klebsiella*, *Acinetobacter* and *Enterobacteriaceae* | 13295 | Non-protocolised<br>Components<br>Computerised decision support tool | 1 Positive study<br>2 No change to Abx usage<br>3 ↑ susceptibility to imipenem for *Pseudomonas*, *Acinetobacter* and *Enterobacter*<br>4 ↑ susceptibility to gentamicin for *Pseudomonas* and *Enterobacter*<br>5 No change to LOS | 1 Limited patient characteristics<br>2 No information on mortality |
| Sharma *et al*[75] | 2010 | 21206622 | Retrospective observational study<br>Follow-up 4 mo | Antibiotic use<br>Antibiotic resistance | 177 | Non-protocolised<br>Components<br>Antibiotic restriction | 1 Negative study<br>2 ↓ of carbapenem usage<br>3 ↑ in beta-lactam usage | 1 Medical ICU only<br>2 No information on overall antibiotic usage<br>3 4 mo follow-up period<br>4 No pre-intervention arm<br>5 Male predominance<br>6 High baseline Acinetobacter isolates<br>7 High baseline resistance rate |
| Raymond *et al*[68] | 2011 | 11395583 | Prospective cohort study<br>Follow-up 1 yr | Mortality<br>Duration of treatment<br>Antibiotic cost<br>LOS | 1456 | Non-protocolised<br>Components<br>Rotating antibiotic schedule | 1 Positive study<br>2 ↓ in infection rate by 25%<br>3 ↓ in infections caused by resistant organisms<br>4 ↓ in usage of aminoglycosides, vancomycin and antifungals<br>5 ↑ in usage of clindamycin<br>6 ↓ in mortality from 38.1% to 15.5%<br>7 No change to LOS | 1 No information on overall antibiotic usage<br>2 High baseline mortality rate |
| Dortch *et al*[67] | 2011 | 21091186 | Retrospective observational study<br>Follow-up 8 yr | Incidence of infection caused by MDR organisms<br>Antibiotic use | 20846 | Non-protocolised<br>Components<br>Antibiotic guidelines<br>Antibiotic prophylaxis<br>Rotating antibiotic schedules | 1 Positive study<br>2 Significant ↓ of total broad spectrum antibiotic usage<br>3 ↓ in total infection rate<br>4 ↓ in MDR Pseudomonas, Acinetobacter and Enterobacter isolates | 1 Surgical ICU only<br>2 High baseline respiratory infection rate<br>3 High baseline Enterobacter infection rate<br>4 Concomitant infection control policy |
| Slain *et al*[57] | 2011 | 21687626 | Retrospective observational study<br>Follow-up 7 yr | Antibiotic use<br>Antibiotic resistance | N/A | Non-protocolised<br>Components<br>Prospective audits<br>Antibiotic restriction<br>Staff education<br>Antibiotic guidelines<br>Rotating antibiotic schedules | 1 Positive study<br>2. Overall ↓ of DDD<br>3 Fluctuations due to resistance and change in protocols<br>4 ↑ in resistance to ciprofloxacin, tazocin, cefepime | 1 Pseudomonas infections only<br>2 Limited patient characteristics<br>3 No information on mortality or LOS |

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|---|---|---|---|---|---|---|---|---|
| Chiu *et al*[73] | 2011 | 21085051 | Prospective observational study<br>Follow-up<br>1 yr | Antibiotic use | 190 | Non-protocolised<br>Components<br>Antibiotic guideline | 1 Negative study<br>2 No change to overall antibiotic usage<br>3 ↓of vancomycin usage | 1 Neonatal ICU only<br>2 Limited patient characteristics<br>3 Limited resistance data<br>4 No information on mortality and LOS |
| Sarraf-Yazdi *et al*[66] | 2012 | 22445457 | Retrospective observational study<br>Follow-up<br>9 yr | Antibiotic use<br>Antibiotic resistance | 321 | Non-protocolised<br>Components<br>Rotating antibiotic schedules | 1 Positive study<br>2 No change in total antibiotic usage<br>3 ↓ in prescribed dosage of target antibiotics<br>4 ↓ in resistance against ceftazidime and tazocin | 1 No LOS or mortality data<br>2 Limited patient characteristics |
| Sistanizad *et al*[72] | 2013 | 24250656 | Prospective cohort study<br>Follow-up<br>9 mo | Antibiotic use<br>Susceptibility of *P. aeruginosa*, *A. baumanni*, *K. pneumonia* and *E. coli* | N/A | Non-protocolised<br>Components<br>Antibiotic restriction | 1 Positive study<br>2. 60% ↓ in imipenem use<br>3 ↑ in carbapenem sensitivity for Klebsiella and Pseudomonas | 1 No mortality and LOS data<br>2 Limited patient characteristic data |
| Rimavi *et al*[58] | 2013 | 23873275 | Prospective cohort study<br>Follow-up<br>3 mo | Antimicrobial use<br>Treatment duration<br>APACHEII score<br>LOS<br>Mechanical ventilation days<br>Mortality rate | 246 | Non-protocolised<br>Components<br>ID specialist input | 1 Positive study<br>2 Significant ↓ in overall antibiotic usage<br>3 ↓ of LOS<br>4 No change to mortality | 1 Medical ICU only<br>2 Follow-up period of only 3 mo<br>3 Limited resistance data |
| Bauer *et al*[71] | 2013 | 23571547 | Retrospective cohort study<br>Follow-up<br>N/A | Duration of mechanical ventilation<br>LOS<br>Mortality | 1433 | Non-protocolised<br>Components<br>Intermittent *vs* extended dosing regimen of cefipime | 1 Positive study<br>2. ↓ of mortality from 20% to 3%<br>3 ↓ of LOS<br>4 ↓ of antibiotic cost per patient by $23183 in extended dosing group | 1 Pseudomonas infection only<br>2 No information on antibiotic resistance<br>3 No follow-up |
| Ramsamy *et al*[65] | 2013 | 23725954 | Retrospective observational study<br>Follow-up<br>1 yr | Antibiotic use<br>Antibiotic resistance | 227 | Non-protocolised<br>Components<br>Antibiotic restriction | 1 Negative study<br>2 6.5% inappropriate broad- spectrum antibiotic usage | 1 Trauma ICU<br>2 No pre-intervention arm<br>3 Limited patient characteristics<br>4 No information on mortality and LOS |
| Apisarnthanarak *et al*[98] | 2014 | 24485368 | Retrospective observational study<br>Follow-up<br>1 yr | Rate of XDR *Acinetobacter* baumanni acquisition rate per 1000 patient days<br>Rate of Acinetobacter baumanni infection or colonisation | 1365 | Not specified | 1 Positive study<br>2 Significant ↓ in XDR Acinetobacter baumanni infection or colonisation rates | 1 Type of ASP not specified<br>2 No information on antibiotic usage<br>3 Concomitant infection control policy (Use of disinfectant-detergent; Enhanced isolation; Active surveillance cultures for all ICU patients) |

LOS: Length of stay; VAP: Ventilator-associated pneumonia; ICU: Intensive care units; ASP: Antibiotic stewardship programme; DDD: Defined daily dose; RCT: Randomised Controlled Trial; APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Ⅱ.

antibiotic treatment initiation triggers to reduce inter-clinician decision tree variability, or inadvertent variations in clinico-biochemical information provided to both arms. Patient or antibiotic selection bias are a few such confounders.

All 9 protocol-based studies were randomised controlled trials, 4 (44%) being multi-centred. Eight studies (89%) were procalcitonin-guided, and the remaining one (11%) was based on clinical scoring system. Only 1 (11%) study looked at the merit of PCT-guided ASP in both escalation and de-escalation of antibiotic treatment, whilst 5 (56%) and 3 (33%) studies, investigated its sole role in de-escalation or escalation, respectively. Six (67%) studies were

**Table 2 Protocol-based antibiotic stewardship programmes**

| Ref. | Year | Pubmed ID | Study type | Outcome | No. of patients | Type of ASP | Major findings | Limitations/Confounding factors |
|---|---|---|---|---|---|---|---|---|
| Singh *et al*[54] | 2000 | 10934078 | RCT<br>Follow-up<br>N/A | 1 LOS<br>2 Mortality<br>3 Proportion of patients with resolution of pulmonary infiltrate | 81 | Clinical Pulmonary Infection Score-based De-escalation | 1 Positive study<br>2 ↓ in total antibiotic days from 9.8 to 3 d<br>3 ↓ of antibiotics cost by $381 per patient<br>4 ↓ in LOS from 14.7 to 9.4 d mean<br>5 Significant ↓ in total antibiotic resistance<br>6 No change to mortality | 1 79% surgical patients<br>2 Mean APACHEII score of 42.7 in intervention group<br>3 Unknown follow-up period |
| Nobre *et al*[47] | 2008 | 18096708 | Single-centred RCT | 1 Antiiotic Antibiotic use<br>2 28-d mortality<br>3 LOS<br>4 Incidence of clinical cure<br>5 Recurrence of infection<br>6 Incidence of nosocomial superinfection | 79 | PCT-based De-escalation | 1 Positive study<br>2 ↓ in duration of treatment from median 9.5 to 6 d<br>3 ↓ in ICU LOS from 5 to 3 d<br>4 ↓ in hospital LOS 21 to 14 d<br>5 No change to mortality | 1 Small study<br>2 Sepsis patients only<br>6 Infections by Pseudomonas, Acinetobacter *etc.* were excluded<br>7 Patients with chronic infections were excluded<br>8 Immunocompromised patients were excluded<br>9 Patients on antibiotics at time of admission were excluded |
| Hochreiter *et al*[48] | 2009 | 19493352 | Single-centred RCT | 1 Antibiotic use<br>2 LOS<br>3 Mortality | 110 | PCT-based De-escalation | 1 Positive study<br>2 ↓ in duration of treatment from median 7.9 to 5.9 d<br>3 ↓ in LOS from median 17.7 to 15.5 d<br>4 No change to mortality | 1 Patients on antibiotics at time of admission were excluded<br>2 Sepsis patients only |
| Schroeder *et al*[49] | 2009 | 19034493 | Single-centred RCT | 1 Antibiotic use<br>2 LOS<br>3 Mortality | 27 | PCT-based De-escalation | 1 Positive study<br>2 ↓ in duration of treatment from 8.3 to 6.6 d<br>3 ↓ in antibiotic cost by 17.8%<br>4 No change to LOS<br>5 No change to mortality | 1 Sepsis patients only |
| Stolz *et al*[55] | 2009 | 19797133 | Multi-centred RCT | 1 No. of days without antibiotics at 28 d<br>2 Number of days without mechanical ventilation<br>3 ICU mortality<br>4 LOS<br>5 Incidence of VAP | 101 | PCT-based De-escalation | 1 Positive study<br>2 27% ↓ in duration of treatment<br>3 No change to mortality<br>4 No change to LOS | 1 VAP patients only |
| Bouadma *et al*[50] | 2010 | 20097417 | Multi-centred RCT (PRORATA trial) | 1 28-d and 60-d mortality<br>2 Number of days without antibiotics at 28 d<br>3 Incidence of recurrence of infection or superinfection<br>4 Days of unassisted breathing<br>5 LOS<br>6 Antibiotic use<br>7 Incidence of MDR organisms | 630 | PCT-based Escalation/ De-escalation | 1 Positive study<br>2 ↓ in duration of treatment from 13.3 to 10.3 d<br>3 No change to mortality<br>4 No change to LOS | 1 Patients on antibiotics on admission were excluded<br>2 Patients with chronic infection were excluded<br>3 Immunocompromised patients were excluded<br>4 90% medical patients<br>5 Close to 50% respiratory/CVS failure, and > 30% CNS failure<br>6 70% pulmonary infection site<br>7 53% did not adhere to algorithm in PCT group |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Jensen *et al*[51] | 2011 | 21572328 | Multi-centred RCT (PASS trial) | 1 28-d mortality | 1200 | PCT-based Treatment escalation | 1 Negative study<br>2 Significant ↑ in duration of tretment (Median: from 4 to 6 d), especially for tazocin and meropenem<br>3 ↑ in LOS from median 5 to 6 d<br>4 No change to mortality | 1 Low resistance and antibiotic usage units<br>2 Incomplete adherence to PCT algorithm |
| Layios *et al*[52] | 2012 | 22809906 | Single-centred RCT | 1 Antibiotic use<br>2 Accuracy of infectious diagnosis<br>3 Diagnostic concordance between intensive care unit physician and ID specialist | 510 | VAP -based Escalation | 1 Negative study<br>2 No change in duration of antibiotic treatment<br>3 No change in DDD<br>4 No change to LOS<br>5 No change in mortality | 1 41% surgery and trauma patients |
| Annane *et al*[53] | 2013 | 23418298 | Multi-centred RCT | 1 Proportion of patients on antibiotics at day 5 | 62 | PCT-based Escalation | 1 Negative study<br>2 Premature termination | 1 Poor clinician compliance with algorithm<br>2 Patients on antibiotics at time of admission were excluded |

LOS: Length of stay; VAP: Ventilator-associated pneumonia; ICU: Intensive care units; ASP: Antibiotic stewardship programme; DDD: Defined daily dose; RCT: Randomised Controlled Trial; APACHEII: Acute Physiology and Chronic Health Evaluation II; PCT: Procalcitonin; CVS: Cardiovascular system; CNS: Central Nervous system; XDR: Extensively Drug-Resistant.

positive studies. The most commonly explored outcome measures were antibiotic usage (8 studies, 89%), ICU LOS (8 studies, 89%) and mortality (8 studies, 89%), followed by antibiotics' cost (2 studies, 22%) and antibiotic resistance (1 study, 11%). Clinician adherence was reported as a major issue in two (22%) studies.

In summary, 29 of 34 non-protocolised ASPs and 6 of 9 protocol-based ASPs were reported as positive studies. PCT guided prescribing, reduced antibiotic usage when used as a de-escalation/stop trigger[47-49], and in one study using PCT for escalation/de-escalation[50] It did not improve outcomes when used as an escalation trigger alone to reduce time-to-appropriate antibiotics[51-53]. PCT has also been effective in reducing antibiotic usage without worsening morbidity or mortality in ventilator associated pulmonary infection[54,55]. No survival benefit in the ICU has yet been demonstrated.

## Discussion

Four basic principles of ASP have been described: Timeliness, appropriateness, adequacy and duration of antibiotic usage[56]. It represents a multifaceted approach that includes many components, and each individual ASP might encompass several, but not all, of them at a given time. These components include audits[57], infectious disease specialist or senior clinician input[58-64], or planned discontinuation/de-escalation of treatment in response to clinical and microbiological outcome data[65]. Other components include rotating antibiotic schedules[57,66-70] changes in prescribing policies involving antibiotic restriction, different dosing regimens or prophylaxis protocols[57,62,65,67,71-84] and a multi-disciplinary team (MDT) approach in treatment initiation and discontinuation, often emphasising feedback and non-punitive atmosphere among staff members[83,85]. Some programmes also encompassed staff education[57,74,76] and computerised decision support platforms[86-91]. Concomitant regional or national infection control campaigns, for example in the United Kingdom between 2003 and 2008, might serve as necessary adjuvants to the success of ASPs.

Additional input comes from ICU-based pharmacy support[92]. Pharmacists are significant drivers in ASPs, with roughly one-fifth of pharmacist intervention in an American trauma centre being ASP related[93]. The MDT approach itself seems to be more effective than purely its components. In a prospective study of Antibiotic stewardship comparing an MDT approach with a non-MDT (involving only the infectious disease physician and ICU pharmacist), the former, which also includes other affiliated healthcare professionals, led to superior outcomes of appropriate antibiotic selection and the rates of antibiotic resistance[94].

Protocol-based ASPs have recently gained popularity. Earlier programmes utilised clinical scoring systems in guiding antibiotic treatment[54], whilst PCT-based ASPs are increasingly being adopted in ICUs. PCT is regarded as a superior biomarker of sepsis compared with many others discovered over the decades, including white cell count, C-reactive protein and interleukin-6. It is relatively unhindered by the issues of slow kinetics and non-specificity faced by the latters[95-97]. Effective infection control and source control remain fundamental to successful ASPs[98]. As has been demonstrated by the systematic review, there is a clear signal

suggesting the potential benefits of ASP, even in non protocolised observational studies. This of course depends on the outcome measured, but in regards decreased antibiotic duration, and cumulative prescribed burden, the results are favourable when PCT is used to guide antibiotic stop decisions. These reductions in antibiotic use have been verified in many PCT guided protocol based RCTs, but not as an antibiotic escalation trigger alone[52,53,98]. Antibiotic reductions in these RCTs are demonstrated in the context of severe sepsis, critically ill surgical patients, single centre and multicentre trials, and in non microbiologically proven severe sepsis[47-51,55]. Moreover concerns regarding increases in AMR have not been borne out. However, the potential for AMR selection through reduced dosing regimens remains possible. Further studies need a common minimum universal standards of antibiotic prescribing practice, that adopt pragmatic core principles, which are adapted to local circumstances.

## UNANSWERED QUESTIONS AND PROSPECTS FOR FUTURE WORK

Antibiotic usage and resistance represent an increasing global concern. The latest figures from the United Kingdom reveal that hospital-acquired infection costs GBP 1 billion annually[99], and USD 4.5 to 5.7 billions in the United States[100]. It is unsurprising that commentaries refer to "crisis" and "catastrophe" when describing possible worst case scenarios of uncontrolled AMR. The wording from the 2014 WHO global report of such a post-antibiotic era emphasises the need for action to prevent such a time. To tackle this increasing challenge, one might envisage a combined approach involving the development of next generation antibiotics (significant development times and costs), new innovations such as nanotechnology in infection control[101], together with strategies to optimise the effective use of currently available antimicrobials. Thus, ASPs involve a delicate interplay between economy, health and clinical evidence. To date the current high level evidence base for ASPs remains limited, with most of the reported studies being observational in nature. Those protocol based RCTs targeting de-escalation of antibiotics have demonstrated reduced usage, and on occasion reduced resistance patterns, length of stay but not manifested as survival benefit. Clinical decision support tools are of increasing interest in this regard.

Strategies to minimise antibiotic usage are multi-faceted. It remains uncertain whether the reported success in literature with regard to ASPs could be attributed to ASP alone, or confounders such as concurrent infection control policies. Should an ASP not by implication require an effective infection control policy? What would be the added value of the ASP? And what components should the ASP adopt? The role and impact of bed occupancy, staffing ratios and infection prevalence on antibiotic stewardship outcomes clearly require incorporation into study design. Further randomised controlled trials or indeed cluster studies, with staggered implementation of ASPs, where effective infection control policies are already in place may be required. Careful study design with appropriate components of the ASP, that could be implemented widely, would be desirable.

The dynamics of antibiotic resistance following the implementation of ASPs has been described as "balloon squeezing effect"[102]. It is believed that the development of antibiotic resistance towards one class of antibiotics, could lead to the emergence of resistance against another class, rendering multi drug resistance. The molecular mechanisms behind this concept remain unclear. However, the use of quinolones for *Pseudomonas aeruginosa* may be relevant. Quinolones selectively upregulate the bacterial membrane efflux system MexEF-OprN, and the loss of co-regulated porin OprD results in carbapenem resistance[103]. In a hypothetical situation where quinolones are routinely introduced empirically in favour of "targeted antibiotics" in a given ASP antibiotic regimen, resistance to both quinolones and carbapenems may develop.

Uncertainties around AMR in ICU being due to antibiotic selection pressure and distinguishing pathogenicity versus bystander effect of resistant organisms will remain a challenge for implementing fixed antibiotic protocols as part of ASPs. The lack of wholescale uptake of selective decontamination of the gut (SDD) or selective oral decontamination (SOD) to reduce rates of sepsis, is an example of this challenge[104,105]. Despite high level evidence for their efficacy, uptake is poor[106,107], with concerns regarding emergence of resistance being borne out in some settings[108].

Further evidence of practical difficulties in implementation of ASPs is the recent RCT of a PCT-based ASP. This was terminated prematurely due to poor clinician adherence to the algorithm[98]. Understanding the rationale behind clinician compliance and lack of it, specific to ASP antibiotic start and stop decisions will be important in designing future studies.

The culture positivity of microbiological isolates among ICU patients with suspected infections is generally low. EPIC II and SOAP studies reported culture positivity in only 51.4% and 60% of patients[2,3]. Furthermore, time required to identify the causative organism far exceed the clinical decision time. Until such time as rapid diagnostics can confidently rule out suspected infection within minutes, and the knowledge that delayed or inappropriate antimicrobials in sepsis equates with

higher mortality, even PCT-guided ASPs might not prevent clinician decision tree analysis based upon opinion. Thus, studies investigating its role in treatment escalation yielded relative limited information to this date. The prospect of novel rapid identification tools to enhance ASP programmes is another crucial facet of ASP[47]. The call here has been heeded, with the announcement of monetary prizes of up to $17 million, and $20 million from the NESTA foundation (a Uinted Kingdom organisation through the Longitude prize 2014), and the United States NIH/Biomedical Advanced Research Authority[7,109,110]. The US Administration also released its *National Strategy on Combating Antibiotic-Resistant Bacteria.* In addition, the President's Council of Advisors on Science and Technology (PCAST) is releasing a related report on *Combating Antibiotic Resistance.* The *National Strategy* provides a five-year plan for enhancing domestic and international capacity to prevent and contain outbreaks of antibiotic-resistant infections; maintain the efficacy of current and new antibiotics; and develop and deploy next-generation diagnostics, antibiotics, vaccines, and other therapeutics. The PCAST report provides recommendations from the President's Council and allied scientific and professional agencies,to act for the development of more effective ASPs[7].

The costs associated with ASP, have so far been limited to those of the prescribed antibiotics. Nonetheless, costs related to staff employment and education, as well as management and information technology, will require necessary health economic analysis.

It is said that, where ASP is today, is infection control programmes thirty years ago[111]. Thus the unanswered questions we encounter today might well hide the solution to the increasing burden of infection and AMR in ICUs and beyond. A multifaceted approach involving key stakeholders - healthcare, industry, technology, economy, security, government, charity and the public is warranted, to overcome AMR and perpetuate the future utility of antibiotics[112]. Refined and tailored Antibiotic stewardship programmes in (and outwith) ICU will be an important part of that partnership.

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