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Use of evidence-based recommendations in an antibiotic care bundle for the intensive care unit

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ABSTRACT

Purpose: To drive decisions on antibiotic therapy in the intensive care unit (ICU), we developed an antibiotic care bundle (ABC-Bundle) with evidence-based recommendations (EBRs) for antibiotic prescriptions.
Methods: We conducted a three-step prospective study. First, a systematic review was performed of the literature reporting EBRs for antibiotic usage in the ICU. Second, we developed an ABC-Bundle through a two-round, RAND-modified Delphi method with an international expert panel, including the most relevant EBRs on a 9-point Likert scale. Those EBRs that were considered mandatory by >50% of the experts were included in the bundle. Third, we assessed the adherence to and applicability of the bundle in two mixed university ICUs.
Results: Out of 1190 potentially relevant articles, 14 (four guidelines, four randomised controlled trials and six systematic reviews) fulfilled the eligibility criteria. Six EBRs were classified as relevant: 1. Provide rationale for antibiotic start; 2. Perform appropriate microbiological sampling; 3. Prescribe empirical antibiotic therapy according to guidelines (Day 1); 4. Review diagnosis; 5. Evaluate de-escalation based on microbiological results (Days 2–5); and 6. Consider discontinuation of treatment (Days 3–5). Daily adherence to the ABC-Bundle, prospectively assessed in 861 days of therapy in 142 ICU patients, ranged from 2% to 37%.
Conclusion: The ABC-Bundle is a novel tool to improve delivery of appropriate antibiotic therapy to ICU patients. The low adherence in the prospective cohorts confirms the significant role that the ABC-Bundle could play in an antibiotic stewardship programme in the ICU setting.

Introduction

Systematic reviews and meta-analyses have shown a significant association between previous antibiotic administration and isolation of methicillin-resistant *Staphylococcus aureus* [1], vancomycin-resistant enterococci [2,3] and multidrug-resistant Gram-negative bacteria [4]. Of even more concern is the inappropriate usage of antibiotics in intensive care units (ICUs); this was found to range from 14% to 79% in patients with severe infections [5], thereby negatively affecting outcomes of infections and increasing healthcare costs [6]. In a multicentre prospective cohort study, the rate of acquisition of antimicrobial-resistant strains in ICU patients per 1000 antibiotic-days was 14 for carbapenems, 9 for glycopeptides and 6 for broad-spectrum cephalosporins and quinolones [7]. However, despite strong evidence of the burden of inappropriate antibiotic usage in ICU patients, a gap exists between best evidence and daily clinical practice. The most common inappropriate usage in this setting includes discordance from local guidelines and the susceptibility pattern of the isolate, unsuitable duration of treatment and lack of treatment de-escalation [5,6].

Although clinicians have been using protocols for decades to guide their work, such as for the management of myocardial infarction,

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the concept of a care bundle was developed only a few years ago [8]. Some improvement in the quality of patient care has been achieved by focusing on the implementation of a group or bundle of evidence-based preventive practices to achieve a better outcome than when implemented individually. This approach has been applied successfully to the management of conditions such as sepsis [9] and the prevention of central venous catheter-related bloodstream infections [10], particularly in the critical care setting.

Little attempt has been made to create a bundle focused on prescribed antibiotics [11]. The main reason for this omission is the lack of evidence-based measures or quality indicators that can be easily applied to antibiotic prescription. Therefore, the main objectives of this study were to identify evidence-based recommendations (EBRs) of appropriate antibiotic usage in the ICU, to develop an easy-to-implement bundle for prescribing and to test the adherence and applicability of the bundle in routine antibiotic management in ICU patients.

Methods

This was a three-phase study with the following components: 1. Systematic review of the literature reporting recommendations for appropriate antibiotic usage in the ICU; 2. Development of an antibiotic care bundle (ABC-Bundle), including the most relevant recommendations through a two-round, RAND-modified Delphi method with an international expert panel; and 3. Measurement of the adherence to and applicability of the bundle in two mixed university ICUs.

Systematic review of the literature

A search for literature published between January 2000 and June 2012 with no language restriction was conducted using the MEDLINE and COCHRANE databases. The following combinations of medical subject headings (MeSH) and free text terms were utilised: (intensive care unit OR ICU) AND (antibiotic OR therapy) AND (infection OR stewardship) AND (fever OR pneumonia OR vap OR ventilator-associated pneumonia OR catheter-related infection OR sepsis OR septic shock). Abstracts of retrieved articles were screened to identify relevant studies. National and international guidelines, randomised controlled trials (RCTs) and systematic reviews and references of the included articles that recommended or tested any kind of intervention of appropriate antibiotic use in adult ICU patients, regardless of the type of infection, were eligible for inclusion. Quality of evidence and strength of guidelines according to the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system [12] and the Society of Critical Care Medicine's rating system for references and recommendations [13] were also reported. Three reviewers (GDA, GR and FDM) independently extracted the data from the literature to identify EBRs. A fourth reviewer (ET) was consulted in the event of disagreement among the three reviewers. Data from each article were then verified for consistency and accuracy and entered in a database.

Identification of EBRs and development of the ABC-bundle

The results from the systematic review were used to define a first set of relevant EBRs that were potentially appropriate for the ABC-Bundle. The selected EBRs were evaluated by an international expert panel using the Delphi method, a group-facilitation technique designed to transform individual opinions into group consensus with two or more rounds of data collection [14]. A panel of 11 opinion leaders in intensive care, infectious diseases, clinical microbiology, infection control/hospital hygiene and public health was formed after consultation with the European Society of Clinical Microbiology and Infectious Diseases and the European Society of Intensive Care Medicine. This panel participated in two rounds of review. First, each expert completed a questionnaire to score the relevance of each potential EBR to follow good quality of antibiotic therapy in the ICU in terms of (according to the relevance) the following clinical, ecological and economic variables: 1. Patients' health benefits; 2. Development of bacterial resistance; and 3. Healthcare costs. The rating was performed on a 9-point Likert scale from extremely irrelevant (1) to extremely relevant (9). Based on this scoring, an EBR was considered relevant if the median score was ≥8 and if ≥70% of respondents scored it in the top tertile (i.e., scores of 7, 8 or 9). Each expert then selected the three most important EBRs for assessing the quality of antibiotic therapy in the ICU. The EBRs that no one selected were excluded. Lastly, each expert categorised the remaining recommendations as mandatory, optional or unsuitable for inclusion in an ABC–Bundle for ICUs. The EBRs that more than half of the experts considered mandatory were then selected. This process was finalised in a second round, in which the expert panel had the opportunity to comment on the proposed EBRs, to add or modify potential EBRs and to approve the final bundle.

Measurement of adherence to the ABC-bundle elements

Adherence and clinical applicability of the ABC-Bundle were tested in a multicentre, prospective observational study conducted over a 6-month period in an 11-bed mixed ICU within a 700-bed Dutch university teaching hospital and an 18-bed mixed ICU within a 1500–bed Italian university teaching hospital. A trained research assistant joined the medical round on a daily basis, reviewed the charts of all patients admitted to the ICU, and collected the following data from admission sheets, medical and nursing records, medication charts and microbiological and radiological testing reports: age, sex, Simplified Acute Physiology Score (SAPS) II, reason for admission, comorbidities, length of ICU stay, antibiotic therapy and adherence to the ABC-Bundle recommendations. The ICU clinicians were blinded to the study objectives and were not aware of the bundle components, with the exception of the heads of the two departments. Adherence to the elements of the ABC-Bundle was expressed as a percentage of compliance. A dedicated form with local indications for microbiological sampling and empirical therapy as well as the definition of the bundle components was provided to the dedicated personnel. De-escalation was defined as a change in the initial antimicrobial therapy from an empirical broad-spectrum characteristic to a narrower–spectrum one (either by changing the antimicrobial agent, discontinuing an antimicrobial combination or both) according to culture results or for other clinical reasons.

Discontinuation of therapy was reported in case of consideration of therapy interruption in patients with negative microbiological results and clinical improvement. In cases of negative microbiological culture, the denominator was adjusted down. Reliability, potential opportunity for quality improvement and case-mix stability were used to assess applicability of the bundle EBRs. Reliability was considered acceptable if Cohen's kappa coefficient of agreement between two data reviewers of a sample of records was >0.4. EBRs with a performance score >85% were defined as having limited opportunity for improvement. Finally, case-mix stability was studied by analysing the distribution of outcome according to age (≥60 or <60 years old), sex and SAPS II score (≤40 points, 41 to 64 points, ≥65 points).

Results

Systematic review of the literature

The literature search identified 1190 potentially relevant papers. After excluding studies (single case reports, duplicates and articles

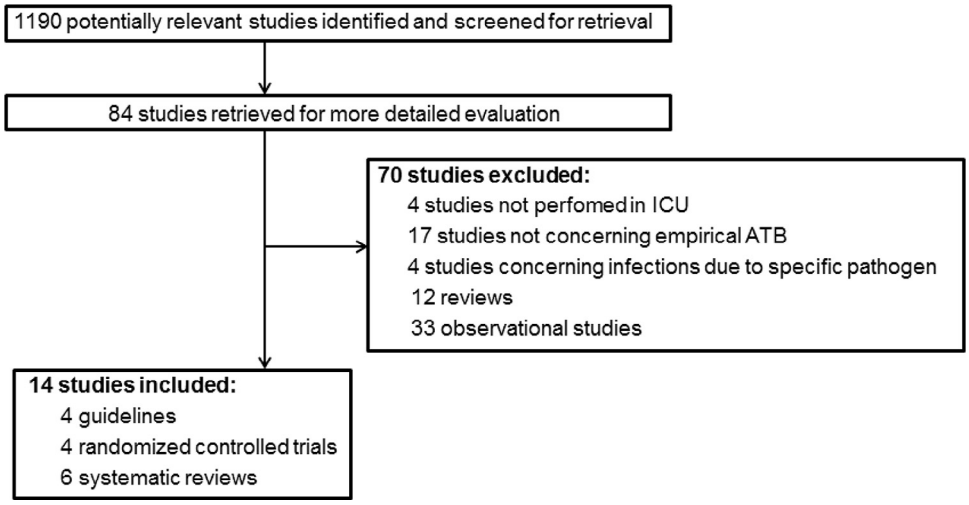

Fig. 1. Flow Chart of the review process. ICU, intensive care unit; ATB, antibiotic therapy.

that did not discuss antibiotic therapy in ICUs based on abstract review), 84 full-text papers were further evaluated. Of these papers, 70 articles were excluded according to the criteria shown in Fig. 1. Thus, 14 studies met the eligibility criteria: four guidelines [13,15–17], six systematic reviews [18–23] and four RCTs [24–27]. The guidelines focused on the management of fever [13], sepsis [17], ventilator–associated pneumonia [16] and antibiotic administration in patients with severe injuries [15]. The systematic reviews and RCTs analysed the efficacy of diagnostic tests, including procalcitonin (PCT) to improve empirical antibiotic therapy in ICU patients [18–27].

Development of EBRs and the ABC-bundle

Ten EBRs for proper antibiotic usage in ICU patients considered most important according to retrieved literature [13,15–17] were extracted (Table 1). Five EBRs dealt with therapy initiation, and five addressed the decision to continue or discontinue antibiotics. All EBRs were supported by only a low or very low level of evidence. During the first round of Delphi, the expert panel eliminated three EBRs because of insufficient relevance, failure to appear among the top three recommendations for good antibiotic prescription in ICUs, or strict applicability only to documented severe sepsis or septic shock. The seven remaining EBRs were used to derive an ABC-Bundle for the first 5 days of antibiotic therapy. In the second round, the expert panel reviewed the bundle again and chose six EBRs for the final bundle. The final ABC-Bundle was approved by all the experts.

The ABC-Bundle lasts for 5 days and contains six EBRs: 1. Provides rationale for starting antibiotics in patient charts; 2. Appropriate microbiological sampling is performed according to local or international guidelines; 3. Empirical antibiotic therapy is prescribed according to local or international guidelines; 4. Diagnosis is reviewed based on the microbiological results; 5. De-escalation is evaluated based on the microbiological results; and 6. Discontinuation of treatment is considered according to local or international guidelines and the clinical picture. EBRs 1, 2 and 3 were selected for performance on the first day. EBR4 and EBR5 should be performed daily from Day 2 to Day 5, and EBR6 should be performed daily from Day 3 to Day 5 (Table 2).

Measurement of adherence to and applicability of the ABC-bundle in clinical practice

The adherence to the ABC-Bundle was measured in a 6-month prospective observational cohort study including 142 patients with 861 days of antibiotic therapy. Table 3 describes patient characteristics. Adherence to the single indicators ranged from 2.4% to 100%, whereas adherence to the overall bundle was 8.5%. The lowest compliance was observed for the consideration of early discontinuation of therapy on Days 3 through 5 (range, 2.4–8). The highest compliance was observed for the review of diagnosis based on the microbiological results on Days 2 through 5 (range, 75.3–100) (see Table 4). A sample of 25 antibiotic courses was used to test interobserver agreement between reviewers (reliability). All EBRs

Table 1
Extracted Evidence-Based Recommendations (EBRs).

		Relevance (Likert score), mean (±SD), [range min–max]
EBR1	Provide rationale for starting antibiotics in patient charts	8 (±1), [6–9]
EBR2	Perform appropriate microbiological sampling according to local or international guidelines	8.5 (±0.6), [7–9]
EBR3	Prescribe empirical antibiotic therapy according to local or international guidelines	7.9 (±1.1), [5–9]
EBR4	Review diagnosis based on microbiological results	7.6 (±1.7), [3–9]
EBR5	Evaluate de-escalation based on microbiological results	7.8 (±2.1), [2–9]
EBR6	Consider discontinuation of treatment according to local or international guidelines and to the clinical picture	7.7 (±1), [6–9]
EBR7	Empirical antibiotic treatment should be guided by serum procalcitonin level	6.4 (±1.8), [3–9]
EBR8	Antibiotics should be started within 4 h	7.6 (±2.6), [1–9]
EBR9	Interruption of antibiotic treatment should be guided by serum procalcitonin level	4.8 (±2.4), [1–8]
EBR10	Dosage should be evaluated daily based on renal function	7.3 (±1.9), [3–9]

SD, standard deviation.

Table 2
The Antibiotic Care Bundle (ABC-Bundle).

Evidence-Based Recommendations (EBRs)		Days of therapy				
		1	2	3	4	5
EBR1	Provide rationale for starting antibiotics in patient charts	x				
EBR2	Perform appropriate microbiological sampling according to local or international guidelines	x				
EBR3	Prescribe empirical antibiotic therapy according to local or international guidelines	x				
EBR4	Review diagnosis based on microbiological results		x	x	x	x
EBR5	Evaluate de-escalation based on microbiological results		x	x	x	x
EBR6	Consider discontinuation of treatment according to local or international guidelines and to the clinical picture			x	x	x

Table 3
Characteristics of the 142 patients involved in the blind observational study on adherence to the bundle components in two ICUs.

	ICU-1	ICU-2	Significance
Patients, n	108	34	n.a.
Antibiotic courses	236	67	$P = 0.667$
Total antibiotic days, n	683	238	$P = 0.377$
Age in years, mean (95%CI)	62.2 (58.91–65.49)	62.9 (67.14–68.66)	n.a.
Male/Female Ratio	1.67/1	1.5/1	$P = 0.953$
SAPS II, mean (95%CI)	49 (44.7–53.3)	47.7 (39.6–55.2)	n.a.
Length of antibiotic therapy in days, mean (95%CI)	9 (7.5–10.5)	7 (5.0–9.2)	$P = 0.544$

ICU, intensive care unit; ICU-1, Italian ICU; ICU-2, Dutch ICU; SD, standard deviation; CI, confidence interval; SAPS, Simplified Acute Physiology Score; n.a., not applicable.

received a k-score ≥0.4. Two EBRs (EBR1 and EBR4) showed moderate reliability. The remaining indicators had good or very good performance. Three EBRs (EBR2, 3 and 4) showed high mean performance rates, but none were consistently >85%, thus revealing a limited opportunity for improvement. Case-mix analysis showed a stable distribution of all indicators over the three predefined variables (age, sex and SAPS II score).

Discussion

Increasing antimicrobial resistance and a high rate of inappropriate antibiotic prescription have significantly threatened outcomes for ICU patients. Marquet et al. recently performed a systematic review and meta-analysis on inappropriate antibiotic therapy in critically ill patients with bloodstream infections [5]. The rate of inappropriate prescription ranged from 14% to 79% of the patients, with almost half of the included studies reporting an incidence of 50% or more. Studies measuring 28-day or 60-day mortality reported significantly higher mortality rates (more than 30%) in patients not receiving appropriate antibiotics [5].

Past mitigation efforts have not bundled measures describing appropriate antibiotic usage. Our study defined, for the first time, an evidence-based bundle (ABC-Bundle) with EBRs for antibiotic prescription in ICU patients. Using the Delphi method, an expert panel selected the six most relevant EBRs to be considered in the first 5 days of antibiotic therapy in the ICU. On the first day of antibiotic use, the rationale for starting antibiotics should be documented, and microbiological sampling and empirical antibiotic therapy should be prescribed in accordance with the applicable guideline. From Day 2 to Day 5, the diagnosis should be reviewed and de-escalation evaluated daily based on the microbiological results. From Day 3 to Day 5, discontinuation of therapy should be considered daily.

The measurement of current adherence to the selected EBRs in the ABC-Bundle showed that the overall bundle application was applied only in less than 10% of the cases. Thus, there is a need to improve compliance with EBRs in clinical practice. The components of the ABC–bundle are measures generally accepted by clinicians as elements of care that should be delivered as usual practice, although our systematic review and assessment of the guidelines using the GRADE system showed that these recommendations were based on a low/very low level of evidence. In public health policy, there are often strong recommendations based on low levels of evidence (i.e. hand hygiene to reduce the spread of carbapenemase-producing *Acinetobacter baumannii*) [28]. According to the GRADE approach, prevention of outcomes with high patient-importance (in our case, inappropriate antibiotic therapy and selection of resistant strains) may lead to strong recommendations. In these situations, despite very low–quality evidence of the benefits, experts can consider that the burden (clinical, ecological and economical) is strongly in favour of the recommendation. In 2014, a systematic review showed that more than 50% of strong recommendations in World Health Organisation (WHO) guidelines were based on low evidence [29].

Documentation in the patient charts of the rationale for starting antibiotics has been associated with improved antibiotic prescribing [30]. In a French 10-bed mixed ICU, an intervention

Table 4
Evidence-Based Recommendations (EBRs) adherence rate per day in the 2 ICUs (%).

	Day 1		Day 2		Day 3		Day 4		Day 5	
	ICU-1	ICU-2	ICU-1	ICU-2	ICU-1	ICU-2	ICU-1	ICU-2	ICU-1	ICU-2
EBR1	7	82								
EBR2	83	75								
EBR3	60	85								
EBR4			75	88	91	100	80	96	80	96
EBR5			12	29	8	20	13	18	12	9
EBR6					2	4	4	4	4	8
Total	7	37	7	19	1	2	2	2	2	8

ICU, intensive care unit; ICU-1, Italian ICU; ICU-2, Dutch ICU.

including weekly audit and feedback resulted in improved documentation of antibiotic prescription reassessment, but it did not improve the quality of discontinuation, streamlining and de-escalation of antibiotic prescriptions [31]. The recent guidelines on antimicrobial stewardship developed by the UK National Institute for Health and Care Excellence clearly advise documentation of the clinical diagnosis (including symptoms) in the patient's record and clinical management plan when prescribing any antimicrobial therapy [32].

Evaluating actual inappropriate antibiotic therapy was not a goal of our study and can only be evaluated in a prospective, multicentre study with an adequate sample size.

The UK guideline also underlines the importance of appropriate microbiological sample collection before prescribing and review of the prescription when the results are available.

The expert panel selected guideline-driven empirical antibiotic prescription as a first-day component of the ABC-Bundle. According to the guidelines of the Infectious Diseases Society of America, empirical antibiotic therapy should follow local antibiotic guidelines and, if not available, national or international guidelines [13]. Implementation of computerised region-adapted guidelines for antibiotic therapy has been associated with reduction of both antibiotic exposure and ICU mortality [33]. In the emergency department of a 439-bed teaching hospital in the US, education of prescribers about local antimicrobial resistance rates for urinary tract infections significantly increased consistency of therapy choice with recommendations from 44.8% to 83% ($P < 0.001$) [34]. In Canada, internal guideline pocket cards were included in an educational programme, and after implementation of treatment recommendations based on local resistance, empirical antibiotic selection improved [35].

Empirical broad-spectrum antimicrobial therapy should be de-escalated to mitigate the risk of emergence of resistance [36]. Early evaluation of de-escalation (Day 2) and discontinuation (Day 3) of therapy is an essential component of the ABC-Bundle. However, the debate continues on the interval within which de-escalation should be performed, on whether the shortening of antibiotic therapy duration should be included in a de-escalation definition and on the timing of de-escalation [37]. In our study, compliance with evaluation of therapy discontinuation (in cases of negative cultures and clinical patient improvement) or de–escalation (following positive culture results) was very low. Low compliance was due to the lack of consideration of de-escalation and not due to failure to document those considerations.

Biomarkers that can identify patients who require antibiotic therapy, distinguish between responders and non-responders, and help to optimise antibiotic treatment decisions among critically ill patients on a reliable and timely basis are needed [38]. The expert panel extensively discussed the inclusion of the PCT assay before starting antibiotic therapy in the ABC-Bundle. Although PCT concentration reflects both the systemic response to bacterial infection and its severity, its accuracy in distinguishing ICU patients with and without infection remains low, mainly because of a lack of specificity and the time lapse between infection onset and the PCT elevation [39]. Hence, the panel agreed not to use PCT as a marker to start or withhold antibiotic therapy for ICU patients. However, if new evidence emerges that supports the introduction of the PCT assay, the ABC-Bundle could easily be adapted.

We tested the bundle in two countries (the Netherlands and Italy) with differences in overall workload, case-mix of patients, healthcare systems and accounting, local epidemiology and indications and prescription habits; however, both ICUs showed a very similar low compliance with the bundle components. The similar results in the two settings might also translate to other healthcare systems. Nevertheless, the applicability of EBRs should always be tested in practice first, because data recorded are different in every country, thus affecting the feasibility, validity and reliability of data collection [40].

Our study has limitations. There are no guidelines for determining consensus, sample size and sampling techniques for the Delphi approach, and some concerns have been raised about the reliability of the technique. However, the lack of drop-outs of our respondents as well the selection of experts through two different societies and backgrounds should have reduced the risk of bias. The analysis of EBRs was restricted to guidelines and RCTs that, although considered the sources for the best evidence, could have missed some data from cohort studies that could play a role in antibiotic prescription primarily in community settings. The testing of adherence and feasibility was only performed in two ICUs. However, the two settings were selected in two countries with different epidemiology of antibiotic resistance and health systems to increase the generalisability and transferability of our results. At the time of the study, both hospitals had local antibiotic therapy indications and formularies but not an antimicrobial stewardship programme. The goal of the study was to provide antimicrobial stewardship with a further tool to increase effectiveness and results. The ABC–bundle was not developed to work without guidelines for empirical antibiotic therapy or appropriate microbiological stewardship. A prospective RCT is needed to define the cost–effectiveness of the bundle.

The ABC-Bundle is a novel tool to improve the delivery of appropriate antibiotic therapy to patients in the ICU that could be included in an antimicrobial stewardship programme. The global threat imposed by antimicrobial-resistant microorganisms to the efficacy of current and future therapies has made the appropriate antibiotic prescribing in severely ill patients an imperative. The implementation of the ABC-Bundle will improve empirical therapy.

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References

[1] Tacconelli E, De Angelis G, Cataldo MA, Pozzi E, Cauda R. Does antibiotic exposure increase the risk of methicillin-resistant Staphylococcus aureus (MRSA) isolation? A systematic review and meta-analysis. J Antimicrob Chemother 2008;61:26–38.

[2] Carmeli Y, Samore MH, Huskins C. The association between antecedent vancomycin treatment and hospital-acquired vancomycin-resistant enterococci: a meta-analysis. Arch Intern Med 1999;159:2461–8.

[3] de Bruin MA, Riley LW. Does vancomycin prescribing intervention affect vancomycin-resistant enterococcus infection and colonization in hospitals? A systematic review. BMC Infect Dis 2007;7:24.

[4] MacAdam H, Zaoutis TE, Gasink LB, Bilker WB, Lautenbach E. Investigating the association between antibiotic use and antibiotic resistance: impact of different methods of categorising prior antibiotic use. Int J Antimicrob Agents 2006;28:325–32.

[5] Marquet K, Liesenborgs A, Bergs J, Vleugels A, Claes N. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. Crit Care 2015;19:63.
[6] Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother 2010;54:4851–63.
[7] Tacconelli E, De Angelis G, Cataldo MA, Mantengoli E, Spanu T, Pan A, et al. Antibiotic usage and risk of colonization and infection with antibiotic-resistant bacteria: a hospital population-based study. Antimicrob Agents Chemother 2009;53:4264–9.
[8] Cooke FJ, Holmes AH. The missing care bundle: antibiotic prescribing in hospitals. Int J Antimicrob Agents 2007;30:25–9.
[9] Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, Holanda MS, Ortiz F, Llorca J, et al. Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. Crit Care Med 2010;38:1036–43.
[10] Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006;355:2725–32.
[11] Pulcini C, Defres S, Aggarwal I, Nathwani D, Davey P. Design of a 'day 3 bundle' to improve the reassessment of inpatient empirical antibiotic prescriptions. J Antimicrob Chemother 2008;61:1384–8.
[12] Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
[13] O'Grady NP, Barie PS, Bartlett JG, Bleck T, Carroll K, Kalil AC, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med 2008;36:1330–49.
[14] Dalkey N, Helmer O. An experimental application of the Delphi Method to the use of experts. Manage Sci 1963;9:458–67.
[15] West MA, Moore EE, Shapiro MB, Nathens AB, Cuschieri J, Johnson JL, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core—standard operating procedures for clinical care VII—Guidelines for antibiotic administration in severely injured patients. J Trauma 2008;65:1511–19.
[16] Minei JP, Nathens AB, West M, Harbrecht BG, Moore EE, Shapiro MB, et al. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core–standard operating procedures for clinical care. II. Guidelines for prevention, diagnosis and treatment of ventilator-associated pneumonia (VAP) in the trauma patient. J Trauma 2006;60:1106–13, discussion 1113.
[17] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296–327.
[18] Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 2004;39:206–17.
[19] Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med 2006;34:1996–2003.
[20] Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med 2011;171:1322–31.
[21] Kopterides P, Siempos II, Tsangaris I, Tsantes A, Armaganidis A. Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. Crit Care Med 2010;38:2229–41.
[22] Heyland DK, Johnson AP, Reynolds SC, Muscedere J. Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. Crit Care Med 2011;39:1792–9.
[23] Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis 2007;7:210–17.
[24] Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med 2011;39:2048–58.
[25] Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J Respir Crit Care Med 2008;177:498–505.
[26] Hochreiter M, Kohler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. Crit Care 2009;13:R83.
[27] Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463–74.
[28] Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect 2014;20(Suppl. 1):1–55.
[29] Alexander PE, Bero L, Montori VM, Brito JP, Stoltzfus R, Djulbegovic B, et al. World Health Organization recommendations are often strong based on low confidence in effect estimates. J Clin Epidemiol 2014;67:629–34.
[30] Schuts EC, Hulscher ME, Mouton JW, Verduin CM, Stuart JW, Overdiek HW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:847–56.
[31] Pulcini C, Dellamonica J, Bernardin G, Molinari N, Sotto A. Impact of an intervention designed to improve the documentation of the reassessment of antibiotic therapies in an intensive care unit. Med Mal Infect 2011;41:546–52.
[32] National-Institute-for-Health-and-Care-Excellence. Antimicrobial stewardship. In: NICE, editor. NICE Quality Standard. 2016. p. 1–39.
[33] Nachtigall I, Tafelski S, Deja M, Halle E, Grebe MC, Tamarkin A, et al. Long-term effect of computer-assisted decision support for antibiotic treatment in critically ill patients: a prospective 'before/after' cohort study. BMJ Open 2014;4:e005370.
[34] Percival KM, Valenti KM, Schmittling SE, Strader BD, Lopez RR, Bergman SJ. Impact of an antimicrobial stewardship intervention on urinary tract infection treatment in the ED. Am J Emerg Med 2015;33:1129–33.
[35] Popovski Z, Mercuri M, Main C, Sne N, Walsh K, Sung M, et al. Multifaceted intervention to optimize antibiotic use for intra-abdominal infections. J Antimicrob Chemother 2015;70:1226–9.
[36] Garnacho-Montero J, Escoresca-Ortega A, Fernandez-Delgado E. Antibiotic de-escalation in the ICU: how is it best done? Curr Opin Infect Dis 2015;28:193–8.
[37] Weiss E, Zahar JR, Lesprit P, Ruppe E, Leone M, Chastre J, et al. Elaboration of a consensual definition of de-escalation allowing a ranking of beta-lactams. Clin Microbiol Infect 2015;21:e1–10.
[38] Albrich WC, Harbarth S. Pros and cons of using biomarkers versus clinical decisions in start and stop decisions for antibiotics in the critical care setting. Intensive Care Med 2015;41:1739–51.
[39] Brechot N, Hekimian G, Chastre J, Luyt CE. Procalcitonin to guide antibiotic therapy in the ICU. Int J Antimicrob Agents 2015;46(Suppl. 1):S19–24.
[40] van den Bosch CM, Geerlings SE, Natsch S, Prins JM, Hulscher ME. Quality indicators to measure appropriate antibiotic use in hospitalized adults. Clin Infect Dis 2015;60:281–91.