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Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP)

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Abstract

Background: Antimicrobial de-escalation (ADE) is a strategy of antimicrobial stewardship, aiming at preventing the emergence of antimicrobial resistance (AMR) by decreasing the exposure to broad-spectrum antimicrobials. There is no high-quality research on ADE and its effects on AMR. Its definition varies and there is little evidence-based guidance for clinicians to use ADE in the intensive care unit (ICU).

Methods: A task force of 16 international experts was formed in November 2016 to provide with guidelines for clinical practice to develop questions targeted at defining ADE, its effects on the ICU population and to provide clinical guidance. Groups of 2 experts were assigned 1–2 questions each within their field of expertise to provide draft statements and rationale. A Delphi method, with 3 rounds and an agreement threshold of 70% was required to reach consensus.

Results: We present a comprehensive document with 13 statements, reviewing the evidence on the definition of ADE, its effects in the ICU population and providing guidance for clinicians in subsets of clinical scenarios where ADE may be considered.

Conclusion: ADE remains a topic of controversy due to the complexity of clinical scenarios where it may be applied and the absence of evidence to the effects it may have on antimicrobial resistance.

Keywords: Antimicrobial de-escalation, De-escalation, Antimicrobial resistance, Stewardship

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Introduction

International guidelines recommend the empirical use of broad-spectrum antimicrobial therapy (AMT) to minimize the risk for initial inadequate antimicrobial treatment and associated mortality risk in patients with severe infections [1].

This recommendation is based on the association between timely and adequate antimicrobial therapy with lower mortality [2]. However, the use of broad-spectrum antimicrobial treatments is one of the major drivers for the emergence of bacterial resistance [3, 4].

Antimicrobial de-escalation (ADE) consists in modifications of the empirical AMT that was developed as a strategy to prevent the emergence of antimicrobial resistance (AMR) by decreasing the overall exposure to those agents [5–7].

ADE is recognized as an important aspect of antimicrobial stewardship programs (ASPs) [8, 9]. It is often considered as the 'default" practice whenever broad-spectrum antibiotics are empirically prescribed. While broadly recommended it does not have a clear definition and there is little guidance to what is evidence-based best practice for ADE in the intensive care unit (ICU) (Fig. 1).

Justification of the project

Through systematic review of the literature, this group concluded that there is no high-quality research on ADE in the ICU and its definitions vary [10]. Available literature includes observational studies and one small RCT (Tables 1 and 2). Observational studies reported association of ADE with better clinical outcomes. In the studies that reported severity of illness, ADE was performed in patients with lower or improving severity scores when compared with patients that did not receive ADE. This is indicative of selection bias, and it is likely that ADE was performed in patients a lower risk of an adverse outcome. Systematic review of that literature concluded that ADE is likely to be a safe strategy, but that there is too much bias in the available studies to consider the results to be robust evidence [10]. Further, the ecological outcomes and whether ADE reduces the emergence of AMR remains to be studied.

Existing gaps in the literature have prevented the development of evidence-based guidelines for clinical decision-making. Guidance for clinicians on how and when to carry out ADE in critically ill patients is required.

The Infection Section of the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Critically Ill Patients (ESGCIP) led this project with the aims of answering practical questions for physicians dealing with ADE in critically ill adult patients and developing a guidance document carried out by expert opinion leaders.

Methodology

Expert panel

The coordinators of this project (J.G.M., M.B.) named by the Infection Section of the ESICM and the ESGCIP designed the methodology and the different topics to be included. A group of experts were invited to participate based on their expertise in the field of diagnosis and treatment of infections in critically ill patients. They were selected among the authors of a recently published systematic review on the topic of ADE in the ICU and within the members of the ESICM Infection section and ESCMID ESGCIP.

Methodological choices

There was no funding available to allocate to the project. The expert panel collectively believed that ADE is an area of controversy where little to no evidence was available and that producing a practical document was important. It was decided to pursue the project, acknowledging that the unavailability of dedicated staff to conduct extensive search, review and grading would lead to weaken the methodology of the project.

The expert panel decided to build on the work that had just been completed [10], and to update and reuse the documents that were available from that work. The literature search was continuously updated. Evidence and PICO tables were updated with any new scientific publication as it became available.

Grading from the 14 previously reviewed documents was made available, and further documents were grading according to the level of confidence of the expert panel. Recommendations Assessment, Development, and Evaluation (GRADE) system methodology was not followed [11].

The above-mentioned systematic review highlighted the bias in the literature, consisting in cohort studies that collectively demonstrated an improvement in patients' mortality with ADE compared to no-ADE. This is further described in question 2. It was prospectively decided to not use pooled estimates of outcomes which would have risked picturing a positive but biased plot of the outcomes after ADE in ICU patients.

The panel recognizes these choices as an important limitation to the methodology of the document. The panel followed the initial aims to provide a practical document rather that an absolute review of the evidence.

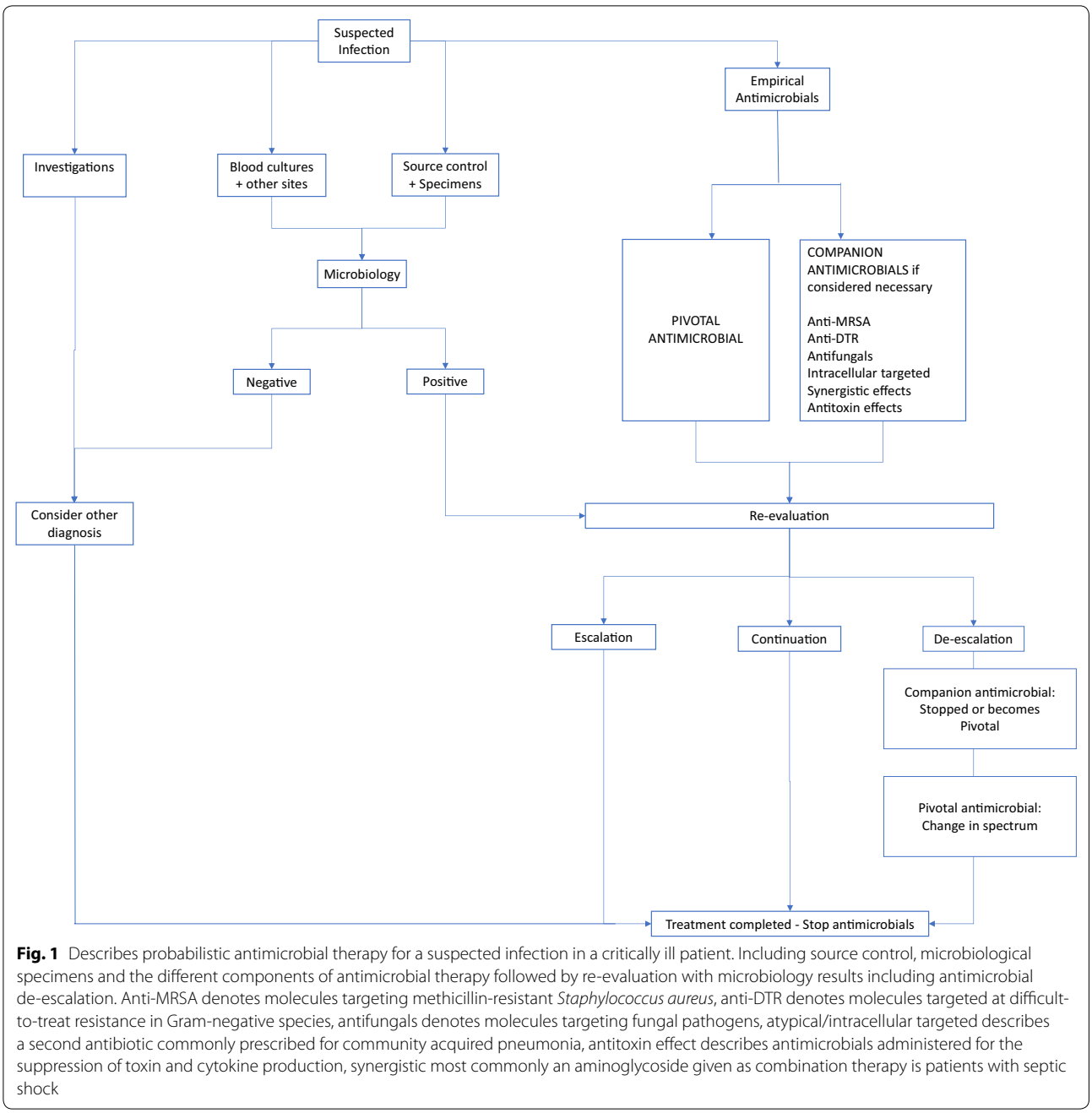

Fig. 1 Describes probabilistic antimicrobial therapy for a suspected infection in a critically ill patient. Including source control, microbiological specimens and the different components of antimicrobial therapy followed by re-evaluation with microbiology results including antimicrobial de-escalation. Anti-MRSA denotes molecules targeting methicillin-resistant *Staphylococcus aureus*, anti-DTR denotes molecules targeted at difficult-to-treat resistance in Gram-negative species, antifungals denotes molecules targeting fungal pathogens, atypical/intracellular targeted describes a second antibiotic commonly prescribed for community acquired pneumonia, antitoxin effect describes antimicrobials administered for the suppression of toxin and cytokine production, synergistic most commonly an aminoglycoside given as combination therapy is patients with septic shock

Design of the questions

The coordinators of the project drafted a list of questions to be addressed in this project which was then circulated via email to the expert panel and updated until a consensus was reached. Questions were finally refined via a 3-round Delphi.

Questions were targeted to define ADE and its effects on the adult ICU population followed by guidance for clinicians for specific situations.

The aim of the questions was to provide practical statements to questions important in clinical practice. The population, intervention, comparison, and outcomes (PICO) format was used for questions relating to intervention and guidance.

Search strategy

A search of MEDLINE (1966–2018), EMBASE (all years) and the Cochrane library was conducted to identify suitable publications using the following search terms

Table 1 Summary of recommendations on antimicrobial de-escalation in critically ill patients from the ESICM and ESCMID task force

	Recommendations
Definitions	**Q1: What is the definition of antimicrobial de-escalation for critically ill patients receiving empirical antimicrobials for an infection?**
	1. Replacing broad-spectrum antimicrobials with agents of a narrower spectrum or a lower ecological impact. or
	2. Stopping components of an antimicrobial combination. Two different situations can be included in this case
	2.a. Stopping of an antimicrobial agent administered in combination therapy to provide double cover for certain pathogens
	2.b. Stopping of an antimicrobial agent administered in the empirical regimen to cover pathogens that are not finally isolated in the clinical cultures
	3. The early discontinuation of all antimicrobial therapy if infection is ruled out is not considered as de-escalation. (Definition, low quality of evidence.)
	Q2: Does the panel recommend a numerical score to measure the ecological impact of the empirical antimicrobial regimen and can this score be used to guide antimicrobial de-escalation?
	We recommend research is undertaken to develop multidimensional scores to measure the local ecological impact of empirical antimicrobial regimens and guide ADE. (Moderate recommendation; low quality of evidence.)
Effects of ADE	**Q3: In critically ill patients receiving antimicrobials for an infection, what are the effects of antimicrobial de-escalation compared to no de-escalation on mortality and length of stay?**
	The ADE strategy is likely safe with regard to patients' outcomes. (Statement of fact; moderate quality of evidence.)
	Q4: In critically ill patients receiving antimicrobials for an infection, what are the effects of antimicrobial de-escalation compared to no de-escalation on the total duration of antimicrobial therapy?
	ADE is associated with a risk of increase in total duration of antimicrobial therapy. We recommend that ADE and duration of antimicrobial therapy are assessed separately but as part of the global stewardship strategy. (Statement of fact; low quality of evidence.)
	Q5: In critically ill patients receiving antimicrobials for an infection, what are the effects of antimicrobial de-escalation compared to no de-escalation on the development of resistance to antimicrobials?
	No recommendation can be made
Practice recommendations	**Q6: In critically ill patients receiving antimicrobials for an infection, when is it recommended to perform de-escalation of the empirical antimicrobial regimen?**
	We recommend ADE is performed within 24 h of definitive culture results and antibiograms availability. (Strong recommendation; low quality of evidence.)
	Q7: In critically ill patients receiving antimicrobials for an infection, are recommendations for or against antimicrobial de-escalation different for certain bacterial pathogens? For which?
	Recommendations for or against ADE are similar for all bacterial pathogens except for difficult-to-treat pathogens in patients with a high risk of death. (Moderate recommendation, low quality of evidence.)
	Q8: In critically ill patients receiving antifungal agents for invasive candidiasis, does the panel recommend antifungal de-escalation compared to no de-escalation?
	We recommend ADE of antifungal agents after clinical and microbiological resolution of invasive candidiasis when the pathogens are susceptible to azole antifungal agents. (Strong recommendation; low-quality evidence.)
	Q9: In critically ill patients receiving antimicrobials for a culture-negative infection, does the panel recommend antimicrobial de-escalation compared to no de-escalation?
	We recommend that consideration is given to alternate non-infectious diagnosis and stopping all or part of the antibiotic regimen in critically ill patients with culture-negative infections. (Moderate recommendation; low-quality evidence.)
	Q10: In neutropenic critically ill patients, does the panel recommend antimicrobial de-escalation compared to no de-escalation?
	We suggest ADE can be applied in neutropenic critically ill patients. (Moderate recommendation, low quality of evidence.)
	Q11: Are recommendations for or against antimicrobial de-escalation different depending on the source of infection?
	We suggest that ADE can be applied in all sources of infection. (Weak recommendation; low quality of evidence.)
	Q12: In critically ill patients receiving antimicrobials, does the panel recommend the use of biomarkers when considering antimicrobial de-escalation?
	No recommendation can be made
	Q13: In critically ill patients who are de-escalated, does the use of therapeutic drug monitoring (TDM) versus no TDM improve outcome?
	No recommendation can be made

A team of 16 experts drafted the 13 recommendations, based on the available evidence and their expertise. A 3-round Delphi method was used to establish the final recommendations presented here

("antibiotics" OR "antimicrobials" OR "antibacterials") AND ("de-escalation" OR "de-escalate" OR "narrowing" OR "step-down" OR "stepdown" OR "streamline") AND ("icu" OR "intensive care" OR "critical care" OR "septic shock" OR "severe sepsis" OR "sepsis"). The resulting outputs were combined excluding duplicate results. Search results were restricted to fully published studies in the English language. Abstracts were scanned for suitability and the full text retrieved for all potentially relevant studies. Reference lists were reviewed to identify additional relevant studies. Results were cross-checked and identical to the previously conducted systematic review and associated MEDLINE alert [10].

Record of count of retrieved records was not kept and is not available.

A MEDLINE alert was created to remain informed of any new studies being published with the same search string until the date of the last draft of this document.

Critical review, consensus methodology

In view of the lack of high-level evidence, panel members were asked to provide narrative answers based on their knowledge and experience in the field.

Three types of statements were used: a definition, statements of facts when evaluating the effects of ADE and recommendations to guide practice. The later were classified as strong, moderate or weak according to the panel's consensus and level of confidence.

The writing committee (A.T., J.G.M., M.B.) wrote the first draft which was sent to the rest of the group for their critical review. Finally, provided answers were reviewed and discussed by the panel.

In view of the multiple controversies, a Delphi approach was used to reach consensus on the 13 questions within the guideline. Questions and statements were prepared by the writing committee according to discussions on the drafts of the document. An online tool was prepared to anonymously vote for the questions and statements and was distributed via an e-mail link. Experts responses on each of the items were anonymously collected by the online tool. Results were analysed and summarized in a report after each round. A pre-specified rate of over 70% similar answers was required to reach agreement. A report describing aggregated group responses was sent to participants after each round.

Where agreement was not reached, another Delphi round was prepared for those questions and statements, for a maximum of 3 rounds. If agreement was not reached following 3 rounds or if it was agreed that the evidence was insufficient to make a recommendation, we pre-specified that the statement would be "no recommendation can be made".

Details and a summary of the Delphi are available in the electronic supplement.

Question 1: what is the definition of antimicrobial de-escalation for critically ill patients receiving empirical antimicrobials for an infection?

Definition

1. Replacing broad-spectrum antimicrobials with agents of a narrower spectrum or a lower ecological impact, or:
2. Stopping components of an antimicrobial combination. Two different situations can be included in this case.
   - 2a. Stopping of an antimicrobial agent administered in combination therapy to provide double cover for certain pathogens.
   - 2b. Stopping of an antimicrobial agent administered in the empirical regimen to cover pathogens that are not finally isolated in the clinical cultures.
3. The early discontinuation of all antimicrobial therapy if infection is ruled out is not considered as de-escalation.

Strength

Definition; low quality of evidence.

Rationale

Early adequate antimicrobial therapy is associated with lower mortality in patients with septic shock [12]. The surviving sepsis guidelines make a strong recommendation for the very early administration of broad-spectrum antibiotics to patients with sepsis or septic shock [1]. As there is initial uncertainty as to which pathogen will be causing the infection, the use of broad-spectrum therapy increases the chances that the causative pathogen will be susceptible to the treatment.

In cases of severe infection where very broad spectrum is indicated, initial antimicrobial therapy may combine several agents, including a pivotal antibiotic and one or several companion antibiotics for the following reasons [13]:

- Broadening the spectrum of antimicrobial therapy by administering different agents with different spectrum of activity. This will increase the chances that any potential pathogen will be susceptible to at least one of the administered agents.
- Improve the killing characteristics of the treatment by using agents with a synergistic effect.
- Prevent or delay the emergence of resistance.

Table 2 Summary of the included studies

Author	Year	Population no. of pt studied	ADE rates	ADE in negative cultures	ADE details	ADE to occur on or before specified day of therapy
Randomized controlled trials						
Leone	2014	ICU patients with severe sepsis *N* = 116	n/a	n/a	Smaller spectrum, ranking: carbapenem > piperacillin–tazobactam or ceftazidime or cefepime or ertapenem > ticarcillin > 3rd generation cephalosporin > aminopenicillin + clavulanate > aminopenicillin or methicillin	When antibiogram available for pivotal beta-lactam. The companion drug (aminoglycoside or fluoroquinolone or macrolide) to be stopped at day 3
Other, non-randomized studies						
Alvarez-Lerma	2006	ICU patients with HAP treated with imipenem	25.3%[a] 51.9% in susceptible strains	Yes	Smaller spectrum or fewer drugs If pseudomonas is isolated imipenem changed to piperacillin + tazobactam or anti-pseudomonal cephalosporin. If no pseudomonas isolated change to a non-anti-pseudomonal beta-lactam. Aminoglycosides and glycopeptides to be withheld if possible	Between 3rd and 5th days
Giantsou	2007	ICU patients with VAP *N* = 113	40.5%	Not specified	Smaller spectrum (using ranks) or fewer drugs Stopping oxazolidinone in absence of MRSA and aminoglycoside/quinolones in absence of pseudomonas Ranking according to activity spectrum against Gram-negative bacteria: 4-carbapenems, 3-extended spectrum penicillins, 2-quinolone/aminoglycosides, 1-beta-lactams	At day 3 or when the patient's clinical response and microbiological information permitted
Eachempati	2009	Surgical ICU patients with VAP *N* = 138	55%[a]	No	Smaller spectrum	Between 2nd and 3rd days
De Waele	2010	Surgical ICU patients receiving meropenem *N* = 113	41.8%	Yes	Smaller spectrum	Before 3rd day
Morel	2010	All ICU patients *N* = 116	45%	Yes	Smaller spectrum (using ranks) or fewer drugs or early cessation of all antibiotics: an antibiotic with activity against nfGNB (imipenem–cilastatin, piperacillin–tazobactam, ceftazidime or ciprofloxacin) replaced by a molecule without nfGNB activity. An antibiotic with activity against MRSA replaced by a molecule with activity against MSSA A third-generation cephalosporin replaced by a group A penicillin	Before 5th day for reducing number of antibiotics, before 3rd day for early cessation
Joung	2011	Patients with ICU acquired pneumonia. *N* = 137	33.7[a]	Yes (27%)	Smaller spectrum (using ranks) or fewer drugs or early stop carbapenem > piperacillin + tazobactam > cefepime or 3rd generation cephalosporin	Before 5th day if cultures negative and 48 h of defervescence. Not specified for reducing spectrum

Table 2 (continued)

Author	Year	Population no. of pt studied	ADE rates	ADE in negative cultures	ADE details	ADE to occur on or before specified day of therapy
Heenen	2012	Patients with hospital-acquired infections, severe sepsis treated with broad-spectrum beta-lactams *N* = 169	81%[a]	Yes, reported separately	Smaller spectrum (using ranks) or fewer drugs From meropenem to any other b-lactam. From ceftazidime, cefepime, or piperacillin + tazobactam to amoxicillin–clavulanic acid or any other type of penicillin From vancomycin to any type of penicillin	Before 5th day
Gonzalez	2013	ICU patients receiving antibiotics for an infection *N* = 365	51%	Yes (40.2%)	Smaller spectrum or fewer drugs or early stop	Before 5th day
Knaak	2013	ICU patients with HAP, VAP or HCAP *N* = 113	62%	Yes	Smaller spectrum (using ranks) or fewer drugs Gram negative: carbapenem > piperacillin–tazobactam, > cefepime > fluoroquinolone Gram-positive: vancomycin > nafcillin or cefazolin	Within 24 h of culture results
Mokart	2013	Neutropenic patients with severe sepsis admitted to the ICU for > 48 h *N* = 101	44%[c]	Yes	Smaller spectrum or fewer drugs	Within the ICU admission
Garnacho-Montero	2014	ICU patients with severe sepsis or septic shock *N* = 628	45%[a]	Yes (0.5%)	Smaller spectrum or fewer drugs	Once culture results available
Paskovaty	2015	Patients with cancer admitted to the ICU with severe sepsis *N* = 101	58%[c]	Yes	Smaller spectrum or fewer drugs or early stop	Before 5th day
Bailly	2015	ICU patients treated with antifungals for invasive candidiasis *N* = 647	22% ADE or stop 9.9% ADE only[c]	Yes	Switch from another antifungal to fluconazole or stop	Before 5th day
Moraes	2016	ICU patients with severe sepsis or septic shock *N* = 224	67%[b]	Yes	Smaller spectrum or fewer drugs or early stop	Before 5th day
Weiss	2016	ICU patients with Gram-negative-bacteria VAP with microbiologically possible ADE *N* = 182	53.4%[b]	No	Use of a previously published consensus definition Smaller spectrum (using ranks): imipenem/meropenem/doripenem > ertapenem > piperacillin + tazobactam/fourth-generation cephalosporin/anti-pseudomonal third-generation cephalosporin Third-generation cephalosporin/ureido/carboxy-penicillin > amoxicillin + clavulanic acid > amoxicillin	Before 5th day

Table 2 (continued)

Author	Year	Population no. of pt studied	ADE rates	ADE in negative cultures	ADE details	ADE to occur on or before specified day of therapy
De Bus	2016	ICU patients receiving anti-pseudomonal beta-lactam antibiotics *N* = 478	25%	Yes	Smaller spectrum (using ranks) or fewer drugs carbapenems + 2nd antibiotic with Gram-negative coverage > carbapenems > non-carbapenem anti-pseudomonal beta-lactams or fluoroquinolones used for anti-pseudomonal activity. > Other beta-lactams or fluoroquinolones used for community acquired infection (levofloxacin	Not specified
Turza	2016	ICU patients with an infection *N* = 2658	37.4%	Yes	Smaller spectrum (using ranks) or fewer drugs	Not specified
Trupka	2017	Mechanically ventilated ICU patients with pneumonia *N* = 283	49.5%[c]	Yes	Smaller spectrum (using ranks) or fewer drugs. carbapenem > cefepime > ureidopenicillin or monobactam > quinolone > cefriaxone	Not specified
Khan	2017	ICU patients with VAP *N* = 108	29.6%	Yes (9.1%)	Smaller spectrum or fewer drugs	Within 24 h of final culture and antibiotic sensitivity results
Jaffal	2018	Patients receiving antifungals *N* = 190	20% of which 10% early stop and 10% smaller spectrum	Yes (20%)	Smaller antifungal spectrum or early stop	Before 5th day
Li	2018	Trauma patients with VAP	39.7%[c]	Yes	Smaller spectrum or fewer drugs or early stop	Not specified
Cowley	2019	ICU patients with culture-negative nosocomial pneumonia	32%	Yes (100%)	Anti-MRSA agent discontinuation	Within 4 days of initiation

ADE in negative cultures denotes if ADE could be considered in patients with negative cultures, if specified % of patients with negative cultures in the ADE group

N number of patients

[a] ADE rates of appropriate antibiotic therapy

[b] Only where ADE is possible

[c] If includes all patients without details

The panel specifies that while there was in vitro and indirect evidence for some antimicrobial combinations and double cover in providing synergistic antimicrobial effects or preventing resistance, clinical data for this effect is lacking [14, 15].

ADE is proposed as a strategy to minimize the overall exposure to broad-spectrum agents.

It is often conducted when microbiological results become available, species and/or susceptibilities. It consists of changing the antimicrobial regimen to a different regimen that has minimal ecological impact while retaining activity on the targeted pathogens. Its timing and the case of culture-negative infections are discussed in questions 6 and 9, respectively.

The underlying rationale is that by reducing the duration of exposure to broad-spectrum agents within an antimicrobial treatment, ADE may reduce the ecological impact of that treatment.

It is common belief that antimicrobials with activity on a large spectrum of pathogens are worse in terms of emergence of resistance when compared with narrower spectrum alternatives. While this is sometimes true, and some broad-spectrum agents should be reserved to the cases without other treatment options, the relationship between spectrum and emergence of resistance

is complex. Some narrow spectrum agents have been described to have worse ecological impact than of broader spectrum alternatives [16].

As shown in Table 1, there is variability in the definition of ADE. It has been described as:

- A reduction of the spectrum of antimicrobials by replacing an agent with one of a smaller spectrum [17–32]. The use of a ranking of agents' spectra of activity was provided by some but not all studies [18, 23, 24, 28, 32, 33].
- Decreasing the number of antimicrobials in combination therapy [17–22, 25, 27–32, 34].
- Discontinuation of all antibiotics [22, 27, 28, 31].

Early discontinuation of all antibiotics is effective to decrease the exposure to antibiotics and subsequent selection pressure.

It may be performed because:

- An infection is not present.
- A shorter duration is considered adequate to treat an infection.

Early discontinuation has been described as ADE by several authors [22, 27, 28, 31].

Early discontinuation and ADE are two different concepts aimed at similar targets. To avoid confusion early discontinuation of all antimicrobial therapy has not been included in the proposed definition of ADE.

The panel recommends that antimicrobials should be stopped as soon as they are not required. If they need to be continued and a narrower option is available for the considered pathogen, ADE should be considered.

ADE is sometimes considered as a single component of care, as defined in this document. The panel strongly believes that ADE should be considered as part of a broader ASP program within the overall evaluation of the ICU patients to whom an antibiotic has been prescribed, taking into account all the other parameters of managing ICU patients with severe infections [8, 9].

As a summary, the evidence for a definition of ADE is low because of the inconsistency of how ADE was defined in the different studies available. As both escalation and de-escalation conceptually require a treatment before and after, there was inconsistency in the inclusion of early cessation of all antibiotics in the definition of ADE. Finally, despite the great variability of ADE definitions in the literature, there was an overall consistency in targeting a lesser ecological impact.

Question 2: does the panel recommend a numerical score to measure the ecological impact of the empirical antimicrobial regimen and can this score be used to guide antimicrobial de-escalation?

Recommendation

We recommend research is undertaken to develop multidimensional scores to measure the local ecological impact of empirical antimicrobial regimens and guide ADE.

Strength

Moderate recommendation; low quality of evidence.

Rationale

Two studies have ranked antibiotics to provide a classification that could be used for ADE purposes [35, 36]. Rankings for the same antibiotics are different between the two, highlighting the complexity of providing a unified score. Madaras-Kelly and colleagues ranked antibiotics according to their antimicrobial activity spectrum [35]. They used a Delphi method to define the elements of an ADE spectrum score with a panel of 41 experts (physicians and pharmacists). The score was then computed for each antibiotic according to the susceptibilities of the different micro-organisms in a database of clinical specimens. Scores for 27 antibiotics from nine different classes ranged from 4 (metronidazole) to 49.75 (tigecycline) out of a maximum of 60.

The score was validated against expert opinion in a set of 20 antibiotic regimen changes. Change in spectrum score was not significantly correlated with mean expert opinion, illustrating the questionable validity of computed scores in clinical practice.

Weiss et al. and a group of 28 French-speaking experts (physicians, pharmacists and microbiologists) used a Delphi method to define ADE [36]. They restricted to define ADE specifically for beta-lactam antibiotics and their activity on Gram-negative micro-organisms. They provided a 6-rank classification of beta-lactam antibiotics according to both spectrum and resistance promoting potential. Reaching an agreement of 71% for the ranking of ureido/carboxy-penicillins, 3rd and 4th generation anti-pseudomonal cephalosporins required 4 Delphi rounds. They defined switching from combination therapy to monotherapy as ADE with a 92% expert consensus opinion, regardless of the molecule withdrawn.

Significant differences exist between the two scores. Madaras-Kelly et al. rank a wide range of antimicrobials

[35], where Weiss et al. looked at one class only [36]. Rankings differ within the 2 classifications systems and there is poor agreement between the two scores: when applying Madaras-Kelly spectrum score to the first antibiotic in each of the Weiss ranks, they would rank (lowest to highest scores): 1,3,2,5,6,4.

Weiss highlighted the difficulty to rank drugs within a single class of antimicrobials if ecological consequences and spectrum are taken in account. This is further complicated when several classes are compared as their consequences will vary depending on the clinical and institutional settings.

As shown in Table 2, ranks were used to assess for ADE in 9/22 studies. All differed and only one study by the Weiss and colleagues used one of the published scores in a clinical cohort. All studies that used a ranking system or a score to measure the empirical regimen used the same score to measure or guide ADE.

There is inconsistency between available scores and moderate evidence that designing a unifying score is not achievable. This is illustrated by the ranking of fluoroquinolones when compared to broad-spectrum beta-lactams. Both are active against a large number of bacteria, they promote resistance by different mechanisms on different targets, and their importance as reserve antibiotic agents vary in time and space. Depending on the setting switching one to the other may represent ADE, no change or escalation.

Where a score is required for antimicrobial stewardship (AMS) services, we recommend that institutions develop a multidimensional score that applies to their setting. While no unifying framework is available, we recommend scores developed to assist stewardship strategies and ADE should include the three following items:

(1) Antimicrobial activity and spectrum of the drug:
   (a) Mechanisms of action.
   (b) Variety of micro-organisms that are intrinsically susceptible or resistant.
(2) Risk of bacterial selection within the microbiota:
   (a) At the source of infection.
   (b) On the intestinal and general microbiota of the patient, including biliary concentrations and activity on anaerobic bacteria.
   (c) On colonization resistance.
(3) Impact of the drug on the population. This will vary:
   (a) For each institution and community.
   (b) In time as microbial ecology evolves.
   (c) With local strategies such as antimicrobial restriction and attempts at reducing specific pressures.

Question 3: in critically ill patients receiving antibiotics for an infection, what are the effects of antimicrobial de-escalation compared to no de-escalation on mortality and length of stay?

Statement

The ADE strategy is likely safe with regard to patients' outcomes.

Strength

Statement of fact; moderate quality of evidence.

Rationale

Available evidence is derived from observational studies and two randomized controlled trials (RCT). Kim and colleagues published an RCT in 2012 comparing the effects of "imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation". This RCT studied two very different initial antimicrobial therapies rather than ADE and was excluded from our analysis [30]. Included studies are described in table esup 1. We will only consider the second RCT by Leone and colleagues and pooled results of observational studies as evidence [10, 21].

This RCT did not show a significant difference in mortality between ADE versus a continuation strategy [31% ADE vs 23% continuation, $p=0.55$; HR 1.31, 95% CI (0.64–2.67), $p=0.49$] [21]. With regard to its primary endpoint, the trial failed to show non-inferiority of the ADE strategy in terms of ICU length of stay (15.2 ± 15 for ADE vs 11.8 ± 12.6 days for continuation, non-inferiority margin 2 days.).

Most observational studies reported an unchanged ICU and/or hospital length of stay [22, 23, 27, 31, 32, 37–41], whereas one described an increase [24] and two reported a decrease in ICU length of stay with ADE [18, 42].

In a previous systematic review, with mortality as an endpoint, pooled results of available studies suggested that ADE is associated with lower mortality [10, 43]. This potential benefit was derived from the results of observational studies [10]. In observational studies there is an inherent bias by indication. Where investigated, ADE was performed in patients with improving illness severity or factors of good prognosis when compared with the patients that did not undergo ADE [17, 19, 20, 22, 24–28, 31, 32, 38, 41]. Few studies included clinical markers of improvement (such as SOFA score variations) and adjusted for them as potential confounders [20, 22, 23, 31, 41, 42, 44]. Even the best statistical adjustment cannot accurately measure what happens at the bedside and how

clinicians decide on a management strategy. It is postulated that in observational studies clinicians chose the ADE strategy more frequently when patients were clinically improving. In some ways ADE may be perceived as a clinical marker of the patient improving rather than a treatment decision leading to better patient outcomes [10].

All studies have limitations and most have imprecisions on how they measure the results. Results are inconsistent and publication bias is possible. The quality of the evidence is low.

Question 4: in critically ill patients receiving antimicrobials for an infection, what are the effects of antimicrobial de-escalation compared to no de-escalation on the total duration of antimicrobial therapy?

Statement

ADE is associated with a risk of increase in total duration of antimicrobial therapy. We recommend that ADE and duration of antimicrobial therapy are assessed separately but as part of the global stewardship strategy.

Strength

Statement of fact; low quality of evidence.

Rationale

Several clinical trials in hospitalized patients with severe infections document the safety of shorter antibiotic courses [45–47]. None of those trials mandated ADE within their protocols, even when a pathogen was identified.

The link between ADE and shorter courses of therapy is weak. Most trials of shorter courses of antibiotic therapy have not mandated ADE, even if a pathogen is identified [46–48]. They aimed to ensure that all the patients received initially appropriate AMT and source control when required.

In the only RCT on ADE, the strategy may have increased the total duration of antimicrobial therapy: ADE 14.1 ± 13.4 days vs continuation 9.9 ± 6.6 days ($p = 0.04$) [21]. The total duration of treatment was increased, but the duration of the initial treatments was similar. The authors hypothesize this was related to the increase in the number of superinfections in the ADE group. These results should be interpreted with caution, as when considering medians and analysed with a non-parametric statistical test those differences were non-significant: ADE 9 [2–66] days vs continuation 8 [2–34] days ($p = 0.11$).

Other potential reasons for ADE may increase the total duration of treatment include errors in counting treatment days or increasing them by a little when the prescription is changed to ensure the patient receives the full treatment duration. The perceived safety of narrow spectrum alternatives may diminish the incentive to decrease duration of antimicrobial therapy as it is globally recommended.

There were differences between cohort studies if early cessation of all antimicrobials was included or not in the definition of ADE. When the group of patients assessed as having received ADE included those that had all antibiotics stopped early, this may have caused a spurious correlation between ADE and decrease the duration of antimicrobial therapy [22, 27, 42]. Of the 6 cohort studies that did not include early cessation of antibiotics in the definition of ADE three reported a similar [17, 23, 38], one a decrease [41] and two an increase [19, 24] in total antimicrobial duration with ADE when compared to continuation.

There is low quality of the evidence that ADE may be associated with an increase in the total duration of AMT. Results of the cohort studies are inconsistent and the only RCT showed an increase in the duration of antimicrobial therapy with ADE. The panel puts a high value in maintaining short durations of AMT whenever feasible and recommends clinicians give special attention to duration of antimicrobial therapy in patients who receive ADE.

Question 5: in critically ill patients receiving antimicrobials for an infection, what are the effects of antimicrobial de-escalation compared to no de-escalation on the development of resistance to antimicrobials?

Statement

No statement can be made.

Rationale

ADE has been recommended as a strategy to decrease the overall use of broad-spectrum antibiotics. By limiting prolonged exposure to those antibiotics, it is inferred that it may decrease selection pressure and subsequently prevent the emergence and acquisition of resistance to antimicrobials [1].

The acquisition of multidrug-resistant organisms (MDR) has been studied as an endpoint in few studies on ADE in the ICU [21, 23, 24, 31]. None of these studies described a significant association between ADE and acquisition of MDR. Further, the direction of the effect varied between the studies.

In a retrospective study of ICU patients receiving antibiotics, De Bus and colleagues specifically investigated the effects of ADE of anti-pseudomonal

beta-lactam antibiotics and did not find a significant difference in the emergence of MDR at day 14 (18.6% continuation vs 23.5 ADE, $p = 0.22$).

In a retrospective cohort study of 182 ICU patients with VAP, ADE of pivotal beta-lactam was carried out in 38% of the episodes [23]. This strategy was associated with a non-significant reduction in the acquisition of extended spectrum beta-lactamase-producing (ESBL) Enterobacteriaceae (1.4% vs. 8.2%, $p = 0.07$) in the ADE group. There was no difference on the global rate of MDR acquisition at day 21 (14.3% ADE vs 21.3% continuation, $p = 0.32$).

In a retrospective study of 229 ICU patients, Gonzalez and colleagues did not find a difference in MDR carriage [31], and the only RCT published to date was not designed to investigate this variable [21].

Indirect evidence from the MERINO trial comparing piperacillin–tazobactam vs meropenem for ceftriaxone resistant Gram-negative bacteremias did not find a reduction of subsequent detection of carbapenem-resistant organisms in the carbapenem sparing arm (3.2% vs 2.1%) [49].

Clinical data comparing the effects of individual or sequential antibiotic use on the intestinal microbiota of ICU patients is not available. A recent review on the impact of different beta-lactams on the intestinal microbiota describes the particularly harmful effects of β-lactam/β-lactamase inhibitor combinations on colonization resistance. This challenges some perceptions of the relative harms of carbapenems and their alternatives. It particularity reminds us that antibiotics commonly assessed as narrower spectrum than others may have worse ecological consequences [16].

The available evidence with regard to the effects of ADE on the emergence of resistance to antimicrobials is inconclusive due to the retrospective and observational nature or the indirectness of available research.

As outlined in our proposal for a new ADE scoring system (see rationale for question 2), to prevent emergence of resistance, further research on ADE will need to take in account the effects on colonization resistance and the ecological consequences of each agent and not only their clinical spectra.

Question 6: in critically ill patients receiving antimicrobials for an infection, when is it recommended to perform de-escalation of the empirical antimicrobial regimen?

Recommendations

We recommend ADE is performed within 24 h of definitive culture results and antibiogram availability.

Strength

Strong recommendation; low quality of evidence.

Rationale

Timing of ADE has been variable defined. Ranging from 3 to 5 from days the start of the empirical regimen [17, 18, 22, 23, 25–27, 29–31, 37, 40, 42] to the day when culture results were available [20, 21, 32, 39]. Several manuscripts did not provide a specific day when ADE should be performed [19, 24, 28, 38, 41].

Ideally ADE should happen as early as possible to minimize the exposure to the broader spectrum regimen.

If broad-spectrum empirical therapy was required to cover for some specific pathogens or resistance phenotypes, it is only when the final culture results are available (including antibiogram) that these can been excluded with a reasonable degree of confidence.

While this has not been specifically investigated, there is a strong rationale for doing ADE when the final culture results are available, including the antibiograms and to allow for 24 h to receive, evaluate and act upon those results. Based on this rationale the panel makes a strong recommendation.

While molecular rapid diagnostic testing (MRDT) offers the possibility of an early detection of some pathogens and resistance patterns, they have mostly been investigated as a means to target the initial antimicrobial therapy [50]. There is very little data on their use for ADE. A recent retrospective study to validate a MRDT-based AMS strategy pointed at a small (4.8%) risk of inappropriate ADE when the test was used [51]. In addition, the association between very early ADE and treatment failure has not been evaluated in any study and no recommendation can be made regarding MRDT and ADE at the time of preparing this document.

Question 7: in critically ill patients receiving antimicrobials for an infection, are recommendations for or against antimicrobial de-escalation different for certain bacterial pathogens? For which?

Recommendations

Recommendations for or against ADE are similar for all bacterial pathogens except for difficult-to-treat pathogens in patients with a high risk of death.

Strength

Moderate recommendation, low quality of evidence.

Rationale

ADE has not been evaluated for specific pathogens. Indirect evidence is presented below for pathogen groups where it is available.

Problematic pathogens differ according to geographical differences, local ecology and case mix. They were defined as difficult-to-treat pathogens. This may include MDR, extensively drug-resistant (XDR) or pan-drug resistance patterns accordingly [52]. For Gram-negative micro-organisms a recently published definition of difficult-to-treat resistance (DTR) is available and includes: intermediate or resistant to all reported agents in carbapenem, β-lactam, and fluoroquinolone categories [53].

Staphylococcus aureus

Indirect evidence is available for *Staphylococcus aureus* from a post hoc analysis of treatment strategies for VAP in a large RCT of diagnostic strategies [54]. Joffe et al. describe a subgroup of patients with *S. aureus* recovered from their enrolment culture; of these 78% received ADE (87% decrease spectrum, 13% stop). They had lower baseline APACHE II scores and day 28 mortality [54]. While the risk of bias is high, this may indicate safety of ADE for this subgroup of patients.

Gram-negative pathogens and multidrug resistance

Identification of MDR isolates, *Pseudomonas* spp. and other non-fermenting Gram-negative bacilli either as causative agents or as colonizers has been associated with not performing ADE in multiple reports [10, 17, 22, 26, 27, 31, 44, 55, 56].

Polymicrobial infections and/or intra-abdominal foci have been associated with reduced likelihood of de-escalation [20, 22, 26, 32]. In a prospective study of 311 patients with hospital-acquired (HA) intra-abdominal infections (IAI), Montravers and colleagues describe the safety and feasibility of ADE in polymicrobial infections [57]. The identification of MDR organisms and non-fermenting GNB were associated with lower rates of ADE.

However, in a cohort of patients with VAP, Souza-Oliveira et al. reported 45.6% of infections caused by MDR pathogens (mainly *A. baumannii*, MRSA and *P. aeruginosa*) and no difference in mortality after ADE as to the MDR or susceptible status [58].

Indirect evidence from two non-ICU studies should be mentioned as a word of caution when considering ADE in ESBL, XDR or DTR. The Merino RCT was aimed at showing non-inferiority of piperacillin–tazobactam compared with meropenem in patients with ESBL bloodstream infection (BSI). The trial was stopped because of significantly higher mortality in the piperacillin–tazobactam arm [49], which may argue against ADE from carbapenem to piperacillin–tazobactam in that specific setting.

In a multinational cohort study of Carbapenem Resistant Enterobacteriaceae (CRE) BSI the INCREMENT investigators describe a protective effect of combination therapy in the group of patients with higher risk of death [59]. This may suggest continuing combination therapy and not de-escalate the companion antibiotic in high severity patients with difficult-to-treat GNB infections.

However, as far as *A. baumannii* is concerned, indirect evidence from a large RCT on carbapenem-resistant micro-organisms, showed that combination treatment was not superior to colistin monotherapy and the addition of meropenem to colistin did not improve clinical failure in severe *A. baumannii* infections [60]. A secondary analysis of this trial showed that colistin monotherapy was associated with a better outcome compared to colistin–meropenem combination therapy among patients infected by colistin-resistant isolates [61]. These results may suggest that de-escalation to monotherapy with colistin should be considered when the infecting pathogen is carbapenem-resistant *A. baumannii*. In those cases, we recommend avoiding underdosing colistin, especially in patients receiving CRRT where very high doses may be required.

The quality of the evidence for ADE for specific pathogens is low, with imprecision and bias due to subgroup analysis of observational studies. The panel does recommend caution when ADE is considered in ESBL, XDR and DTR. This recommendation is subject to indirectness of the evidence. The panel puts a high value in maximizing the chances treatment of success for difficult-to-treat pathogens.

Question 8: in critically ill patients receiving antifungal agents for invasive candidiasis, does the panel recommend antifungal de-escalation compared to no de-escalation?

Recommendations

We recommend ADE of antifungal agents after clinical and microbiological resolution of invasive candidiasis when the pathogens are susceptible to azole antifungal agents.

Strength

Strong recommendation; low quality of evidence.

Rationale

In critically ill patients with sepsis and suspected or documented invasive candidiasis, echinocandins are recommended as first-line empiric treatment for their broader spectrum of activity and fungicidal activity, excellent

safety profile and fewer drug–drug interactions, when compared to fluconazole [62, 63].

Candida krusei is intrinsically resistant to fluconazole and globally the azoles have less activity against *C. glabrata* and *C. krusei* than against other *Candida* species. Moreover, recent surveillance studies suggest that triazole resistance among *C. glabrata* isolates has increased to a degree that is it difficult to rely upon these agents for therapy in the absence of susceptibility testing [64].

An open-label non-comparative trial [65] and several smaller pilot studies [66, 67] showed similar outcomes in terms of clinical + microbiological response at the end of treatment with or without ADE of echinocandins. An azole-susceptible micro-organism, clinically stable patients, negative repeat blood cultures and at least 5 days of echinocandin therapy were required before switch to oral fluconazole or voriconazole could be performed.

A post hoc analysis of the AmarCAND2 study showed that, in non-neutropenic critically ill adult patients with documented or suspected invasive candidiasis, de-escalation of systemic antifungal therapy within 5 days was not associated with increased day-28 mortality (RR 1.12, 95% CI 0.76–1.66) but it was associated with decreased systemic antifungal consumption [42].

More recently, in critically ill patients with proven candidemia, de-escalation of the empirical echinocandin to fluconazole was performed in 37% of the cases and this reduction of spectrum was not associated with a higher mortality or the occurrence of long-term complication [68]. Lower 90-day crude mortality rates in the ADE compared with continuation groups (15.9% vs 58.7%) are according to the authors likely explained by the higher proportion of *C. parapsilosis* and lower SOFA scores in this subgroup.

There is now evidence that *Candida* colonization-based antifungal prescription of fluconazole and caspofungin has caused significant ecological changes, especially for *C. glabrata* and *C. parapsilosis*, without any impact on candidemia incidence and on Candida-related mortality [69]. Recently, Jensen et al. showed that, following treatment for invasive candidiasis, colonizing mucosal microbiota may be an unrecognized reservoir of resistant *Candida*, especially *C. glabrata* [70]. Patients exposed to azoles for at least 7 days had a significantly larger proportion of species intrinsically less susceptible to azoles among oral isolates than among initial blood isolates. A similar shift toward species less susceptible to echinocandins was not observed after echinocandin exposure for the same amount of time. However, acquired resistance to fluconazole and to anidulafungin was common in *C. glabrata* isolates from patients exposed to either azoles or echinocandins.

Finally, a population-based laboratory surveillance study included patients with candidemia in 4 metropolitan areas including 7.9 million persons and 80 hospitals [71]. The proportion of *C. glabrata* non-susceptible to echinocandins significantly increased during the 2008–2014 period. Prior echinocandin exposure was the main risk factor for *C. glabrata* echinocandin non-susceptibility and presence of *FKS* mutations. The occurrence of non-susceptible *C. glabrata* without prior echinocandin exposure suggested cross-transmission of resistant organisms.

Therefore, a decrease in echinocandin consumption with the target to prevent FKS mutations-related *Candida* non-susceptibility is desirable.

The quality of the evidence is low due to the observational nature of the trials, indirect due to post hoc analysis or inclusion of non-ICU patients. The panel puts high value in decreasing echinocandin use while providing the best possible patient outcomes.

For those patients we emphasize the need for adequate dosing strategies. In fact, a growing body of evidence suggests that antifungal therapy is frequently underdosed in treatment of invasive candidiasis in critically ill patients. Around one-third of fluconazole-treated patients failed to achieve minimum recommended PK/PD target exposures [72] and this is an independent risk factor for death [73]. Dosages of fluconazole of 400 mg/day have a high probability of treatment failure when the 24 h fluconazole MIC is $\geq$ 4 mg/L [74]. In the critically ill, a loading dose of 12 mg/kg/day followed by 6 mg/kg/day should be used and if the patient is on CRRT doses up to 9 mg/kg/day are needed [75].

In conclusion the use of an ADE strategy for antifungal therapy seems to be possible and safe. Transition from an echinocandin (or amphotericin B) to an azole (fluconazole or voriconazole) is recommended for patients who are clinically stable, have isolates that are susceptible to the azole and have negative repeat blood cultures (in the case of candidemia) following initiation of antifungal therapy. This transition may be safely performed within 5 days after initiation of antifungal therapy, as long as the criteria defined above are attained, but this time is variable and ultimately dependent on patient response.

Question 9: in critically ill patients receiving antimicrobials for a culture-negative infection, does the panel recommend antimicrobial de-escalation compared to no de-escalation?

Recommendations

We recommend that consideration is given to alternate non-infectious diagnosis and stopping all or part of the

antibiotic regimen in critically ill patients with culture-negative infections.

Strength

Moderate recommendation; low quality of evidence.

Background and rationale

Identified studies found that the absence of an identified pathogen was either a risk factor for not performing ADE or by design an exclusion criterion from the study.

One of the inclusion criteria of the only available RCT was appropriate empirical antimicrobial therapy and positive microbiological cultures [21]. Observational studies have defined a positive culture as a prerequisite for the decision to or a factor strongly associated with performing ADE [24, 37, 55, 76]. Other studies have selected their population as patients where ADE is microbiologically possible, implying a positive culture result and a narrower antibiotic option available that would have in vitro activity against the pathogen [23]. One cohort study specifically investigated ADE in patients with culture-negative nosocomial pneumonia [34].

As described in Table 2, 19 of the 23 retrieved studies on ADE included patients with negative cultures [17, 19, 20, 22, 24, 27–32, 34, 37–42, 77]. Of those, 7 included early cessation of all AMT in the definition of ADE [22, 27, 28, 31, 37, 40, 42].

The effects of negative cultures on decision-making and ADE are variable and where reported, the rates of negative culture in the ADE subgroup vary from 0.5% to 40%. However, appropriate AMT and the corollary positive cultures is consistently described as a factor that positively influences ADE [10].

In a study of patients with ICU acquired pneumonia, Joung and colleagues found that 29.4% of culture positive and 42.9% of culture-negative patients received ADE, respectively [28]. In culture-negative patients, perceived severity may influence decision-making as patients who received ADE had lower severity scores than those who did not.

In another retrospective single center study from France including 229 patients of which 72.5% had a community acquired infection. Infectious sites included lung (55%), urinary tract (9.6%) and abdomen (9.6%). De-escalation was employed in 44% of culture-negative episodes, without any reported worsening mortality [31].

In a secondary analysis of a Canadian multicenter trial of patients with suspected VAP randomized to bronchoscopy or endotracheal aspirate cultures, Joffe et al. analysed safety of targeted treatment (TT) [54]. Among 327 patients with negative enrolment cultures, 270 were classified as TT, 144 of whom underwent de-escalation (defined as discontinuation of antibiotics per protocol). Patients on TT had less severe clinical progression of infection and MODS, lower δ MODS, more days alive and off broad-spectrum antibiotics, fewer mechanical ventilation days, and similar mortality compared with NoTT. A lower pre-test likelihood of VAP in the TT group demonstrates the rigorous clinical assessment that is required in decision-making to de-escalate without microbiological confirmation.

Finally, in a retrospective study of 279 patients with culture-negative nosocomial pneumonia, Cowley and colleagues described the safety of stopping an anti-MRSA agent while other antibiotics were either continued or de-escalated. There was no difference in 28-day mortality and treatment failure. Patients who received ADE of the anti-MRSA agent had lower incidences of acute kidney injury (AKI) [34]. While ICU and hospital length of stay after the index date were shorter, the total duration of care was not affected [34].

In this patient group of culture-negative infections, when cessation of all antimicrobials is not possible, consideration should be given to ADE and stopping companion antibiotics of combination therapy.

In those studies, it is unknown which patients with negative cultures had an infection. Some may have had an early cessation of AMT because the clinician thought that there was no infection, and this was classified as ADE.

The evidence is graded as low due to the imprecision and inconsistency of the results, the observational nature of the study and indirectness of the evidence derived from secondary analysis of RCT. Further the panel places high value in early cessation of AMT rather than ADE where it is possible.

Question 10: in neutropenic critically ill patients, does the panel recommend antimicrobial de-escalation compared to no de-escalation?

Recommendation

We suggest ADE can be applied in neutropenic critically ill patients.

Strength

Weak recommendation, low quality of evidence.

Rationale

ADE in neutropenic patients has been specifically assessed in three observational studies accounting for 213 patients [19, 78, 79]. Rates of ADE ranged from 44 to 57%. There were no associations between ADE and worse patient outcomes in any of the reports.

Up to now, only one study has evaluated ADE in neutropenic critically ill patients. Mokart et al. compared

ADE and continuation therapy in an observational prospective study that included 101 neutropenic patients in the ICU [19]. There was no association between ADE and 30-day or 1-year mortality.

In a cohort of 105 cancer patients Paskovaty et al. described an association of ADE with shorter ICU and hospital LOS [22]. They reported that 24 (23%) patients were neutropenic on ICU admission. However, the rate of neutropenia at the time of de-escalation was not reported and no specific analysis was performed on this subgroup.

Thus, de-escalation during neutropenia was assessed on a small number of patients. The results of these studies are consistent, suggesting that de-escalation is safe in the neutropenic patient. European guidelines suggest a de-escalation approach, with initial broad-spectrum antibiotics in patients colonized with resistant pathogens, complicated presentation, and in centers with high incidence of resistant bacteria [80].

The quality of the evidence is low due to the observational nature of the studies, indirectness for 2/4 reports and imprecision for the last one.

The number of neutropenic patients tested in arms undergoing de-escalation and the quality of studies only support weak recommendations for this process in those patients.

Question 11: are recommendations for or against antimicrobial de-escalation different depending on the source of infection?

Recommendations

We suggest that ADE can be applied in all sources of infection.

Strength

Weak recommendation; low quality of evidence.

Rationale

We sought to investigate the evidence for ADE in different sources of infection. Of studies reporting on ADE in specific sources, outcome data were available on pneumonia, intra-abdominal infections and bloodstream infections.

(a) In critically ill patients receiving empirical antibiotics for pneumonia, does antibiotic de-escalation result in unchanged clinical cure, unchanged mortality and reduction of antibiotic resistance?

We identified and analysed 2 RCTs, 4 prospective cohort studies, and 5 retrospective cohort studies [17, 18, 23, 25, 28, 32, 34, 38, 39, 41, 55, 58]. As previously described 1 of the RCTs evaluated 2 different antibiotic regimens rather than ADE and was excluded from the analysis [30]. A post hoc subgroup analysis of the other RCT on patients with pneumonia did not show a difference in ICU length of stay or superinfection episodes (39% vs 22%, $p = 0.2$) with or without ADE [21]. Clinical cure and mortality were not described for this subgroup.

Variable definitions of ADE were used, and included a shorter duration of AMT in three studies [28, 55, 58]. One of the cohort studies reported on clinical cure and found no difference [34]. In all but one study [41], mortality was numerically lower compared to non-deescalated patients, and in 4 studies that difference was also statistically significant [18, 28, 32, 55]. As reported previously [10], patients who were de-escalated often had lower severity of disease scores at the moment of de-escalation.

Only one study reported the impact of de-escalation on antibiotic resistance, and did not demonstrate any significant effect [23].

ADE was inconsistently defined in the different studies. Studies included patients with HAP, HCAP, and VAP. No distinction could be made between these different types of pneumonia. We conclude that the quality of evidence supporting use of this intervention is low to very low due to the observational design, and indirectness.

(b) In critically ill patients receiving empirical antibiotics for intra-abdominal infections (IAI), does antibiotic de-escalation result in unchanged clinical cure, unchanged mortality and reduction of antibiotic resistance?

One retrospective cohort study on ICU patients with postoperative peritonitis reported on patients' outcomes following ADE [57]. There were no differences in clinical progress at day 7, morbidity or 28-day mortality with or without ADE. Data on clinical cure were not reported; there was no difference in duration of antimicrobial therapy or the emergence of antibiotic resistance in both groups.

In the general ICU, ADE was not associated with different mortality depending on the source of infection or when considering medical vs surgical patients [20]. However, IAI have been identified as a factor for not performing ADE [26].

In IAI there is a potential risk for undiagnosed anaerobic pathogens due to the low yield of cultures for those pathogens. Consideration should be given to maintaining anti-anaerobic coverage in patients with IAI undergoing ADE.

We conclude that the quality of evidence supporting use of this intervention is low.

(c) In critically ill patients receiving empirical antibiotics for bacteremia, does antibiotic de-escalation result

in unchanged clinical cure, unchanged mortality and reduction of antibiotic resistance?

No relevant studies were identified. In many studies reporting on ADE in critically ill patients, patients with bacteremia were included, and this has not been identified as a source of failure. Indirect evidence is available from a post hoc analysis of a cohort study that included 4% of ICU patients [81]. Mortality, clinical failure and length of stay were similar with or without ADE in this group of patients with Enterobacteriaceae BSI.

Further, as opposed to IAI, BSI are more commonly monomicrobial with a lower risk of unidentified microorganisms. In this respect, we believe that ADE can be considered in patients with bacteremia.

Question 12: in critically ill patients receiving antimicrobials, does the panel recommend the use of biomarkers when considering antimicrobial de-escalation?

Recommendation

No recommendation can be made.

Rationale

No relevant studies on the use of biomarkers to guide ADE were identified.

Procalcitonin (PCT) has been extensively investigated as a decision-making aid for the decision of stopping antibiotics in ICU patients with infection [82].

Several studies have evaluated the contribution of PCT-guided algorithms to antibiotic discontinuation, reduction of overall treatment duration or antibiotic cessation if the probability of sepsis was very low. PCT guidance was repeatedly associated with a decrease in total antibiotic consumption but this issue is out of the scope of this project.

PCT has been evaluated to escalate antibiotic spectrum in a randomized control trial but never to de-escalate once culture results are available [83].

In none of these studies the antibiotic decisions guided by PCT can be considered as de-escalation as defined in the current consensus report.

Question13: in critically ill patients who are de-escalated, does the use of therapeutic drug monitoring (TDM) versus no TDM improve outcome?

Recommendation

No recommendation can be made.

Rationale

Our search strategy did not retrieve any reports on ADE comparing the outcomes of patients who received TDM and those that did not receive TDM.

No relevant studies were identified regarding the use of TDM in patients following ADE and the following evidence is subject to indirectness. A simulation study described a lower probability of PK/PD target attainment with narrow than broad-spectrum antibiotics [77], hinting at a risk of not achieving PK/PD targets with ADE.

There are numerous papers which describe the importance of adequate antibiotic exposure as a determinant of clinical cure or mortality [84–87], although not development of resistance, in critically ill patients.

The panel puts high value in maximizing chances of achieving adequate PK/PD targets for all antimicrobial treatments. We suggest that TDM be performed where possible in critically ill patients who are receiving antibiotics.

Where TDM is not available, then dosing regimens that are appropriate for the drug and the clinical scenario should be carefully selected to ensure therapeutic drug exposures are achieved.

Future directions

Our recommendations are based on low-quality evidence. Further, regional variations in practices, prevalence of specific pathogens and susceptibility patterns cannot all be addressed by the current literature. We urgently require research on one of the common strategies used by many ASPs and ICU clinicians around the world.

It is important to emphasize that ADE should not be implemented as a standalone component of care, but as part of a multifaceted AMS strategy.

There is a strong rationale for the safety of ADE. The Simplify trial is currently recruiting in 19 Spanish hospitals. This multicentre, open-label RCT investigates the non-inferiority of ADE vs continuation of anti-pseudomonal beta-lactams [88]. Although not specifically recruiting in the ICU, by targeting the specific population of Enterobacteriaceae BSI it is likely to provide quality indirect evidence on the safety of ADE. Practices have been investigated worldwide by The Diana multicenter cohort study on the Determinants of antimicrobial use and de-escalation in the ICU (ClinicalTrials.gov Identifier: NCT02920463). This study should bring important information on the safety and effectiveness of ADE in a range of ICU settings.

Other avenues for research include improved in vitro evidence with the use of the novel hollow-fiber models

and the study of the effects of ADE on the microbiome of ICU patients.

As a practice to decrease the emergence of resistance, ADE requires a cluster-randomized MRCT to investigate the effects of an ICU-wide strategy, where periods with ADE could be compared to periods without ADE for all the patients in the ICU. Evaluation of the effects will require systematic sampling of colonization for all patients for extended periods, ideally paired with investigation of the microbiome, at least in a subgroup of patients. This is expected to require substantial funding. Further, as an area of dogma with little evidence, we may face difficulties recruiting participating centers for clinicians lacking equipoise.

Conclusion

This document provides guidance for clinicians on a widely used strategy aiming to prevent the emergence of resistance to antibiotics. However, as described, ADE remains a topic of controversy due to the complexity of clinical scenarios where it may be applied and the absence of evidence to the effects it may have on antimicrobial resistance.

This group endeavors to complete already existing and design new research to provide high-quality evidence to guide clinical practice on ADE in the near future.

Electronic supplementary material

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Compliance with ethical standards

Conflict of interest

Dr. Tabah has nothing to disclose. Dr. Bassetti reports grants and personal fees from PFIZER, grants and personal fees from MSD, grants and personal fees from MENARINI, grants and personal fees from ANGELINI, personal fees from ASTELLAS, personal fees from NABRIVA, grants and personal fees from PARATEK, personal fees from GILEAD, personal fees from BASILEA, personal fees from CIDARA, personal fees from MOLTENI, outside the submitted work. Dr. Kollef's efforts are supported by the Barnes-Jewish Hospital Foundation. Dr. Zahar reports personal fees from MSD, personal fees from Correvio, personal fees from Pfizer, outside the submitted work. Dr. Paiva has nothing to disclose. Dr. Timsit reports grants and personal fees from Pfizer, grants and personal fees from Merck, personal fees from Astellas, grants and personal fees from Biomerieux, personal fees from 3 M, during the conduct of the study; personal fees from Nabriva, personal fees from Bayer pharma, outside the submitted work. Dr. Roberts reports personal fees and non-financial support from Biomerieux, grants and personal fees from MSD, personal fees from Astellas, personal fees from Infectopharm, grants from The Medicines Company, outside the submitted work. Dr. Schouten has nothing to disclose. Dr. Giamarellou has received research grants from Pfizer, MSD, Angelini. Dr. Rello reports personal fees from Navriba, grants from BAYER, personal fees from Pfizer, personal fees from Anchoagen, outside the submitted work. Dr. De Waele reports grants from Research Foundation Flanders, during the conduct of the study; other from Bayer, other from Pfizer, other from MSD, other from Grifols, other from Accelerate, outside the submitted work. Dr Shorr has served as a speaker for, received research support from, or been a consultant to: Astellas, Merck, Nabriva, Paratek, Shinogi, and Tetraphase. Dr. Leone reports personal fees from MSD, personal fees from Pfizer, during the conduct of the study; grants, personal fees and non-financial support from AMOMED, personal fees from AGUETTANT, personal fees from ASPEN, personal fees from OCTAPHARMA, personal fees from ORION, outside the submitted work. Dr. Poulakou reports personal fees from Angelini, personal fees from MSD, grants and personal fees from Pfizer, grants from Roche, outside the submitted work. Dr. Depuydt has nothing to disclose. Dr. Garnacho-Montero has nothing to disclose.

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