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ORIGINAL

Antimicrobial de-escalation in the critically ill patient and assessment of clinical cure: the DIANA study

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Abstract

Purpose: The DIANA study aimed to evaluate how often antimicrobial de-escalation (ADE) of empirical treatment is performed in the intensive care unit (ICU) and to estimate the effect of ADE on clinical cure on day 7 following treatment initiation.

Methods: Adult ICU patients receiving empirical antimicrobial therapy for bacterial infection were studied in a prospective observational study from October 2016 until May 2018. ADE was defined as (1) discontinuation of an antimicrobial in case of empirical combination therapy or (2) replacement of an antimicrobial with the intention to narrow the antimicrobial spectrum, within the first 3 days of therapy. Inverse probability (IP) weighting was used to account for time-varying confounding when estimating the effect of ADE on clinical cure.

Results: Overall, 1495 patients from 152 ICUs in 28 countries were studied. Combination therapy was prescribed in 50%, and carbapenems were prescribed in 26% of patients. Empirical therapy underwent ADE, no change and change other than ADE within the first 3 days in 16%, 63% and 22%, respectively. Unadjusted mortality at day 28 was 15.8% in the ADE cohort and 19.4% in patients with no change [$p = 0.27$; RR 0.83 (95% CI 0.60–1.14)]. The IP-weighted relative risk estimate for clinical cure comparing ADE with no-ADE patients (no change or change other than ADE) was 1.37 (95% CI 1.14–1.64).

Conclusion: ADE was infrequently applied in critically ill-infected patients. The observational effect estimate on clinical cure suggested no deleterious impact of ADE compared to no-ADE. However, residual confounding is likely.

Keywords: Antimicrobial de-escalation, Intensive care unit, Bacterial infection, Empirical therapy, Clinical cure

Introduction

Antimicrobial de-escalation (ADE) is a treatment strategy pursuing early adequate antimicrobial therapy as well as a reduction in the overall use of broad-spectrum agents, with the aim to contain subsequent emergence of multidrug resistance [1–4]. De-escalation may be

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achieved through replacement of a broad-spectrum antimicrobial by an antimicrobial agent with a narrower spectrum or a lower ecological impact or by discontinuation of one or more antimicrobials of empirical combination therapy [4–7]. Internationally, ADE is recognized as a key component of antimicrobial stewardship [8–10].

Information on how often ADE is performed in everyday practice on a world-wide scale is lacking. Whereas the extended prevalence of infection in intensive care studies provided more insight in the global epidemiology of infections and antimicrobial use in critically ill patients; international studies mapping complete antimicrobial treatment courses in intensive care unit (ICU) patients are unavailable at present [11, 12].

Many observational studies and few randomized controlled trials (RCT) evaluated ADE and the impact thereof on patient outcome. RCTs have been unable to show convincing evidence that ADE is definitely safe, while systematic reviews have indicated a positive influence of ADE on mortality [4, 13–15]. Controversies regarding the safety of ADE nonetheless still exist as various definitions were used and antimicrobials were predominantly de-escalated in patients with microbiologically confirmed infections and a favorable clinical course. As such, observational studies are prone to bias [16].

The aims of the DetermInants of Antimicrobial use aNd de-escalAtion in critical care (DIANA) study were to determine how often ADE of an empirically prescribed therapy is performed in an ICU population and to estimate the effect of ADE on clinical cure on day 7 following initiation of empirical therapy, while adequately accounting for drivers of ADE that may evolve over time and also affect clinical outcome.

Methods

The DIANA study was a multicenter international observational cohort study investigating adult critically ill patients receiving empirical antimicrobial therapy for suspected or confirmed bacterial infections in the ICU. An international steering committee was established in 2015 and consisted of members of the European Society of Intensive Care Medicine (ESICM) Infection section. A network of national coordinators recruited investigators, coordinated study participation and monitored local ethics committee approval at each participating center. The Ghent University Hospital Ethics Committee approved the study (registration number B670201629297). The study was not funded and participation was voluntary. The trial was registered in ClinicalTrials.gov (NCT02920463).

Take-home message

ADE was performed within 3 days following empirical prescription in only 16% of critically ill-infected patients, despite the fact that half of the empirical prescriptions consisted of combination therapy and one-quarter contained a carbapenem. The observational effect estimate on clinical cure suggested no deleterious impact of ADE compared to no-ADE; however, residual confounding is likely to be present.

Participants

Patients were eligible for inclusion if they were 18 years or older and admitted to an ICU with an anticipated need of at least 48 h of ICU support. An empirical antimicrobial therapy had to be initiated in the ICU or no more than 24 h prior to ICU admission to treat a community-, healthcare-, hospital- or ICU-acquired bacterial infection. Antimicrobial therapy was defined as empirical in case the causative pathogen and susceptibility pattern were unidentified at the time of initiation of the antimicrobials. Patients could be included once. Informed consent was either obtained or waived according to local ethics committee requirements. Participating ICUs were asked to include all consecutive patients who were eligible during a convenient 2-week period, or an extended time period to provide the opportunity to include 10 patients. Patients could be included from October 2016 until May 2018.

Data collection

Data were submitted through an Electronic Data Capture platform (CASTOR™) [17]. Patient, infection and antimicrobial treatment-related data were collected from the day of study inclusion (day 0), defined as the start date of empirical antimicrobial therapy, until day 28. No interventions or measurements other than those that were standard of care were performed.

Patient-related data included: age; sex; co-morbidities; previous antimicrobial and hospital exposure; admission category and diagnosis. Severity of illness was evaluated using Acute Physiology And Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II on the day of ICU admission; Sequential Organ Failure Assessment (SOFA) scores were collected on the day of ICU admission, day 0 and day 3 (online supplement 1). The presence (i.e., multi-drug-resistant (MDR) pathogens present on ICU admission and/or detected before day 2) or emergence (i.e., MDR pathogens detected between day 2 and day 28 and not present before) of MDR pathogens was evaluated. Multi-drug resistance was defined as a pathogen producing extended-spectrum beta-lactamase (ESBL) or carbapenemase, *Stenotrophomonas maltophilia*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* sp., or a

pathogen resistant to 3 or more antimicrobial classes in accordance with the publication of Magiorakos et al. [18]. MDR-tables were constructed as guidance (online supplement 2). The need for supportive therapy, number of days in the ICU and hospital, ICU and hospital mortality were recorded until day 28. The clinical response of the patient for the initial infection was assessed by the treating clinician on day 7. Clinical cure was defined as survival and resolution of all signs and symptoms related to the infection.

Infection-related data included: source, need for source control, causative pathogens and susceptibility patterns. Antimicrobial treatment-related data included: type and timing of all antimicrobial agents that were initiated. Indications for stopping, switching or addition of an agent were recorded. Infection relapse, defined as an infection with the same causative microorganism and source that occurred after discontinuation of all antimicrobial agents for the primary infection, was evaluated until day 28. Additional antimicrobial therapy following study inclusion and antimicrobial-free days were assessed at 28 days following inclusion.

In addition, each participating ICU had to provide information on local antimicrobial resistance, organizational aspects of the ICU and presence of antimicrobial stewardship interventions in the ICU, e.g., multidisciplinary staff meetings and local antimicrobial treatment guidelines.

Data management

Data monitoring was performed by two investigators (LDB, KDS)

Antimicrobial treatment courses were classified based on the first modification of therapy (or the absence thereof) that took place between day 0 and day 3 as: "no change" (empirical therapy was maintained without modification between day 0 and day 3); "ADE" or "other change".

For the current analysis, ADE was defined as: (1) discontinuation of one or more antimicrobials of the empirical combination therapy which were considered by the treating physician to be not (or no longer) necessary for treatment of the infection within the first 3 days of initiation of empirical therapy (e.g., stopping vancomycin on day 2 following initial treatment with piperacillin-tazobactam combined with vancomycin); (2) replacement of an antimicrobial agent by another drug with the intention of the treating physician to narrow the spectrum of activity within the first 3 days of empirical therapy (e.g., replacement of meropenem by amoxicillin-clavulanate on day 2). In addition, physicians were asked to justify these decisions and specify the reason for treatment modification.

"Other change" was defined as: (1) the addition or replacement of an antimicrobial agent by the treating clinician within the first 3 days of empirical therapy, based on clinical deterioration or lack of clinical improvement, the presence of resistant causative and/or colonizing pathogens and/or presumed inadequacy of the initial treatment (e.g., not concordant with guidelines); (2) replacement of an antimicrobial agent within the first 3 days of empirical therapy due to side-effects of antimicrobials.

Statistical analysis

Frequencies (percentages) are reported as descriptive summary statistics for categorical variables and medians and interquartile range (IQR) (25th to 75th percentile) for continuous variables. Distributional differences for categorical patient outcomes were evaluated using a Pearson Chi-squared test or Fisher's exact test when appropriate. The Mann–Whitney *U* test was used for comparison of non-normally distributed continuous outcomes. Risk ratios were reported for binary variables, along with 95% confidence intervals (CIs). Unadjusted outcome analyses were performed comparing ADE and "no change" patients, and "other change" and "no change" patients.

Two primary outcome measures were defined: The incidence of ADE and clinical cure on day 7. Statistical analysis was tailored so as to emulate a hypothetical randomized trial to estimate the effect of ADE on clinical cure on day 7 (see online supplement 3 for additional statistical information) [19–23]. Inverse probability (IP) weighting was used to control for time-varying confounding that might affect both the decision of ADE on each day within the considered 4-day time period and clinical cure on day 7. Selection of these confounders was based on subject matter knowledge by means of a Delphi approach within the steering committee [24, 25]. Immunosuppression status, delta SOFA (defined as SOFA day 0 minus SOFA day 3), need and effectiveness of source control and identification of causative microbiology were selected by the panel and included in the analysis. Susceptibility pattern of the causative pathogen was selected but not included in the analysis due to incomplete timing-related data. Two additional covariates were included: (1) the continent where the ICU was located to account for missing data in certain regions; (2) the number of empirical agents to enable multiple subgroup and sensitivity analyses. Sensitivity analyses entailed inclusion of SOFA day 0, inappropriate empirical therapy and MDR colonization as covariate. The results are presented as absolute weighted risks, relative risk and 95% CI.

Post hoc power and sample size calculations using the IP weighted analysis were performed.

Statistical analysis was performed using R Statistical Software (version 3.4.2; The R Foundation for Statistical Computing. Vienna, Austria) using the packages geepack, ipw, multcomp and splines [26–30].

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies and the recommendations to optimize reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship (STROBE-AMS) were followed [31, 32].

Results

Participating intensive care units

A total of 152 ICUs in 28 countries participated; 48% in Europe, 38% in Asia, 9% in America and 5% in Australia and New-Zealand (online supplement 4). Ninety percent of participating centers were teaching hospitals, 81% were mixed ICUs and 76% worked in a closed ICU organization. Infectious disease specialists, microbiologists and clinical pharmacists joined regular multidisciplinary staff meetings in 28%, 24% and 22% of centers, respectively. Local ADE guidelines were used in 25.4% of centers. Baseline methicillin resistance of the *S. aureus* isolates was 10% (IQR 3–26) in the participating ICUs; vancomycin resistance of the *enterococcus* species isolates 0% (IQR 0–3). ESBL production was reported in 11% (IQR 5–21) of *enterobacteriaceae* isolates, whereas carbapenemase production was reported in 1% (IQR 0–5). Detailed center characteristics are presented in online supplement 5.

Overall patient, infection and treatment characteristics

A total of 1495 patients were available for analysis (online supplement 6). Median age was 65 (IQR 51–75) years, 61.5% were male and 66.6% were medical admissions. Patients were colonized with MDR pathogens prior to initiation of empirical antimicrobial therapy in 11.5%. Patient characteristics are detailed in Table 1. Infection and treatment characteristics are described in Table 2. Combination therapy was prescribed in 50% of empirical courses. The most frequently prescribed agents were anti-pseudomonal penicillins in combination with a beta-lactamase inhibitor, carbapenems and third-generation cephalosporins in 29.6%, 26% and 19.3% of patients, respectively (Table 3). Infections were microbiologically confirmed in 55.8%. Empirical therapy was considered inappropriate by the treating clinician based on the susceptibility pattern of the causative pathogen and triggered treatment modification in 10% of patients. Median number of days in the ICU and hospital following the onset of the infection were 8 (IQR 5–18) in ICU survivors and 26 (IQR 13–28) days in hospital survivors, respectively. The 28-day mortality rate was 19.8%.

Proportion of ADE patients

During the first 3 days, empirical antimicrobial therapy was de-escalated in 16% (240/1495) and not changed in 63% (934/1495). In 22% (321/1495) of patients, another treatment change was performed. Five percent (75/1495) of patients died during the first 3 days of therapy. A detailed description of the treatment modifications between day 0 and day 7 is available in online supplement 7.

Description of ADE

ADE consisted mainly of discontinuation of one or more components of combination therapy [52% (125/240)], whereas 35% (84/240) of ADE consisted of replacement of an antimicrobial agent by another drug. Both ADE approaches were applied in 13% (31/240) of ADE patients. The absence of microbiological confirmation and dual coverage of causative pathogens were the most prevalent incentives for discontinuation of a component of combination therapy. ADE in the form of replacement was mainly based on identification and susceptibility pattern of the causative pathogen (Table 4). The antimicrobial classes that were discontinued most often as components of a combination therapy were glycopeptides ($n=46$), aminoglycosides ($n=43$) and macrolides ($n=29$). The most frequently performed switches in the setting of ADE were: piperacillin-tazobactam to a third-generation cephalosporin and piperacillin-tazobactam to penicillin in combination with a beta-lactamase inhibitor. De-escalated beta-lactam prescriptions complied with the ranking developed by Weiss et al. in 91% (69/76) of the patients [33]. Online supplement 8 contains detailed information on ADE practices. ADE took place on day 0, day 1, day 2 and day 3 in 21%, 30%, 25% and 25% of ADE patients, respectively.

Patient, infection and treatment characteristics associated with ADE

The distribution of sex, age, pre-existing co-morbidities and immunosuppression status of patients was comparable in the ADE and "no change" cohort. Prior healthcare exposure occurred in 53.3% of ADE patients and in 44.0% of "no change" patients. Differences in antimicrobial treatment exposure between hospital admission and empirical treatment initiation and pre-existing MDR colonization between the ADE and "no change" cohorts were small (52.5% vs. 49.9%, and 8.8% vs. 10.5%, respectively) (Table 1).

Severity of illness at ICU admission, SOFA day 0 and SOFA day 3 had comparable distributions in the ADE and

Table 1 Patient characteristics

	Treatment			
	Tota *n* = 1495	No change *n* = 934; 62.5%	ADE *n* = 240; 16.1%	Other change *n* = 321; 21.5%
Age (years)	65 [51–75]	66 [51–75]	65 [54–74]	65 [51–76]
Male sex	919 (61.5%)	561 (60%)	152 (63.3%)	206 (64.2%)
Apache II score on ICU admission	19 [14–25]	18 [13–24]	19 [15–27]	20 [14–25]
SAPS II score on ICU admission	43 [31–57]	42 [30–56]	42 [32–56]	43 [33–59]
SOFA score on ICU admission	7 [4–10]	7 [4–10]	7 [5–10]	7 [5–10]
Hospitalization duration prior to initiation of empirical antimicrobials (days)	1 [0–5]	1 [0–5]	1 [0–3]	1 [0–6]
Antimicrobial exposure between day of hospitalization and initiation of empirical antimicrobials	775 (51.8%)	466 (49.9%)	126 (52.5%)	183 (57%)
Admission category				
Medical	996 (66.6%)	609 (65.2%)	175 (72.9%)	212 (66%)
Surgical	425 (28.4%)	275 (29.4%)	55 (22.9%)	95 (29.6%)
Trauma	70 (4.7%)	47 (5%)	9 (3.8%)	14 (4.4%)
Burns	3 (0.2%)	3 (0.3%)	0	0
Admission diagnosis[a]				
Cardiovascular/vascular	300 (20.1%)	187 (20%)	51 (21.3%)	62 (19.3%)
Digestive	351 (23.5%)	228 (24.4%)	48 (20%)	75 (23.4%)
Hematological	49 (3.3%)	32 (3.4%)	8 (3.3%)	9 (2.8%)
Metabolic	99 (6.6%)	65 (7%)	11 (4.6%)	23 (7.2%)
Neurological	298 (19.9%)	204 (21.8%)	41 (17.1%)	53 (16.5%)
Pregnancy related	14 (0.9%)	9 (1%)	3 (1.3%)	2 (0.6%)
Renal/genito-urinary	209 (14%)	111 (11.9%)	42 (17.5%)	56 (17.4%)
Respiratory	584 (39.1%)	364 (39%)	95 (39.6%)	125 (39%)
Trauma and skin	151 (10.1%)	86 (9.2%)	27 (11.3%)	38 (11.8%)
Other	50 (3.3%)	32 (3.4%)	6 (2.5%)	12 (3.7%)
Co-morbidities	1065 (71.2%)	658 (70.4%)	179 (74.6%)	228 (1%)
Chronic pulmonary disease	279 (18.7%)	163 (17.5%)	49 (20.4%)	67 (20.9%)
Chronic hepatic disease	105 (7%)	61 (6.5%)	19 (7.9%)	25 (7.8%)
Chronic renal failure	185 (12.4%)	112 (12%)	30 (12.5%)	43 (13.4%)
Diabetes mellitus	372 (24.9%)	214 (22.9%)	69 (28.8%)	89 (27.7%)
Cardiovascular disease	567 (37.9%)	353 (37.8%)	98 (40.8%)	116 (6.1%)
Solid tumor	193 (12.9%)	107 (11.5%)	36 (15%)	50 (15.6%)
Hematologic malignancy	66 (4.4%)	36 (3.9%)	16 (6.7%)	14 (4.4%)
Cerebrovascular disease	153 (10.2%)	103 (11%)	19 (7.9%)	31 (9.7%)
No data available on co-morbidities	51 (3.4%)	33 (3.5%)	2 (0.8%)	16 (5%)
Healthcare exposures[b]	691 (46.2%)	411 (44%)	128 (53.3%)	152 (47.4%)
Immunosuppression status[c]	240 (16%)	137 (14.7%)	42 (17.5%)	61 (19%)
Colonization with MDR pathogens prior to initiation of empirical antimicrobials[d]	172 (11.5%)	98 (10.5%)	21 (8.8%)	53 (16.5%)

Results are shown as *n* (%) or median [IQR] where applicable

ADE antimicrobial de-escalation, *APACHE* acute physiology and chronic health evaluation, *ICU* intensive care unit, *MDR* multidrug-resistant, *SAPS* simplified acute physiology score, *SOFA* sequential organ failure assessment

[a] Multiple admission diagnoses may be assigned to one patient

[b] Hospitalization for ≥ 2 days in the 12 months prior to study inclusion, antimicrobial exposure in the last 3 months prior to study inclusion, resident in a nursing home or long-term care facility, receiving chronic hemodialysis or receiving invasive procedures (at home or in an outpatient clinic) in the last 30 days prior to study inclusion

[c] Congenital immunodeficiency, neutropenia (absolute neutrophil count < 1000 neutrophils/µl), patient receiving corticosteroid treatment (prednisolone or equivalent > 0.5 mg/kg/day for > 3 months prior to study inclusion), solid organ transplant patient receiving immunosuppressive treatment, bone marrow transplant patient receiving immunosuppressive treatment, administration of chemotherapy within 1 year prior to study inclusion, administration of radiotherapy within 1 year prior to study inclusion, patient with autoimmune disease receiving immunosuppressive treatment, HIV or AIDS

[d] Defined as all MDR pathogens presumed to be already present on ICU admission, within 1 year prior to study inclusion combined with all MDR pathogens not present on ICU admission and detected before day 2 (day 0 is considered start date of the empirical antimicrobial therapy)

Table 2 Infection and treatment characteristics

	Treatment			
	Total *n* = 1495	No change *n* = 934; 62.5%	ADE *n* = 240; 16.1%	Other change *n* = 321; 21.5%
Infection characteristics				
Source of infection[a]				
Abdominal	272 (18.2%)	170 (18.2%)	37 (15.4%)	65 (20.2%)
Cardiovascular and intravascular	50 (3.3%)	27 (2.9%)	11 (4.6%)	12 (3.7%)
Catheter-related	46 (3.1%)	25 (2.7%)	5 (2.1%)	16 (5%)
Respiratory	717 (48%)	464 (49.7%)	106 (44.2%)	147 (45.8%)
Skin	107 (7.2%)	54 (5.8%)	23 (9.6%)	30 (9.3%)
Uro-genital	149 (10%)	76 (8.1%)	34 (14.2%)	39 (12.1%)
Other	117 (7.8%)	71 (7.6%)	22 (9.2%)	24 (7.5%)
Unknown	171 (11.4%)	119 (12.7%)	22 (9.2%)	30 (9.3%)
Diagnostic certainty (range 1–10)	10 [8–10]	10 [8–10]	10 [9–10]	10 [8–10]
Septic shock	334 (22.3%)	201 (21.5%)	71 (29.6%)	62 (19.3%)
SOFA day 0	7 [4–10]	7 [4–10]	7 [510]	7 [5–9.5]
SOFA day 3[b]	5 [3–8]	5 [38]	4 [2–8]	6 [4–9]
Microbiologically documented infection	834 (55.8%)	448 (48%)	178 (74.2%)	208 (64.8%)
Polymicrobial infection	275 (18.4%)	162 (17.3%)	39 (16.3%)	74 (23.1%)
Bacteremia	293 (19.6%)	132 (14.1%)	78 (32.5%)	83 (25.9%)
Need for source control	349 (23.3%)	192 (20.6%)	65 (27.1%)	92 (28.7%)
Effectiveness of source control on day 3 (n = number of patients who need source control)	214/349 (61.3%)	116/192 (60.4%)	49/65 (75.4%)	49/92 (53.2%)
Treatment characteristics				
Empirical antimicrobial prescription				
Monotherapy	753 (50.4%)	538 (57.6%)	43 (17.9%)	172 (53.6%)
Combination therapy	742 (49.6%)	396 (42.4%)	197 (82.1%)	149 (46.4%)
2 Antimicrobial agents	519	285	119	115
3 Antimicrobial agents	181	95	59	27
4 Antimicrobial agents	38	15	18	5
5 Antimicrobial agents	4	1	1	2
Duration of treatment for the infection under study (days)	10 [7–16]	9 [6–15]	10 [7–15]	12 [7–17]
Inappropriate empirical antimicrobial prescription[b]	151 (10%)	67 (7.2%)	10 (4.2%)	74 (23.1%)

Results are shown as *n* (%) or median [IQR] where applicable

ADE antimicrobial de-escalation, *SOFA* sequential organ failure assessment

[a] Multiple infection diagnoses may be assigned to one patient; infection focusses with an overall frequency of less than 3% were included in the 'other infection diagnosis' category and include: bone and joint infections; central nervous system infections; neutropenic fever; other unspecified infections

[b] Presence of a causative pathogen resistant to the initial agent(s) leading to addition or replacement of the empirical antimicrobial prescription

"no change" cohort. Septic shock at presentation was more prevalent in ADE compared to "no change" patients (29.6% vs. 21.5%, respectively). ADE patients had higher rates of microbiological confirmation (74.2% vs. 48%, respectively), bacteremia (32.5% vs. 14.1%, respectively) and need for source control (27.1% vs. 20.6%, respectively) compared to "no change" patients. Online supplements 9 and 10 contain details related to causative microbiology and resistance patterns. The use of empirical antimicrobial combination therapy differed between both strategies [82.1% (ADE) vs. 42.4% ("no change")], but the overall treatment durations were comparable (10 days (IQR 7–15) in ADE cohort vs. 9 days (IQR 6–15) in "no change" cohort) (Table 2).

Outcome

Delta SOFA and rate of clinical cure on day 7 were higher in ADE compared to "no change" patients [2 (IQR 0–4) vs. 1 (IQR 0–3); $p < 0.001$ and 57.9% vs. 42.7%; RR 1.34 (1.18–1.52); $p < 0.001$, respectively]. Emergence of MDR was 7.5% in ADE patients compared to 11.9% in "no change" patients (RR 0.63 (0.39–1.01); $p = 0.06$,). Infection relapse rate and antimicrobial-free days at day 28

Table 3 Empirical antimicrobial therapy

Overall use	Treatment			
	Total $n=1495$	No change $n=934$	ADE $n=240$	Other change $n=321$
Antipseudomonal penicillins + β-lactamase inhibitor	442 (29.6%)	265 (28.4%)	91 (37.9%)	86 (26.8%)
Carbapenems	389 (26%)	248 (26.6%)	65 (27.1%)	76 (23.7%)
Third-generation cephalosporins	289 (19.3%)	170 (18.2%)	57 (23.8%)	62 (19.3%)
Glycopeptides	258 (17.3%)	145 (15.5%)	72 (30%)	41 (12.8%)
Penicillins + β-lactamase inhibitor	202 (13.5%)	138 (14.8%)	24 (10%)	40 (12.5%)
Fluoroquinolones	153 (10.2%)	89 (9.5%)	26 (10.8%)	38 (11.8%)
Macrolides	119 (8%)	54 (5.8%)	41 (17.1%)	24 (7.5%)
Aminoglycosides	110 (7.4%)	39 (4.2%)	52 (21.7%)	19 (5.9%)
Nitroimidazoles	86 (5.8%)	41 (4.4%)	21 (8.8%)	24 (7.5%)
Clindamycin	75 (5%)	49 (5.2%)	12 (5%)	14 (4.4%)
Linezolid	69 (4.6%)	40 (4.3%)	17 (7.1%)	12 (3.7%)
Penicillins	40 (2.7%)	15 (1.6%)	15 (6.3%)	10 (3.1%)
Fourth-generation cephalosporins	36 (2.4%)	20 (2.1%)	9 (3.8%)	7 (2.2%)
Azoles	36 (2.4%)	22 (2.4%)	3 (1.3%)	11 (3.4%)
Echinocandins	36 (2.4%)	25 (2.7%)	5 (2.1%)	6 (1.9%)
Second-generation cephalosporins	28 (1.9%)	15 (1.6%)	7 (2.9%)	6 (1.9%)
First-generation cephalosporins	24 (1.6%)	12 (1.3%)	2 (0.8%)	10 (3.1%)
Tetracyclines	22 (1.5%)	13 (1.4%)	2 (0.8%)	7 (2.2%)
Tigecycline	22 (1.5%)	13 (1.4%)	5 (2.1%)	4 (1.2%)
Polymyxins	19 (1.3%)	9 (1%)	3 (1.3%)	7 (2.2%)
Folate pathway inhibitors	18 (1.2%)	13 (1.4%)	1 (0.4%)	4 (1.2%)
Daptomycin	10 (0.7%)	7 (0.7%)	1 (0.4%)	2 (0.6%)
Polyenes	4 (0.3%)	3 (0.3%)	1 (0.4%)	0
Fosfomycin	3 (0.2%)	2 (0.2%)	0	1 (0.3%)
Rifampin	3 (0.2%)	1 (0.1%)	2 (0.8%)	0
Fifth-generation cephalosporins	1 (0.07%)	0	1 (0.4%)	0
Antifungal antimetabolites	1 (0.07%)	1 (0.1%)	0	0
Monobactams	1 (0.07%)	1 (0.1%)	0	0
Monotherapy—top 10	***n*=753**	***n*=538**	***n*=43**	***n*=172**
Antipseudomonal penicillins + β-lactamase inhibitor	234 (31.1%)	165 (30.7%)	18 (41.9%)	51 (29.7%)
Carbapenems	159 (21.1%)	112 (20.8%)	12 (27.9%)	35 (20.3%)
Penicillins + β-lactamase inhibitor	130 (17.3%)	102 (19%)	4 (9.3%)	24 (14%)
Third-generation cephalosporins	89 (11.8%)	64 (11.9%)	4 (9.3%)	21 (12.2%)
Fluoroquinolones	48 (6.4%)	35 (6.5%)	1 (2.3%)	12 (7%)
Glycopeptides	16 (2.1%)	11 (2%)	1 (2.3%)	4 (2.3%)
First-generation cephalosporins	16 (2.1%)	9 (1.7%)	1 (2.3%)	6 (3.5%)
Second-generation cephalosporins	13 (1.7%)	8 (1.5%)	1 (2.3%)	4 (2.3%)
Fourth-generation cephalosporins	12 (1.6%)	9 (1.7%)	1 (2.3%)	2 (1.2%)
Tetracyclines	6 (0.8%)	2 (0.4%)	0	4 (2.3%)
Combination therapy—top 10	***n*=742**	***n*=396**	***n*=197**	***n*=149**
Glycopeptides	242 (32.6%)	134 (33.8%)	71 (36%)	37 (24.8%)
Carbapenems	230 (31%)	136 (34.3%)	53 (26.9%)	41 (27.5%)
Antipseudomonal penicillins + β-lactamase inhibitor	208 (28%)	100 (25.3%)	73 (37.1%)	35 (23.5%)
Third-generation cephalosporins	200 (27%)	106 (26.8%)	53 (26.9%)	41 (27.5%)
Macrolides	114 (15.4%)	49 (12.4%)	41 (20.8%)	24 (16.1%)

Table 3 (continued)

Combination therapy—top 10	*n* = 742	*n* = 396	*n* = 197	*n* = 149
Aminoglycosides	107 (14.4%)	37 (9.3%)	52 (26.4%)	18 (12.1%)
Fluoroquinolones	105 (14.2%)	54 (13.6%)	25 (12.7%)	26 (17.4%)
Nitroimidazoles	84 (11.3%)	41 (10.4%)	21 (10.7%)	22 (14.8%)
Penicillins + β-lactamase inhibitor	72 (9.7%)	36 (9.1%)	20 (10.2%)	16 (10.7%)
Clindamycin	72 (9.7%)	46 (11.6%)	12 (6.1%)	14 (9.4%)

were comparable in both treatment groups. Both median number ICU and hospital days were smaller in ADE than in "no change" patients [7 days (IQR 4–12) vs. 9 days (IQR 5–19); $p < 0.001$ and 19 days (IQR 10–28) vs. 27 days (IQR 14–28); $p < 0.001$, respectively]. Mortality at day 28 was 15.8% in ADE and 19.4% in "no change" patients (RR 0.83 (0.6–1.14); $p = 0.27$,). Details on patient outcome are described in Table 5.

Analysis of clinical cure in ADE patients using inverse probability weighting

The estimated relative risk of survival and clinical cure, survival without clinical cure and mortality on day 7 in ADE patients versus patients in whom ADE was not performed on day 3 or earlier were 1.37 (95% CI 1.14–1.64), 0.66 (95% CI 0.47–0.92) and 1.32 (95% CI 0.95–1.83), respectively. IP weighted risks and detailed results of subgroup and sensitivity analyses can be found in online supplement 11. Post hoc power and sample size calculations are available in online supplement 12.

Discussion

In this study, investigating empirical antimicrobial therapy for patients with bacterial infections in the ICU, we found that ADE was infrequently applied, despite the fact that combination therapy was prescribed in half of the patients and one-quarter of prescriptions contained a carbapenem. Our observational effect estimate of ADE on clinical cure suggested that ADE performed within 3 days following empirical prescription was not worse compared to no-ADE after adjustment for potential bias and confounding. However, residual confounding remains possible.

Previous studies reported ADE rates between 25 and 81% [4, 34]. Studies with higher percentages of ADE often included patients with lower severity of illness compared to our study or focused on patients in whom ADE was possible due to the broadness of the empirical spectrum and the susceptibility pattern of the causative pathogens [4, 35]. Other studies included only patients with specific types of infections or pathogens [36–38]. These were usually single-center studies, conducted in centers with a special interest in antimicrobial stewardship. Instead, we studied ICU patients and included all empirical antimicrobial therapies, independent of culture results, and therefore provide a more realistic picture of ADE in routine clinical practice.

Table 4 Motivation for ADE

	N (%)
Replacement of an antimicrobial agent by another drug with the intention to narrow the spectrum of activity *(115 ADE treatment courses) (multiple answers possible)*	
Gram's stain results	13/115 (11.3)
Rapid polymerase chain reaction technology	3/115 (2.6)
Identification of the causative pathogen	67/115 (58.3)
Susceptibility pattern of the causative pathogen	54/115 (47)
Negative culture results	10/115 (8.7)
Improvement in organ function	14/115 (12.2)
Improvement in inflammation biomarkers	11/115 (9.6)
Better compliance with local guidelines	11/115 (9.6)
Discontinuation of one or more antimicrobials of the empirical combination therapy which were considered by the treating physician to be not (or no longer) necessary *(156 ADE treatment courses) (only one answer possible)*	
In case of microbiologically confirmed infection, causative pathogen is covered by concomitant antimicrobial therapy	67/156 (42.9)
In case of microbiologically confirmed infection, causative pathogen(s) is not covered by this antibacterial or antifungal agent	30/156 (19.2)
In case of non-microbiologically confirmed infection, this antibacterial or antifungal agent is considered not to be essential	65/156 (41.7)

ADE antimicrobial de-escalation

Another explanation for the lower than expected ADE rate could be the strict definition of ADE that was used, i.e., ADE applied within the first 3 days of initiation of empirical therapy. Previous studies defined timing of ADE in various ways, e.g., within 3 or 5 days following treatment initiation, or aligned with the timing of microbiology results [15, 36, 37, 39–45]. Expanding the ADE time-window to 5 and 7 days would have increased the ADE rate to 21% and 23%, respectively.

Our pragmatic approach of defining ADE based on the intention of the treating clinician to narrow the antimicrobial spectrum was a carefully considered decision. Until now, there is no consensus regarding the hierarchy of antimicrobials and although there have been proposals for ranking antimicrobials, for instance within certain classes, e.g., beta-lactam antibiotics, this is difficult—if not impossible—to apply to all antimicrobials [33, 46]. We observed that 91% of the de-escalated beta-lactam prescriptions in our dataset complied with the ranking developed by Weiss et al. [33]. However, within the ADE population, this ranking definition was only applicable in 31%.

Clinical cure on day 7 in patients following ADE has not been studied before. We attempted to control for potential confounding and performed multiple sensitivity analyses (e.g. adjustment for SOFA day 0, inappropriate empirical therapy and MDR colonization) which did not significantly affect our results. We have to acknowledge however that our data are observational and it is therefore impossible to capture all center, physician, patient and infection-related factors that may impact both treatment-related decision making and our primary outcome. Particular factors related to empirical treatment and infection characteristics appeared to facilitate ADE, e.g., 2 or more empirical agents, adequate empirical prescription, effective source control, improving SOFA scores on day 3 and the detection of causative pathogens to guide ADE. Previous observations indicate that ADE is undertaken more often in patients with an already favorable clinical course, e.g., improving SOFA score, a phenomenon that was also observed in our study [4]. Early clinical improvement may also explain the shorter lengths of stay which we observed in ADE patients compared to patients with no treatment change, a finding that has been inconsistently documented in previous studies and is in contradiction with the results of Leone et al. [4, 15, 34, 37, 39–41, 44]. In contrast to several studies in the literature, we found no difference in mortality between the ADE and "no change" patients [4, 13, 14]. Again, it is generally assumed that ADE is typically performed in patients who are improving or have a good prognosis; therefore, the survival advantage reported in the literature cannot be considered a direct causal effect.

The impact of ADE on MDR emergence has been investigated sparsely and no study has found an association between ADE and MDR occurrence in either direction [15, 34, 41, 44]. We could not demonstrate any difference in the emergence of MDR pathogens following ADE; however, our study was not designed to make firm conclusions about this aspect.

The strengths of the study include the number of patients and the global perspective. With data of 152 centers worldwide, we provide a detailed picture of the practice of ADE as a stewardship intervention in real-life situations.

The limitations of the study are the heterogeneous patient population in terms of geography, types of infections and methods of antimicrobial stewardship. In addition, individual centers only included a limited number of patients over a short-time period. Details on the reasons for not performing ADE were not collected in a prospective way; as such, an explanation for the observed low ADE rate cannot be given. Study design was complicated by the lack of a universally accepted ADE definition. The low quality of evidence supporting the recent ESICM/ESCMID consensus definition of ADE underlines the ongoing controversy [7]. Our definition was reached by consensus and intended to capture real-world practices. As mentioned earlier, expanding the ADE time window to 5 or 7 days would have increased the ADE rate. A priori sample size calculations were complicated by the lack of clinical cure rates in the literature and by the fact that standard sample size formulas do not readily apply to observational analyses that adjust for confounding. Our post hoc analyses, however, may be informative for the planning of future studies, either observational or randomized. Maximal efforts were undertaken to reduce bias by using appropriate statistical methods in terms of target trial emulation. However, it was not possible to determine the exact time when the treating clinicians received information about causative microbiology and acted upon this. Therefore, we made the assumption that this information was available from day 2. Similarly, susceptibility patterns of the causative pathogens could not be included in the outcome analysis. Considering the aforementioned reasons, residual confounding may exist. Finally, clinical cure was evaluated quite early in the clinical course of the ICU patient (day 7) and our analyses do not permit any statements regarding other important outcome measures such as, e.g., infection relapse.

In conclusion, this study showed that ADE within the first 3 days following empirical antimicrobial therapy for suspected bacterial infection in the ICU is only applied in 16% of patients. Our observational effect estimate of ADE—as it was applied and defined in the study

Table 5 Patient outcome

	Total $n=1495$	No change $n=934$; 62.5%	ADE $n=240$; 16.1%	Other change $n=321$; 21.5%	ADE vs no change p value		Other change vs no change p value		% of available data
Δ SOFA[a,b]	1 [0–3]	1 [0–3]	2 [0–4]	0 [-1; 2]	< 0.001		< 0.001		90
Number of days in the ICU[c]									
On vasoactive drugs	2 [0–5]	2 [0–5]	2 [0–4]	3 [0–5]	0.32		0.003		98.3
On invasive mechanical ventilation	3 [0–9]	3 [0–9]	2 [0–8]	4 [0–9]	0.05		0.31		98.4
Receiving renal replacement therapy	0 [0–0]	0 [0–0]	0 [0–0]	0 [0–0]	0.48		0.002		98.5
Antimicrobial-free days (28 days after onset of infection)[d] (n = 1166)	13 [4–19]	13 [4–20]	14 [5–20]	9.5 [2–16]	0.29		< 0.001		85.5
Number of days in ICU following onset of infection under study[c,e] (n = 1219)	8 [5–18]	9 [5–19]	7 [4–12]	10 [5–24]	< 0.001		0.09		99.9
Number of days in hospital following onset of infection under study[c,f] ($n=1166$)	26 [13–28]	27 [14–28]	19 [10–28]	28 [16–28]	< 0.001		0.26		99.9
					p value	Relative risk (95% CI)	p value	Relative risk (95% CI)	
Clinical cure on day 7[g]	650 (43.5%)	399 (42.7%)	139 (57.9%)	112 (34.9%)	< 0.001	1.34 (1.18–1.52)	0.03	0.83 (0.71–0.98)	95.9
Infection relapse[(c)]	103 (6.9%)	61 (6.5%)	22 (9.2%)	20 (6.2%)	0.24	1.37 (0.86–2.18)	0.96	0.96 (0.59–1.56)	96.5
Infections other than the infection under study or a relapse infection[c]	184 (12.3%)	109 (11.7%)	38 (15.8%)	37 (11.5%)	0.12	1.34 (0.95–1.89)	1	0.99 (0.69–1.40)	95.5
Emergence of MDR pathogens between day 2 and day 28[h]	192 (12.8%)	111 (11.9%)	18 (7.5%)	63 (19.6%)	0.06	0.63 (0.39–1.01)	0.001	1.63 (1.23–2.16)	98.7
28-day mortality	296 (19.8%)	181 (19.4%)	38 (15.8%)	77 (24%)	0.27	0.83 (0.60–1.14)	0.07	1.26 (0.99–1.59)	97.8
ICU mortality	243 (16.3%)	145 (15.5%)	28 (11.7%)	70 (21.8%)	0.18	0.76 (0.52–1.11)	0.009	1.42 (1.10–1.84)	97.8

Results are shown as *n* (%) or median [IQR] where applicable. *ADE* antimicrobial de-escalation, *ICU* intensive care unit, *MDR* multidrug-resistant

[a] In subgroup of patients alive at day 3, $n=1420$

[b] Δ SOFA is SOFA score on day 0 minus SOFA score on day 3 of infection

[c] Measured from inclusion (day 0) to day 28

[d] In subgroup of patients alive at day 28

[e] In subgroup of ICU survivors

[f] In subgroup of hospital survivors

[g] Clinical cure is defined as survival and resolution of all signs and symptoms related to the infection under study

[h] MDR definitions are available in the Supplement (eTable 3), Emergence of MDR following the initiation of empirical treatment was defined as detection of MDR pathogens on day 2 or later during the 28-day follow-up period and not present before

population—on clinical cure suggested that ADE was not worse compared with no-ADE. As ADE was mainly performed in patients who were improving clinically, residual confounding by unmeasured factors cannot be ruled out.

Concerted efforts based on specific patient, infection and microbiology-related data and guided by an antimicrobial stewardship team are likely needed to promote ADE. Further research focusing on antimicrobial prescribing behavior is however required to elucidate barriers to ADE.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-020-06111-5) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

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