BRIEF RESEARCH COMMUNICATION

Modification of Initial Empirical Antibiotic Prescription and its Impact on Patient Outcome: Experience of an Indian Intensive Care Unit

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Abstract

Introduction: Data on the overall impact of antibiotic modification following initial empiric prescription in both culture-positive and culture-negative critically ill patients are exiguous.

Materials and methods: In a retrospective analysis of "ANT-CRITIC" study, we classified ICU patients receiving empirical antibiotics who remained in the ICU for >72 hours or till availability of culture results (whichever is longer) into five groups based on culture results and antibiotic modification: negative culture, no change (group I), positive culture, no change (group II), positive culture, de-escalation (group III), positive culture, escalation (group IV) and negative culture, antibiotic modification (group V). Baseline variables and clinical outcomes were compared. Logistic regression analysis was performed to look for independent variables associated with mortality.

Results: 276 prescription episodes were analyzed. Group II was associated with worsening organ dysfunction at 72 hours, lower clinical cure rate at day 7, and higher hospital mortality. There was an independent association between group II prescription and hospital mortality [adjusted OR 2.774 (CI 1.178–6.533), $p = 0.02$]. Group III received longer duration of antibiotic (mean duration = 8.27 ± 4.11 days, median duration = 7 days [IQR 5–11]).

Conclusion: Outcomes of critically ill infected patients differ significantly when they are classified based on culture result and antibiotic modification pattern.

Keywords: Antibiotic stewardship, Culture-negative sepsis, De-escalation, Empirical antibiotic.

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Highlights

- This study aims to look for any association between antibiotic modification strategy following empirical prescription and hospital outcome.
- Failure to de-escalate was independently associated with higher hospital mortality.
- De-escalation group had longer antibiotic course.
- Culture-negative sepsis could be classified into two distinct subsets with clearly different clinical course and prognosis.

Introduction

Empiric prescription of broad-spectrum antibiotics is common in intensive care units (ICUs), aiming to improve the appropriateness of initial antibiotic regimen, which in-turn is associated with better outcome in infected critically ill patients.[1] However, this strategy comes at the cost of often unnecessary prescription, adverse effects of specific antibiotic, and ultimate societal cost of increasing antimicrobial resistance (AMR).[2] Duration of antibiotic exposure is directly correlated with subsequent development of AMR.[3] Antimicrobial de-escalation, by either stopping the nonpivotal antibiotic or by narrowing down the spectrum of pivotal antibiotic or by both, has been suggested as a strategy to reduce the harm from initial broad-spectrum antimicrobial prescription, including burden of AMR.[4] In observational studies, de-escalation strategy was found to be safe and may be associated with decreased mortality, albeit with several residual confounding factors.[5,6] However, in the only randomized trial published till date, de-escalation strategy was not associated with decreased mortality or shorter hospital stay, but was associated with longer duration of antibiotic therapy and increased superinfection.[7] The perceived beneficial effect of de-escalation on AMR has also not been seen consistently in the available literature.[8,9] Moreover, de-escalation strategy may not be feasible in many ICU patients either because patients are not clinically stable or de-escalation is not feasible because of the resistance pattern or nonavailability of positive culture result.[1,10] Several studies have compared culture-negative sepsis with culture-positive ones.[11–13] In one study, culture-negative sepsis had worse outcome, whereas, in others, outcomes were better. Importantly, clinical course of all patients with culture-negative sepsis may not be the same; initial antibiotic

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prescriptions are still modified in many of them, while others continue with the initial regimen.[1]

Given the limited available data on the overall impact of antibiotic modification pattern both in culture-positive and culture-negative sepsis, on the outcome of critically ill patients, especially in Indian scenario, we conducted a retrospective review of "ANTibiotic Prescription Pattern in CRITICally Ill Patients (ANT-CRITIC)" study database published in this journal.[1] "ANT-CRITIC" was a prospective longitudinal study, conducted between 01 June 2020 and 31 July 2021 in the 18-bedded ICU of Fortis-Escorts Hospital, Faridabad, Haryana. "ANT-CRITIC" study looked into all aspects of antibiotic prescription process in an Indian ICU.

Materials and Methods

Ethical approval was obtained for the "ANT-CRITIC" study from the Institutional Ethics Committee (EC/2020/27, 17/06/2020), and the study was registered with the Clinical Trial Registry of India (CTRI/2020/06/026257). During the study period, a total of 502 patients (out of 1014 admitted) received 552 new antibiotic prescriptions during their ICU stay. All new antibiotic prescriptions were assessed for baseline variables at ICU admission (including age, gender, type of admission, severity of illness, and comorbidities), at the time of antibiotic prescription [ICU days before prescription, type of prescriber, and type of prescription – empirical or definitive, hospital-acquired infection, site of infection, and Sequential Organ Failure Assessment (SOFA) score], any antibiotic modifications during the course of treatment with or without culture report, and SOFA score at 72 hours after prescription and outcome (including clinical cure rate at 7 days, duration of antibiotic for the particular episode, hospital outcome, ICU and hospital length of stay, etc.). All new prescription episodes were evaluated for inclusion and exclusion criteria to be included in the present analysis.

Inclusion and Exclusion Criteria

Empirical prescription episodes in which patients stayed in the ICU for at least 72 hours or till relevant culture results were available (whichever was longer) following initial prescription were included in further analysis. The following prescription episodes were excluded from further analysis:

- No evidence of bacterial infection as defined by preexisting criteria.[14]
- Definitive therapy.
- Relevant cultures not sent before antibiotic administration.
- Death before 72 hours or before culture result.
- Shifting out of the ICU before 72 hours or before culture result.

Data Analyzed

All episodes fulfilling inclusion and exclusion criteria were classified into one of five following groups based on the culture results and any change in initial antibiotic prescription:

- Group I: No bacterial growth and no change in antibiotics.
- Group II: Bacterial growth and no change in antibiotics – no scope for de-escalation (IIA) or patient clinically not stable (IIB).
- Group III: Bacterial growth and de-escalation of antibiotics–stoppage of non-pivotal antibiotics (IIIA) or narrowing of the spectrum (IIIB) or both stoppage of nonpivotal antibiotics and narrowing of the spectrum (IIIC).[4] Antibiotics were ranked according to the scoring system suggested by Madaras-Kelly and colleagues for the purpose of de-escalation.[15]
- Group IV: Bacterial growth and escalation of antibiotics.
- Group V: No bacterial growth and change in antibiotics.

Baseline variables at ICU admission (including age, gender, APACHE-II score, Charlson's comorbidity index, and the underlying chronic conditions), variables at prescription (SOFA score, ICU day at prescription, type of prescriber, timing of prescription, site of infection, physiological variables, procalcitonin, lactate, and hospital-acquired infection), and clinical outcome [including change in SOFA score at 72 hours from the baseline value (SOFA), rate of clinical cure at day 7, hospital mortality, and duration of antibiotics] were compared between different groups. Bivariate and multivariate analysis were performed to look for any association between hospital mortality and baseline variables or persistence of organ dysfunction at 72 hours (SOFA) or pattern of antibiotic modification.

Statistical Analysis Plan

Categorical variables were presented as number and percentage (%). Mean ± SD and median with 25th and 75th percentiles (interquartile range, IQR) were used to present quantitative data with normal distribution and with non-normal distribution, respectively. Data normality was checked by using Kolmogorov–Smirnov test. The following statistical tests were applied:

- Qualitative variables were analyzed using Chi-square test. If any cell had an expected value of <5, then Fisher's exact test was used.
- Quantitative and normally distributed variables were analyzed using ANOVA.
- Quantitative and non-normally distributed variables were analyzed using Kruskal–Wallis test.
- Univariate and multivariate logistic regressions were used to find out variables independently associated with hospital mortality.

The data entry was done in the Microsoft EXCEL spreadsheet, and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, *p*-value of less than 0.05 was considered significant.

Results

Out of 552 prescription episodes, 276 episodes were excluded from further analysis by prespecified criteria as shown in Figure 1. The remaining 276 prescription episodes were classified into five groups according to culture result and antibiotic modification pattern. Initial empirical antibiotics prescription in these 276 prescription episodes is provided in Supplementary Table 1.

Comparison of Clinical Characteristics

As shown in Table 1, there were statistically significant differences in age, Charlson's comorbidity index, and diabetes mellitus at ICU admission. Patients in group I and group V were more likely to receive antibiotic prescription earlier in their ICU stay. Except respiratory rate, other physiological parameters were not statistically different between groups that include organ failure score, lactate, or septic shock at initiation. There were significant differences in the site of infection with patients in group III more likely to have lungs as the source (60.98%). Significantly higher percentage of infections were hospital-acquired in groups III and IV (78.05% and 65.63%, respectively).

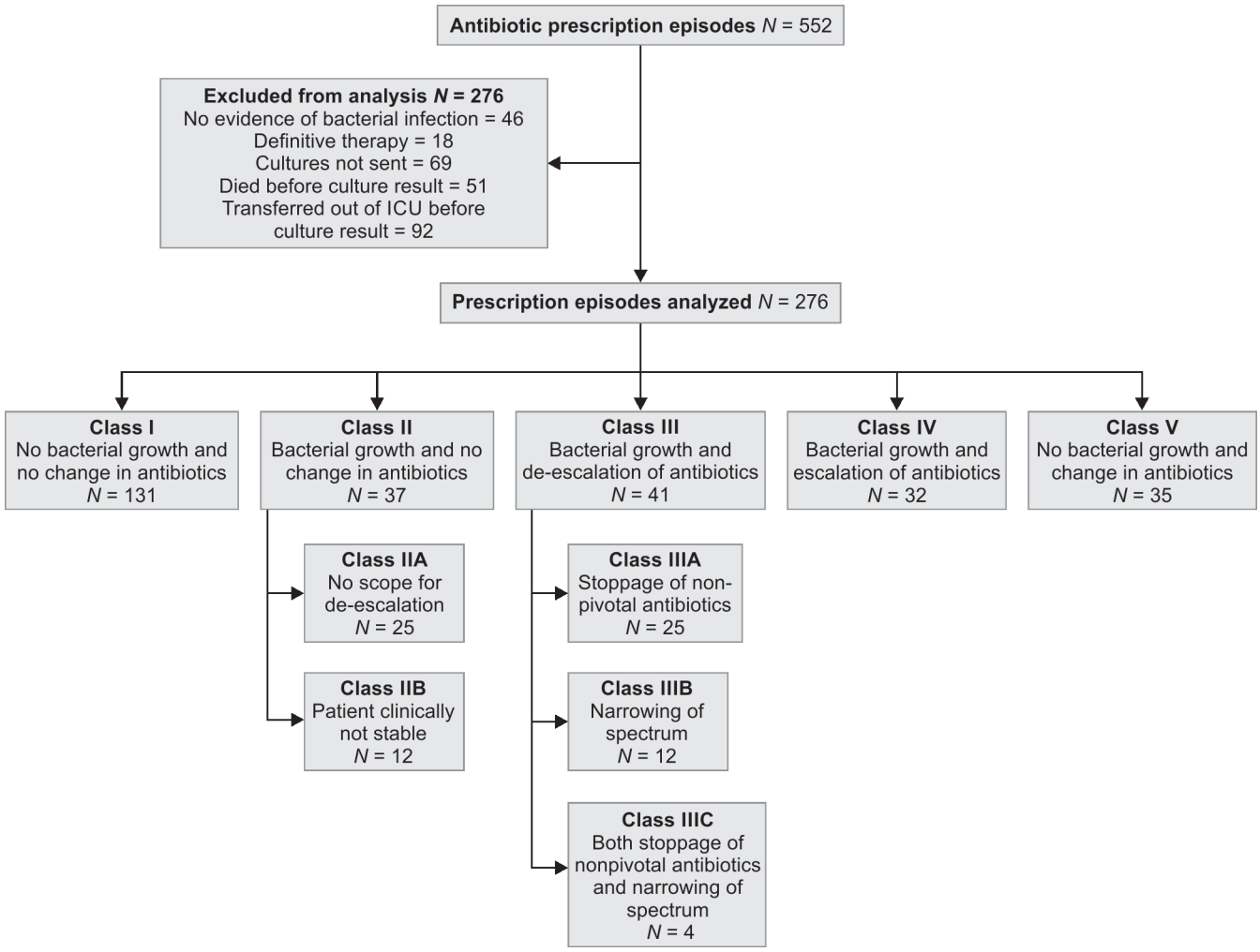

Fig. 1: Antibiotic prescription episodes classified according to culture result and modification of initial empirical prescription

There was significant worsening in SOFA score at 72 hours in groups II, IV, and V. There were significant between-group differences in both rate of clinical cure at day 7 and hospital mortality—lower cure rate and higher mortality observed in groups II, IV, and V. Groups also differ significantly in terms of duration of antibiotic—group III getting longer duration of treatment [mean duration = 8.27 ± 4.11 days, median duration = 7 days (IQR 5–11)] (Table 1).

Predictors of Hospital Mortality

Five baseline variables were found to be independently associated with increase in hospital mortality: male sex [adjusted OR 2.893 (CI 1.455 – 5.748), $p = 0.002$], underlying chronic liver disease [adjusted OR 4.872 (CI 1.694 – 14.013), $p = 0.003$], respiratory rate [adjusted OR 1.053 (CI 1.012 – 1.097), $p = 0.012$], hospital-acquired infection [adjusted OR 2.040 (CI 1.105 – 3.766), $p = 0.023$], and SOFA score at prescription [adjusted OR 1.150 (CI 1.050 – 1.260), $p = 0.003$] (Table 2).

In the univariate analysis, group II and group III prescription patterns were more likely to be associated with hospital mortality when compared with group I pattern. However, in the multivariate analysis, only group II prescription pattern was independently associated with mortality [adjusted OR 2.774 (CI 1.178 – 6.533), $p = 0.02$] (Table 2).

Discussion

In this study, investigating the effects of different antimicrobial modification strategy on patients' outcome, we could establish an independent association between the strategy of no de-escalation, following positive culture result and increased hospital mortality. Our observation of longer duration of antibiotic treatment in the de-escalation group reconfirms findings from published literature. We also observed two distinct subsets of patients with cultural-negative sepsis having clearly different clinical course and outcome.

In a systematic review and meta-analysis of 14 studies, the authors concluded that de-escalation strategy is overall protective against mortality.[5] However, they also pointed out that de-escalation is more likely to be performed when more agents were used initially, in the absence of multidrug-resistant pathogens or when there is an improving severity of score. In our study, the group of patients with culture-positive sepsis in whom de-escalation could not be done had the worst prognosis. However, these patients were also clinically unstable with worsening SOFA score at 72 hours or else de-escalation was not feasible because only a single agent was used initially against multi-drug-resistant pathogens isolated subsequently. In a more recently published international DIANA study, de-escalation

Table 1: Comparison of clinical characteristics at the ICU admission, at the time of antibiotic prescription, and clinical outcome between groups

Parameters	*Class I (N = 131)*	*Class II (N = 37)*	*Class III (N = 41)*	*Class IV (N = 32)*	*Class V (N = 35)*	*Total (N = 276)*	*p*
Characteristics at ICU admission							
Age (years)	63.24 ± 15.43	66.73 ± 14.48	66.54 ± 13.54	66.84 ± 13.7	55.23 ± 15.76	63.6 ± 15.21	0.004‡
Female sex	44 (33.59%)	12 (32.43%)	15 (36.59%)	7 (21.88%)	8 (22.86%)	86 (31.16%)	0.499†
Diabetes mellitus	49 (37.40%)	25 (67.57%)	13 (31.71%)	16 (50%)	10 (28.57%)	113 (40.94%)	0.003†
Chronic liver disease	12 (9.16%)	2 (5.41%)	1 (2.44%)	3 (9.38%)	3 (8.57%)	21 (7.61%)	0.671*
Chronic kidney disease	12 (9.16%)	5 (13.51%)	3 (7.32%)	3 (9.38%)	4 (11.43%)	27 (9.78%)	0.887*
COAD	10 (7.63%)	1 (2.70%)	4 (9.76%)	2 (6.25%)	0 (0%)	17 (6.16%)	0.348*
Chronic heart failure	6 (4.58%)	1 (2.70%)	1 (2.44%)	1 (3.13%)	4 (11.43%)	13 (4.71%)	0.452*
Immunocompromised	4 (3.05%)	1 (2.70%)	3 (7.32%)	1 (3.13%)	2 (5.71%)	11 (3.99%)	0.705*
APACHE-II	17.69 ± 8.26	16.14 ± 6.68	17.51 ± 7.64	17.88 ± 6.99	17.63 ± 8.29	17.47 ± 7.8	0.879‡
Charlson's	4.02 ± 2.71	4.43 ± 2.49	4.54 ± 2.12	4.75 ± 2.33	2.91 ± 2.24	4.1 ± 2.54	0.018‡
Characteristics at the time of antibiotic prescription							
Prescribed by							
Critical care fellow	31 (23.66%)	10 (27.03%)	10 (24.39%)	6 (18.75%)	9 (25.71%)	66 (23.91%)	0.957*
ICU consultant	84 (64.12%)	23 (62.16%)	29 (70.73%)	22 (68.75%)	22 (62.86%)	180 (65.22%)	
Non-ICU consultant	16 (12.21%)	4 (10.81%)	2 (4.88%)	4 (12.50%)	4 (11.43%)	30 (10.87%)	
Out of hour prescription	52 (39.69%)	16 (43.24%)	13 (31.71%)	9 (28.13%)	17 (48.57%)	107 (38.77%)	0.384†
ICU days before prescription	0 (0–1)	1 (0–5)	1 (0–6)	1 (0–4.5)	0 (0–1)	0 (0–2)	0.0008§
Temperature	99.2 ± 1.7	99.7 ± 1.6	100.1 ± 1.9	99.6 ± 1.4	99.4 ± 2.1	99.5 ± 1.7	0.075‡
Heart rate	104.3 ± 23.4	108.76 ± 19.1	106.8 ± 23.0	104.2 ± 23.5	107.9 ± 25.4	105.7 ± 23.0	0.796‡
Respiratory rate	24 (21–29)	24 (20–29)	26 (20–32)	24.5 (22.7–30)	26 (23.5–31)	24 (21.7–30)	0.59§
Vasopressor support							
None	91 (69.47%)	22 (59.46%)	25 (60.98%)	23 (71.88%)	20 (57.14%)	181 (65.58%)	0.535*
Low-dose	24 (18.32%)	11 (29.73%)	7 (17.07%)	6 (18.75%)	10 (28.57%)	58 (21.01%)	
High-dose	16 (12.21%)	4 (10.81%)	9 (21.95%)	3 (9.38%)	5 (14.29%)	37 (13.41%)	
Septic shock	21 (16.03%)	4 (10.81%)	7 (17.07%)	2 (6.25%)	6 (17.14%)	40 (14.49%)	0.598*
Lactate	1.4 (0.9–2)	1.5 (1–1.9)	1.6 (0.9–2.6)	0.95 (0.8–1.5)	1.5 (0.8–2.4)	1.3 (0.9–2.1)	0.235§
TLC	138,00 (9750–207,00)	14,900 (10,000–20,600)	14,400 (9975–22,075)	13,850 (9700–20,150)	15,800 (8400–18,350)	14,200 (9600–20,600)	0.888§
Platelets	0.99 (0.42–5.6)	2.3 (0.55–9.44)	0.9 (0.436–11.27)	1.32 (0.516–3.72)	3.96 (0.838–8.965)	1.28 (0.432–6.948)	0.332§
Source of infection							
Unknown	21 (16.03%)	1 (2.70%)	1 (2.44%)	1 (3.13%)	2 (5.71%)	26 (9.42%)	<0.0001*
Bloodstream	2 (1.53%)	2 (5.41%)	4 (9.76%)	3 (9.38%)	1 (2.86%)	12 (4.35%)	
CNS	4 (3.05%)	1 (2.70%)	1 (2.44%)	0 (0%)	2 (5.71%)	8 (2.90%)	
Intra-abdominal	9 (6.87%)	0 (0%)	0 (0%)	0 (0%)	7 (20%)	16 (5.80%)	
Lung	62 (47.33%)	15 (40.54%)	25 (60.98%)	17 (53.13%)	21 (60%)	140 (50.72%)	
Soft tissue	9 (6.87%)	1 (2.70%)	1 (2.44%)	0 (0%)	0 (0%)	11 (3.99%)	

Urinary tract	24 (18.32%)	17 (45.95%)	9 (21.95%)	11 (34.38%)	2 (5.71%)	63 (22.83%)	
Hospital acquired	53 (40.46%)	22 (59.46%)	32 (78.05%)	21 (65.63%)	12 (34.29%)	140 (50.72%)	<0.0001[†]
ΔSOFA score on day 0	6 (4–8)	6 (4–9)	6 (5–9)	6 (4.75–10.25)	6 (4–9)	6 (4–9)	0.781[§]
Clinical outcome							
ΔSOFA at 72 hours							
Mean ± SD	0.95 ± 3.22	−0.67 ± 2.82	0.76 ± 3.53	−0.59 ± 4.25	−0.62 ± 4.12	0.32 ± 3.53	0.007[§]
Median (IQR)	1 (0–2)	0 (−2 to 1)	1 (−1 to 3)	0 (−3 to 1)	−1 (−4 to 2.25)	0 (−1 to 2)	0.007[§]
Clinical cure at day 7	98 (74.81%)	20 (54.05%)	32 (78.05%)	18 (56.25%)	18 (51.43%)	186 (67.39%)	0.007[†]
Hospital mortality	36 (27.48%)	18 (48.65%)	10 (24.39%)	13 (40.63%)	17 (48.57%)	94 (34.06%)	0.02[†]
Duration of antibiotic							
Mean ± SD	5.68 ± 2.67	6.14 ± 2.99	8.27 ± 4.11	7.53 ± 4.37	6.77 ± 4.18	6.48 ± 3.5	0.002[§]
Median (IQR)	5 (4–7)	6 (4–8)	7 (5–11)	6 (4–10.5)	5 (4–7.5)	6 (4–8)	0.002[§]
Range	1–15	2–14	2–17	2–18	2–19	1–19	

[*]Fisher's exact test. [†]Chi-square test. [‡]ANOVA, APACHE-II, acute physiology and chronic health evaluation-II; COAD, chronic obstructive airway disease; CNS, central nervous system; ICU, intensive care unit; IQR, interquartile range; [§]Kruskal–Wallis Test; SOFA, sequential organ failure assessment

strategy was found to be safe, but the authors pointed toward likely residual confounders to this effect.[6]

Appropriate initial antibiotic prescription is strongly associated with better clinical outcome in multiple previous studies.[16] However, in our study, this positive association was not found to be uniform. While group III patients (initial appropriate antibiotic and de-escalation) had better prognosis compared with group IV patients (initial inappropriate antibiotic and escalation), group II patients (initial appropriate antibiotic and no de-escalation) had similar poor outcome as group IV patients. Both group II and group IV patients had worsening of organ function at 72 hours after starting antibiotic. This variable effect cannot be explained by delayed antibiotic administration alone as all commonly used antibiotics are available in the study ICU itself and perhaps point toward other patient-related factors. A larger multicenter study in future may be able to throw more light on this crucial issue.

In a multicenter randomized trial, Leone and colleagues compared a strategy of de-escalation with narrowing down of the spectrum for pivotal antibiotic versus continuation strategy.[7] The trial failed to show any difference in ICU length of stay between two groups, which was the primary outcome measure. Interestingly, the de-escalation group had significantly longer duration of antibiotic days compared with the control group [median, 9 days versus 7.5 days, p=0.03]. We also observed longer antibiotic days in the de-escalation group compared with other groups. The longer antibiotic days in the de-escalation group may possibly be explained either by survival effect (patients survived longer to receive antibiotic) or due to perceived harmlessness of continuing with narrower-spectrum antibiotic, as pointed out by Bassetti et al.[16] The possibility of "errors in counting total days of therapy" is an unlikely explanation in our study.[17]

In an analysis of a large nationwide database from the United States, patients with culture-negative sepsis had more acute organ dysfunction as well as increased mortality and this effect on mortality was independent from other confounding factors.[11] In contrast, in-hospital mortality, mechanical ventilation days, and hospital length of stay were significantly lower in culture-negative patients with healthcare-associated pneumonia in a single-center study.[12] However, a single-center study from Korea, failed to show any difference in clinical outcome between culture-negative and culture-positive sepsis.[13] Two different subsets of culture-negative patients with differing outcomes observed in our study, can possibly provide an insight into the likely explanation for variable outcomes seen in earlier studies. In one subset, initial antibiotics were never modified, and in these subgroups, organ dysfunction improved at 72 hours with higher rate of clinical cure at day 7 as well as lower hospital mortality. In contrast, the subset of patients in whom antibiotics were modified had worsening organ dysfunction at 72 hours, lower clinical cure rate at day 7, and higher hospital mortality. We believe that there is a scope for early stoppage of empirical antibiotics in the former subgroup and biomarker-guided approach may help in achieving this target.[14,18]

Conclusion

Our data provides deeper insight into the antibiotic modification process in the ICU following initial empiric treatment. The inability to de-escalate culture-positive patients with appropriate initial antimicrobial treatment is independently associated with increased hospital mortality; however, in these patients, de-escalation could not be done either because of resistant organisms isolated

Table 2: Bivariate and multivariate analysis to look for variables associated with hospital mortality

Variable	*Unadjusted odds ratio (95% CI)*	*p*	*Adjusted odds ratio (95% CI)*	*p*
Age	1.005 (0.988–1.021)	0.582		
Gender				
Female	1.000		1.000	
Male	3.047 (1.647–5.637)	0.0004	2.893 (1.455–5.748)	0.002
Comorbidities				
None	1.000			
Diabetes mellitus	0.968 (0.583–1.607)	0.900		
Chronic liver disease	4.375 (1.700–11.257)	0.002	4.872 (1.694–14.013)	0.003
Chronic kidney disease	1.155 (0.507–2.634)	0.731		
COAD	0.112 (0.015–0.855)	0.035	0.328 (0.040–2.683)	0.299
Chronic heart failure	0.567 (0.152–2.112)	0.398		
Immunocompromised	2.414 (0.717–8.127)	0.155		
APACHE-II on ICU admission	1.027 (0.994–1.060)	0.106		
Charlson's comorbidity index	1.023 (0.928–1.128)	0.647		
Prescribed by				
Fellow	1.000			
ICU consultant	1.332 (0.726–2.441)	0.355		
Non-ICU consultant	0.836 (0.319–2.194)	0.717		
Time of prescription				
Day shift	1.000			
Out of hour	0.906 (0.543–1.514)	0.707		
Physiological variables at antibiotic prescription				
Temperature	0.955 (0.830–1.099)	0.521		
Heart rate	1.011 (1.000–1.022)	0.053		
Respiratory rate	1.048 (1.011–1.086)	0.011	1.053 (1.012–1.097)	0.012
Vasopressor support				
None	1.000			
Low-dose	1.400 (0.755–2.597)	0.286		
High-dose	1.947 (0.948–4.000)	0.070		
Septic shock	1.942 (0.986–3.827)	0.055		
Lactate	1.020 (0.908–1.145)	0.742		
TLC	1.000 (1.000–1.000)	0.581		
Procalcitonin	0.999 (0.994–1.004)	0.805		
Source of infection				
Unknown	1.000			
Bloodstream	2.250 (0.552–9.170)	0.258		
CNS	0.321 (0.034–3.064)	0.324		
Intra-abdominal	1.350 (0.364–5.007)	0.654		
Lung	1.456 (0.5932–3.578)	0.413		
Soft tissue	0.500 (0.087–2.860)	0.436		
Urinary tract	0.766 (0.280–2.098)	0.604		
Hospital-acquired infection	2.250 (1.348–3.756)	0.002	2.040 (1.105–3.766)	0.023
SOFA score on day 0	1.183 (1.093–1.281)	<0.0001	1.150 (1.050–1.260)	0.003
No. of empirical antibiotics prescribed initially				
1-Antibiotic	1.000			
2-Antibiotics	1.057 (0.634–1.762)	0.832		
3-Antibiotics	2.024 (0.555–7.378)	0.285		
4-Anibiotics	–	0.993		
Antibiotic appropriateness	0.746 (0.319–1.7420	0.498		
Antimicrobial strategy once culture report is available				
Class I	1.000		1.000	
Class II	2.500 (1.181–5.293)	0.017	2.774 (1.178–6.533)	0.020
Class III	0.851 (0.379–1.912)	0.697	0.568 (0.223–1.443)	0.234
Class IV	1.806 (0.809–4.030)	0.149	1.260 (0.508–3.126)	0.618
Class V	2.492 (1.159–5.360)	0.019	2.334 (0.995–5.473)	0.051

APACHE-II, acute physiology and chronic health evaluation-II; COAD, chronic obstructive airway disease; CNS, central nervous system; ICU, intensive care unit; SOFA, sequential organ failure assessment

or because patients were not clinically stable, documented by worsening SOFA score at 72 hours. De-escalation of antibiotics was associated with better clinical outcome and longer duration of antibiotic treatment. Our study could also clearly identify two different subsets of patients among culture-negative sepsis with potential implication on antimicrobial stewardship program.

Supplementary Material

The Supplementary Table is available online on the website of https://www.IJCCM.org.

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