

Compliance with antimicrobials de-escalation in septic patients and mortality rates: an old subject revisited

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Abstract

Background: To compare the recent de-escalations rates with a six-year earlier study, and mortality associated with de-escalation.

Methods: A prospective multicenter study including septic patients, all were on broad-spectrum antimicrobials (BSA). Excluded from the study patients on antimicrobial prophylaxis, and patients without a microbiological diagnosis, or bacteria were solely BSA-susceptible. The study team made recommendations for antimicrobials de-escalation to the treating physician(s) must an opportunity loomed.

Results: 182 patients were available for analysis. De-escalation was achieved in 43 (24%) patients. The clinical diagnoses, comorbidities, commonly used antimicrobials, the microbiological diagnoses were not different between the two groups (patients with and without de-escalation). Logistic regression analysis showed no correlation between bacterial species and de-escalation (Nagelkerke R² = 0.076). Relapsing sepsis and reinfection were not different ($P > 0.05$). The in-hospital mortality rates for the de-escalated patients were lower ($P = 0.015$) but not on day 30 ($P = 0.354$). The length of the ICU stay and ward stay were not different ($P > 0.05$), but more de-escalated patients were discharged home from the ICU ($P = 0.034$), however, patients without de-escalation were discharged more from the ward ($P = 0.002$).

Conclusion: De-escalation rates increased within six years from 6.7%-24% ($P = 0.000$), with added benefits of shorter ICU stay and less in-hospital mortality

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Introduction

De-escalation is one of the paradigms of a multifaceted antimicrobials stewardship (AMS) that avoids unnecessary use of the broad-spectrum antimicrobials (BSA) and their extended duration, it is mostly based on a microbiological diagnosis and susceptibility [1-4]. The old dictum "hit hard and hit fast" is a principle in treating patients with severe sepsis, it focuses on treating patients appropriately and early [5, 6], this would help improving outcomes without undue delay at a time before a microbiological diagnosis is available [7]. With the rapid evolution of the diagnostic methods with rapid bacterial identification and susceptibility patterns, de-escalation as a concept must be a common practice, especially it is known to ameliorate the BSA sustained pressure upon bacteria, and cause less resistance [8], and adapting to a culture-driven antimicrobial therapy became evidently beneficial; the benefits of de-escalation are being frequently cited for lowering treatment costs, reducing the chances of inducing resistant among bacterial strains, reducing antimicrobials' toxicity and collateral damage of BSA [9-12], none the less many physicians do not feel comfortable with de-escalation: "why change, it works" [13-14]. Earlier in Amman - Jordan, we published a study that showed poor compliance with de-escalation. Now, we aim to re-evaluate the rates of the antimicrobials de-escalation in the same hospitals and almost the same staff after the accreditation by the Joint Commission International (JCI) whom surveillance includes elements of a working stewardship program [15-16]. We plan to test the hypothesis that JCI-driven recommendations convince the hospitals and the physicians in adopting the practice of de-escalation for being an important element of antimicrobial stewardship leading to a better patients' care, and help in lowering resistance rates, cost and mortality. Although there is no adequate information from controlled trials

so far, but observational ones revealing a better outcome in the de-escalated patients [17-20]. Our study aims to respond to skepticism, and if prove useful, it may encourage the practicing physician to de-escalate to a focused antimicrobial therapy when an opportunity arises.

Materials and Methods

Setting

A multicenter prospective study held in Amman – Jordan, between December 2014 to March 2019. It was conducted in three private hospitals; two teaching; The Specialty (Al Takhassusi) and Jordan Hospital and one community service hospital; Al Khalidi, with a total of 650 beds and 52 ICU beds. The three hospitals have no antimicrobials restriction policy. The internal review boards of each hospital approved the study. Daily charts review on antimicrobial prescription, changes in prescription and progress of patients (see inclusion criteria) were monitored. Each study team in the teaching hospitals included a clinical pharmacist and a medical resident, and clinical pharmacists in the community hospital. Follow up on the microbiological data, diagnosis accuracy according to CDC published criteria for nosocomial infections and the microbiologically documented diagnoses for admitted patients with community-associated infections were revised. The clinical pharmacist and/or the medical residents suggested de-escalation to the attending physician when there was an opportunity, the attending physician is the responsible prescriber for accepting or rejecting the de-escalation or escalating the regimen. Thirty days after the patients discharge, they were followed up by phone calls for mortality.

Inclusions and exclusion criteria

Patients were included if they were diagnosed to have documented sepsis, or septic shock associated with community-acquired pneumonia (CAP),

ventilator-associated pneumonia (VAP), catheter-associated urinary tract infections (CAUTI), severe urinary tract infections (UTI), central line-associated blood stream infection (CLABSI), bacteremia of undefined source and blood cultures were available, skin and skin structure infection (SSTI) intra-abdominal infection (IAI) and meningitis, for which BSA agents as mono-therapy or in combination were prescribed [21]. Failure to de-escalate was considered for patients when a bacterial culture and its susceptibility were known, and the causative bacteria could be treated with a focused narrow-spectrum antimicrobial, but the treating physician continued using the initial or an alternative BSA monotherapy or in combination despite the clinical pharmacist advice. Excluded patients those who were not started on BSA agents, were on antimicrobial prophylaxis, there was no clear indication for the use of BSA agents, and all septic patients whom do not have a microbiological diagnosis. The following available agents were considered BSA agents: carbapenems, β -lactam β -lactamase inhibitors, glycylicyclines, respiratory quinolones and the parenteral third and fourth generations' cephalosporins, and combination antimicrobials therapies prescribed in treating seriously sick patients and intended to provide BSA coverage with or without vancomycin or teicoplanin.

Outcome measures

The primary outcome measure is to evaluate the difference in the rates of de-escalated patients from BSA to an appropriate narrow spectrum agent and comparing the rates with a previous study we published earlier in this regard [15]. And to estimate the mortality rates associated with de-escalation compared with patients without de-escalation. Secondary outcome measures were if physicians' attitude were influenced by patients' admission location, comorbidities, clinical diagnosis and microbiological diagnosis.

Statistical analysis

Rates of the antimicrobials de-escalation were calculated, t-student test was used to estimate the difference between the means and proportions. Secondary outcomes were analyzed by Fischer's exact test or χ^2 to demonstrate if there were differences among different estimators. Two-sided $P \leq 0.05$ is considered significant. Logistic regression analysis was used for border line P-value to support relation between the tested variable and the de-escalation. Data were analyzed using SPSS (IBM corporation, version 22, 2018).

Results

There were 182 patients available for analysis. De-escalation was achieved in 43(24%) patients. Males were 109 (59%), there was no significant gender difference between both de-escalation and without de-escalation groups ($P = 0.375$). The clinical diagnoses and comorbidities were not significantly different between the two groups, as well as the commonly used antimicrobials ($P > 0.05$). The microbiological diagnoses showed no significant difference ($P = 0.05$), logistic regression analysis showed no correlation between bacterial species and the de-escalation (Nagelkerke pseudo- $R^2 = 0.076$). Relapsing sepsis and reinfection in both groups were few in numbers and no significant differences were detected ($P > 0.05$), though all the few relapsed cases and most cases in the reinfection were in patients without de-escalated (**Table 1**).

Table 1. Demography and characteristics of patients in the de-escalation study .

Characteristic	De-escalated	Not De-escalated	P-value
	N (%)	N (%)	
Number of Patients (N = 182)	43 (24)	139 (76)	
Age mean* (Years)	61.66	63.45	0.559

Characteristic	De-escalated	Not De-escalated	P-value
Gender¹			
Males	23	86	0.375
Females	20	53	
Clinical Diagnosis			
Bacteremia	12	38	0.464
CAP	3	14	
Sepsis/undefined	7	37	
UTI	15	39	
Others	6	11	
Comorbidities			
DM	26	96	0.739
COPD/Chronic lung disease	3	24	
Skin disease	1	7	
Hematological malignancy	8	9	
Solid Malignancy	5	18	
Immunosuppressive states	10	32	0.128
Others Comorbidities**	29	91	
Microbiological diagnosis			
Enterobacteriaceae	23	51	0.05
S. aureus	7	25	
Lactose non fermenters	3	20	
Enterococci	4	4	
N/A	6	39	
Commonly used antimicrobials*			
Carbapenems	25	75	≥ 0.2
Pipracillin/tazobactam	11	24	
Cephalosporines (3rd and 4th)	7	17	
Tigecycline	0	5	
Colistin	0	1	
Glycopeptides	7	29	0.001
Quinolones	1	33	
Relapse			
Clinical	2	3	> 0.3
Microbiological	0	2	
Microorganism	0	1	
Site ²	1	3	
Reinfection			
Acinetobacter spp.	0	2	0.742
Enterococci	0	1	
Others	0	1	

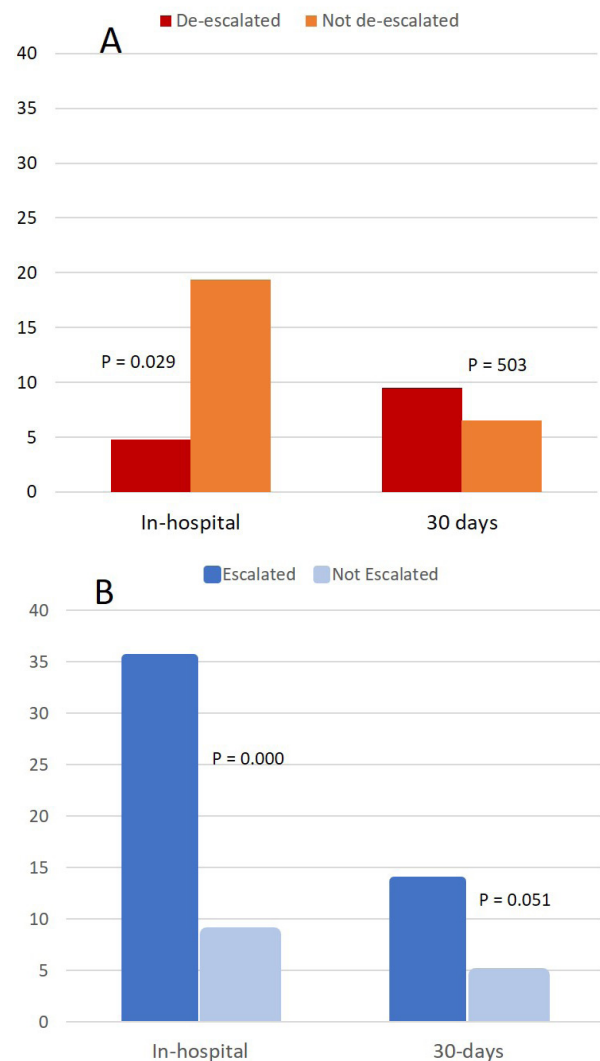
*P-value was tested by ANOVA and was significant.

** : Hypertension, renal failure, CVA, CAD, heart failure and others.

1: By Fisher exact test, 2-sided. 2: 1 VAPin each arm, 1 undefined sepsis and 1 bacteremia.

The in-hospital mortality rates for the de-escalated patients were significantly lower than those without de-escalation (P = 0.029), but there was no mortality difference on day 30 (P = 0.503) (**Figure A**). Patients who were escalated have higher in-hospital mortality than those without de-escalation (P = 0.000), and tendency towards higher mortality on day 30 (P = 0.051) (**Figure B**). The length of the ICU stay and the ward stay were

Figure A, B: In-hospital and 30-days mortality rates for patients.



A) with and without de-escalation; B) for escalation and without escalation. Patients. De-escalated number of patients = 42, and without de-escalation = 139. Escalated number of patients = 52 and without escalation = 130. Note that the 130 without escalation have included those with de-escalation = 43. P-value significance was tested by 2-sided Fisher's exact test

Table 2. The means of the length of stay in the ICU and the hospital ward for patients with de-escalation and without de-escalation .

Characteristic	The mean of the days and the (number of patients)*				P-Value
	De-escalated		Not De-escalated		
	N	%	N	%	
Length of Stay (ICU)	4.81	42	5.7	137	0.584
Length of Stay (ward)	6.37	42	4.93	137	0.097
Transferred from ward to ICU	1.83	7	1.77	32	0.383
Discharged home from ward	1.19	34	1.46	75	0.002
Discharged home from ICU	1.95	2	1.82	25	0.034

*: Two-sided student t-test for the mean length of stay in days

not significantly different ($P > 0.05$) between the two groups, but significantly more de-escalated patient were discharged home directly from the ICU ($P = 0.034$), however, in the ward the patients without de-escalation were discharge sooner ($P = 0.002$) (**Table 2**).

Discussion

The concept of de-escalation came into practice as BSA agents were found not devoid of flaws when used appropriately, not to mention the unjustified regimen, duration, dose and frequency of a therapeutic regimen, where CDI, MRSA, VRE, ESBL and CRE are becoming the major culprit of the wide "and indiscriminate" use of BSA agents [22-27]. The aim of this study was to evaluate the changing rates of de-escalation and the associated mortality, after the JCI enforcement on the antimicrobial stewardship. There was an improvement in the rates of de-escalation, it significantly soared from 6.7% to 24% ($P = 0.000$) in six years (2012 to 2018), though the absolute rise in number is a modest one, but it was almost quadrupled, this is an encouraging step to keep momentum for education, ward suggestions and administrations support in the pursue of better antimicrobial utilization. Recorded rates for de-escalation in several

countries of the world may reach 32.1%-51%, higher than our improved rates [28-30].

The in-hospital mortality was lower in the de-escalated patients ($P = 0.029$), the results of a previous work demonstrated that de-escalation in severe sepsis and septic shock was safe with a lower mortality [19, 31] even in culture negative septic patients with healthcare-associated pneumonia [32]. Escalating the antimicrobial therapy in a subset of patients had significantly higher in-hospital mortality ($P = 0.000$) and tendency towards higher mortality on day 30 ($P = 0.051$), possibly because the treating physicians were hesitant to de-escalate, on the contrary, antimicrobial treatment was escalated in the very sick patients, following the idea "more is better". However, the addition of another antimicrobial did not alter the outcome of those subset of patients, and they had a higher mortality compared with patients without escalation, similar to was found earlier that escalation were associated with a higher mortality in non bacteremic patients with pneumonia, though it was confounded by a higher inappropriate therapy [33]. Notably, the length of ICU Stay and ward stay were not different for both groups ($P > 0.05$), but the hospital discharge were significantly better for patients with de-escalation from the ICU and from the medical ward at home ($P < 0.05$), this also

saves cost as always demonstrated [34]. Needless to stress on the fact that cost saving is of a paramount priority for resources-limited countries.

No differences were noted for transferring patients from the ward to the ICU between the two groups ($P = 0.383$), this highlights the safety of de-escalation, and the patients' likelihood to become sicker and being transferred to the ICU is the same in both groups. Our study was not APACH II or SOFA score adjusted, however, comparisons of many confounders were not significantly different between the two groups (**Table 1**), this may contribute to some robustness of our results. A point to consider is that the data were not segregated into teaching versus not teaching hospital. Another point to consider is the Hawthorne phenomena effect; our study though it was observational, but it was monitored by residents and clinical pharmacist who suggested and observed and phoned the attending physicians for their prescribing practices, this may have added to the improved de-escalation rates [35], this would invite the health care administrators to seriously implement methods and procedures in this regard as education alone may had not been enough. In conclusion, the de-escalation rates improved significantly over time with added benefits of shorter ICU stay, cost saving and less in-hospital mortality. Furthermore, escalating antimicrobial therapy was not associated with a better outcome.

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