Original Article

Etiology and Risk Factors for Late Antibiotic De-Escalation and their Effect on Intensive Care Unit Outcome

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Abstract

Background: Timely antibiotic de-escalation is essential in intensive care unit (ICU) to prevent the development of antibiotic resistance. This study was undertaken to identify the causes and observe the effects of late antibiotic de-escalation on mortality, length of stay, duration of mechanical ventilation, antibiotic-associated adverse effects, incidence of new infections, and growth of drug-resistant organisms in ICU. **Methods:** This retrospective study was conducted in a university hospital. A total of 76 consecutively admitted ICU patients were included after retrieving all information from the hospital database and obviating the need for IEC approval. All the enrolled patients had antibiotics initiated and de-escalated in ICU. Those patients for whom antibiotics were initiated before ICU admission were enrolled if their antibiotic prescription was unchanged on ICU admission. Patients with antibiotic de-escalation outside ICU were excluded. The two groups: N-antibiotic de-escalation <8 days and L-antibiotic de-escalation ≥8 days after ICU admission were compared with respect to all variables and analyzed using software R. **Results:** Of 76 patients, 41 (53.9%) were N and 35 (46.1%) were L. The mean antibiotic duration was 6 ± 1.5 versus 11 ± 3.4 days (N vs. L; $P = 0.04$). Prior antibiotic administration within 30 days was 6 versus 12 (N vs. L; $P = 0.03$). More incidences of "new infections" and drug-resistant organisms occurred in L (19.5% vs. 34.2%; $P = 0.04$ and 9.7% vs. 25.8%; $P = 0.02$, respectively). Prior antibiotic administration was independently associated with higher mortality risk in L (odds ratio – 2.34; confidence interval – 1.45–3.48; $P = 0.01$) and caused greater mortality in L ($P = 0.03$). **Conclusions:** Late antibiotic de-escalation in ICU was caused primarily due to persistence of infection and was associated with higher incidence of "new infections" and drug-resistant organisms and higher mortality in patients receiving antibiotics in the preceding 30 days.

Keywords: Antibiotic de-escalation, causes, intensive care unit outcome

Introduction

Antibiotic de-escalation involves a reduction in the spectrum of empirically administered antibiotics through their discontinuation or replacement with a narrower spectrum of antibiotics based upon clinical and microbiological results. It is an important strategy for rationalizing antibiotic usage and preventing their misuse leading to the emergence of drug-resistant organisms in intensive care unit (ICU).[1-3]

Various studies have reported de-escalation rates varying from 45% to 70% depending on the clinical setting and the antibiotic policy in vogue of the ICU.[4-6] Some studies have identified the hindrances for smooth implementation of antibiotic de-escalation such as inappropriate choice of initial antibiotic and delayed availability of microbiological report.[7] However, there is limited information on the effect of late antibiotic de-escalation on the mortality of critically ill patients in the ICU.

This observational study was conducted to identify the causes of late antibiotic de-escalation and observe the effect on ICU mortality, the ICU length of stay, duration of mechanical ventilation, antibiotic-associated side effects, occurrence of new infections, and growth of multidrug-resistant (MDR) organisms.

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Methods

The retrospective observational study was conducted in a cohort of 76 critically ill consecutively admitted patients in the seven-bedded mixed medical surgical ICU of our university teaching hospital between April 2017 and February 2019. The need for institutional ethics committee approval was obviated due to retrospective design of the study and data being derived only from the ICU database maintained for routine clinical and administrative purposes.

All critically ill patients who were administered broad-spectrum antibiotics and underwent antibiotic de-escalation in the ICU were eligible for enrollment. The patients who were commenced on broad-spectrum antibiotics before ICU admission were enrolled only if there was no change in their antibiotic prescription at the time of ICU admission. The patients in whom antibiotics were substituted at the time of ICU admission who received irregular antibiotics and who were de-escalated outside ICU were excluded.

Antibiotic de-escalation was defined as the discontinuation or replacement of the broad-spectrum antibiotics with narrow-spectrum antibiotics following clinical improvement, change in serum biomarkers, namely procalcitonin (PCT), or culture and sensitivity report of the organisms causing infection.

The duration of empiric broad-spectrum antibiotic was counted from day 1 of administration either in the ICU or elsewhere (ward, operation theater, etc.) if they were continued without interruption in the ICU.

The ICU mortality was defined as death occurring due to any cause during in the ICU.

A new infection was defined as the occurrence of any infection in the ICU that was not present at the time of ICU admission.

The growth of MDR organisms was determined on the basis of culture and sensitivity report of the following organisms with specific antibiotic resistance characteristics: extended-spectrum β-lactamase-producing Gram-negative *Enterobacteriaceae*, such as *Klebsiella* spp., *Escherichia coli*, and *Proteus* spp.; *Pseudomonas aeruginosa* resistant to ceftazidime or carbapenems; other pan-resistant *Enterobacteriaceae* bacteria or those sensitive only to carbapenems; *Acinetobacter* spp. resistant to ampicillin, ampicillin/sulbactam, or carbapenems; methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* (VRE) spp. Other organisms were considered MDR when they were nonsusceptible to one of the three antibiotic classes: antipseudomonal cephalosporins/penicillins, macrolides, carbapenems, fluoroquinolones, aminoglycosides, colistin, and tigecycline.

Recent antibiotic administration was defined as the oral or parenteral intake of any antibiotic in the preceding 30 days of ICU admission for any cause.

The antibiotic adverse effects were diagnosed clinically and included commonly encountered adverse effects such as hypersensitivity reactions, gastrointestinal symptoms, or any specific adverse effect associated with any particular antibiotic.

The patients were grouped into normal de-escalation (N) and late de-escalation (L) depending upon the duration of broad-spectrum antibiotic administration. Since the median duration of empiric broad-spectrum antibiotic treatment in our ICU was calculated 7 days (interquartile range [IQR]: 6–10 days), the patients who were de-escalated before 8 days were grouped under N and the patients' de-escalated on or after 8 days were grouped under L.

The demographic variables, clinical characteristics, and the investigation reports that were retrieved from the database were compared. The duration of ICU stay, duration of mechanical ventilation, and total duration of antibiotic treatment were compared. A logistic regression analysis was performed to identify the risk factors independently associated with mortality after late antibiotic de-escalation by creating appropriate models. The variables which were identified as significant in stepwise approach in the bivariate analysis were introduced in the model. The antibiotic de-escalation (normal vs. late) was added to all the models as a categorical variable. The effect of late antibiotic de-escalation on mortality was checked with the plausibility of interaction with severity of illness, namely Acute Physiology and Chronic Health Evaluation (APACHE) II. Log likelihood ratio tests were used to identify the final model and logistic function was used as a link function for mortality outcome and new infection. For other outcomes, namely duration of mechanical ventilation, duration of ICU stay, antibiotic-associated side effects and new infections, general linear models were constructed and r^2 measure was used for final model selection.

All statistical analysis was performed using software R. The results for continuous variables were expressed as median and IQR while categorical variables were expressed as percentages. The $P < 0.05$ was considered statistically significant. Mann–Whitney U-test was used to compare numerical variables while Chi-square test or Fisher exact test was used for categorical variables.

Results

Out of the total 76 patients enrolled in the study, 41 (53.9%) belonged to N and 35 (46.1%) to L. The demographic profiles of the two groups were similar except that the mean duration for antibiotic administration was longer (6 ± 1.5 vs. 11 ± 3.4 days; $P = 0.04$) and the administration of antibiotics in the preceding 30 days was higher in L (6 vs. 12; $P = 0.03$) [Table 1]. There was no difference between the groups with regard to mortality, duration of mechanical ventilation, length of ICU stay, and the incidence of antibiotic-associated side effects. The occurrence of "new infections" and the growth of drug-resistant organisms were greater in L (19.5% vs. 34.2%; $P = 0.04$ and 9.7% vs. 25.8%; $P = 0.02$, respectively) [Table 1].

Table 1: Demographic and clinical characteristics of the group

Variable	Normal de-escalation (<8 days) (N) (*n*=41)	Late de-escalation (≥ 8 days) (L) (*n*=35)	*P*
Age (years) (mean±SD)	45±11.3	52±9.6	0.09
Sex (male/female)	29/12	20/15	0.16
Diagnosis, *n* (%)			
Respiratory	16 (39)	20 (57.1)	0.22
Cardiac	6 (14.6)	9 (25.7)	0.16
Postoperative	19 (46.3)	13 (37.1)	0.08
Neurological	18 (43.9)	16 (45.7)	0.18
Gastrointestinal	26 (63.4)	21 (60)	0.09
Others	5 (12.2)	3 (8.5)	0.11
Comorbidities (diabetes, hypertension, cardiac, neurological, respiratory illness), *n* (%)	24 (58.5)	22 (62.8)	0.09
APACHE II score (on admission) (mean±SD)	19±4.9	22±8.1	0.07
Antibiotic within 30 days, *n* (%)	6 (13.3)	12 (38.7)	0.03*
Duration of antibiotics (days) (mean±SD)	6±1.5	11±3.4	0.04*
Antibiotic associated side effects, *n* (%)	1 (2.4)	1 (2.8)	0.18
Sepsis, *n* (%)	32 (78.0)	27 (77.1)	0.09
Postsurgical, *n* (%)	16 (39.1)	11 (31.4)	0.22
Length of ICU stay (days) (mean±SD)	11±2.4	14±3.9	0.06
Duration of mechanical ventilation (days) (mean±SD)	4±2.9	6±3.5	0.07
New infection, *n* (%)	8 (19.5)	12 (34.2)	0.04*
Drug-resistant microorganisms, *n* (%)	4 (9.7)	8 (25.8)	0.02*
Mortality, *n* (%)	3 (7.3)	4 (11.4)	0.14

*P<0.05. APACHE: Acute Physiology and Chronic Health Evaluation, SD: Standard deviation, ICU: Intensive care unit

The following causes for late antibiotic de-escalation were identified – (a) persistence of infection despite cultured organisms showing sensitivity to empiric antibiotics, (b) persistence of clinical signs and symptoms of infection and/or elevated serum biomarkers without any growth of organisms in culture, and (c) worsening of clinical signs and symptoms of infection necessitating antibiotic escalation [Figure 1].

The stepwise logistic regression analysis identified antibiotic administration in the preceding 30 days as an independent risk factor for mortality in L [Table 2]. The ICU mortality was greater among patients receiving antibiotics in the preceding 30 days in both the groups but was significantly more in L after adjusting for the length of ICU stay (P = 0.03) [Figure 2].

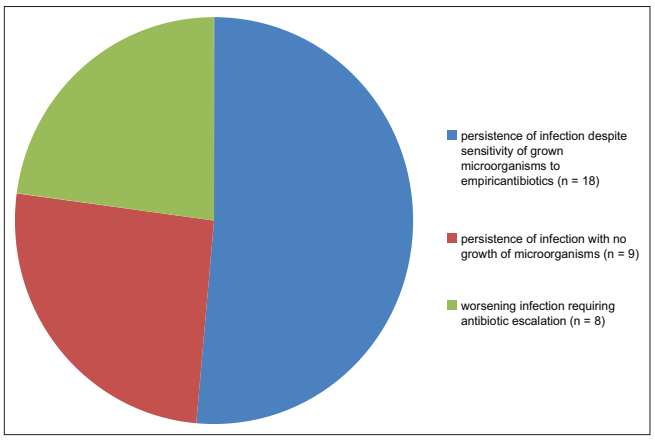

Figure 1: Causes for delayed antibiotic de-escalation (n = 35)

Discussion

Our study found a 53.9% prevalence of timely antibiotic de-escalation which is comparable to the published reports from other parts of the world.[4,8] The late antibiotic de-escalation has been reported in the previous studies more commonly after conditions such as hospital-acquired pneumonia, urosepsis and osteomyelitis and less commonly after acute pancreatitis, meningitis, and skin and soft tissue infections.[9-11] Our study included a mixed population of patients with medical and surgical illnesses and late de-escalation was more common in those with respiratory and cardiac ailments. It was uncommon in postsurgical patients. However, our study sample was small and not powered to derive definite conclusion from these observations.

The main cause for delayed antibiotic de-escalation in our study was the "persistence" of clinical signs and symptoms of infection despite cultured organisms showing sensitivity to the used antibiotics. This was responsible for delayed escalation in nearly half of the patients. The "persistence" of infection in the host despite antibiotic sensitivity has been recently attributed to a nonheritable phenotypic variation of the microorganism which is different from acquired drug resistance. The persistence as Stuff Happens model suggests that both time-and dose-dependent persistence are the result of stochastic errors in metabolism, cell division, and stress responses which is analogous to spontaneous mutations observed in acquired antibiotic resistance.[12] It has also been shown that antibiotic

Table 2: The independent risk factors for mortality in L group by stepwise regression

	OR	CI	*P*
APACHE II (on admission)	1.24	0.84-2.39	0.08
Duration of antibiotic	1.15	0.68-3.24	0.07
Antibiotic within 30 days	2.34	1.45-3.48	0.01*
New infection	1.63	1.21-3.54	0.06
MDR organisms	1.36	0.84-2.56	0.07

APACHE: Acute Physiology and Chronic Health Evaluation, MDR: Multidrug-resistant organisms, OR: Odds ratio, CI: Confidence interval

sensitivity that is commonly measured in the laboratory in a nutrient-rich media is free of most "stressors" present in the "macro ecosystem" of the diseased host. This altered metabolic heterogeneity of the host environment induces infection "persistence" despite organisms exhibiting sensitivity to broad-spectrum antibiotics in the laboratory.[13] Furthermore, biofilm formation also aggravates this bacterial persistence, antibiotic recalcitrance, and infection recurrence.[12]

Both groups in our study were comparable in disease types, severity, and presence of co-morbid illnesses except in that the late de-escalation group had a prolonged antibiotic duration in the ICU and a greater antibiotic usage in the preceding 30 days. It is known from earlier studies that patients with higher usage of antibiotics have greater risk of infection-related hospital admissions over time.[14] On the contrary, a patient with limited antibiotic use shows lower risk of infection and a more pronounced antibiotic response. There are several explanations for this phenomenon. One, a higher antibiotic usage leads to a higher risk of colonization by resistant bacteria in hosts which become normal after a definite period time. Second, if the cause of prior antibiotic administration is linked to a higher prevalence of immunosuppression, then this alters the pharmacodynamic properties of the antibiotics. Third, prior antibiotic administration produces "dysbiosis" of the gut microbiota causing perturbations of the intestinal microbes. This hinders the protection offered by these microbes against the growth of resistant organisms.[15,16] The late de-escalation group in our study is likely to have a combination of all these factors to account for their infection "persistence." Our study is also in agreement with the report of reduced reliability of antibiogram report for hospital-acquired urinary tract infection with prior exposure to >2 antibiotics with regard to the patients with urosepsis.[17] However, some studies have proposed a contrary view to ours and the main objection being that a binary designation of prior antibiotic exposure may be an oversimplification of facts and a stratification based upon the number of exposures is essential to demonstrate the true nonsusceptibility trend.[18,19] The recent Infectious Diseases Society of America guidelines also encourage the development of such antibiograms that are stratified by such parameters which improve the selection of empiric antibiotics.[19]

Our study did not find any difference in the ICU mortality, duration of mechanical ventilation, or the length of the ICU

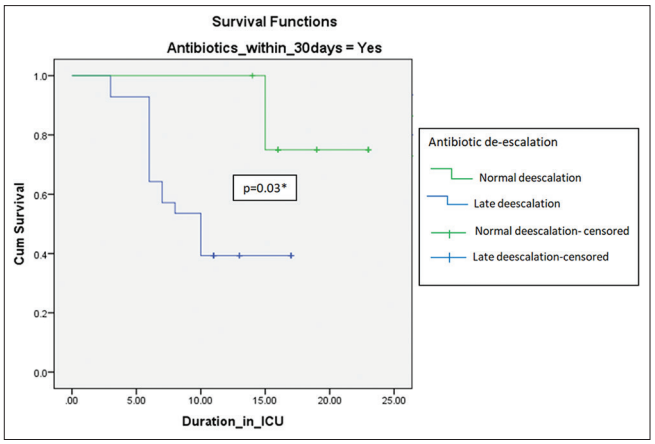

Figure 2: Comparison of survival between N and L among antibiotic recipients within the past 30 days. The figure showing higher mortality with prior receipt of antibiotics within the past 30 days but more in late de-escalation after adjusting for length of intensive care unit stay

stay between the two groups. This shows that the consequences of inappropriate selection of empiric antibiotics can be much different from the consequences of prolonged continuation of appropriately chosen antibiotics. It is also necessary to understand that all patients in our study underwent de-escalation within the ICU and therefore cannot recount for the causes of late de-escalation in the patients who were later de-escalated after shifting to the ward. It is also important to recognize the conditions such as prosthetic valve myocarditis and septic arthritis where the ICU mortality is no different despite continuing antibiotics for long without any de-escalation.[20] Furthermore, mortality after prolonged antibiotic usage in ICU is reported to be more common in infants and children and is attributed to the increased rates of necrotizing enterocolitis. This is, however, uncommon in adults.[21]

Our study has found a higher incidence of "new infection" and growth of drug-resistant microorganisms after late antibiotic de-escalation. "New infection" may develop naturally in any ICU patients and go undetected in the initial stage. These patients may behave in the same way as "persisters" till the organisms are identified in the subsequent cultures. This may also suggest that every bacterial population may consist of a diverse population of "persisters" that can cause "new infection" and mandate strategies for "persister" eradication.[22,23] If such strategies are ineffective or inadequate, these "persisters" can promote the growth of drug-resistant organisms.[22,24] It is also possible that prolonged administration of empiric antibiotics due to delayed de-escalation may be independently linked to the growth of drug-resistant organisms. This accounts for the resistance to specific antibiotics like aminoglycosides to a large extent and to the peptidoglycans to some extent but is mostly linked to the posttranscriptional control of the *ermC* gene.[25]

Our study has found a greater ICU mortality among antibiotic recipients in the preceding 30 days but this was more significant in the late de-escalation group after adjusting for the length of ICU stay. This is a unique finding in our study which has

not been discussed anywhere but possesses strong scientific basis from the microbiological point of view. It is known with certainty that the risk of infection increases substantially when multiorgan dysfunction supervenes in a patient with prolonged ICU stay.[26-28] The immunological basis for this is the suppression of T -cell and impairment of B-cell functions. This immunosuppression may be exacerbated due to lymphocyte exhaustion as a consequence on prolonged antibiotic administration.[29] Several mathematical models support that prolonged antibiotic administration can affect the intracellular toll-like receptor 4 to shift the equilibrium between the pro and anti-inflammatory cytokines causing cytokine perturbation and increasing mortality.[30] Therefore, the higher ICU mortality among antibiotic recipients of the preceding 30 days may be linked to late de-escalation as a result of altered immunological response due to cumulative effect, which is evident on adjustment of the ICU length of stay.

However, our study had some limitations. One, the cut-off period for normal and late de-escalation group was 8 days based upon the calculated median duration of antibiotic de-escalation which was 7 days. This appears to be high and may be due to a large number of admissions occurring after initiation of antibiotics. Moreover, the APACHE II score of our patient was high suggesting severe disease at the time of admission. This may not hold true for patients who are mild to moderately ill in the ICU. Second, our study did not include patients who were shifted to the ward and de-escalated within 8 days. This was done to avoid the confounding effect on ICU mortality which was the objective of our study. However, this has eliminated a sizable group of patients whose profile is not reflected in our results. Third, since sample size calculation was not done and it is not known whether the study was adequately powered to detect the difference in mortality. Fourth, all pertinent drawbacks of a retrospective study are also natural limitations of our study.

Conclusions

To conclude, our study found that "persistence" of clinical signs and symptoms of sepsis despite demonstrable sensitivity of organisms to empiric antibiotics as the main cause of late antibiotic de-escalation. It showed a higher incidence of "new infection" and growth of drug-resistant organisms in patients undergoing late antibiotic de-escalation but no difference in ICU mortality. The receipt of antibiotic within the past 30 days was the risk factor independently associated with mortality in the late de-escalation group. Antibiotic administration within preceding 30 days of ICU admission increased mortality risk for both groups but more for late de-escalation group. However, larger prospective studies are required to confirm these findings along elucidation of further details.

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Conflicts of interest

There are no conflicts of interest.

References

1. Garnacho-Montero J, Escoresca-Ortega A, Fernández-Delgado E. Antibiotic de-escalation in the ICU: How is it best done? Curr Opin Infect Dis 2015;28:193-8.
2. Morel J, Casoetto J, Jospé R, Aubert G, Terrana R, Dumont A, *et al.* De-escalation as part of a global strategy of empiric antibiotherapy management. A retrospective study in a medico-surgical intensive care unit. Crit Care 2010;14:R225.
3. Heenen S, Jacobs F, Vincent JL. Antibiotic strategies in severe nosocomial sepsis: Why do we not de-escalate more often? Crit Care Med 2012;40:1404-9.
4. Ali M, Naureen H, Tariq MH, Farrukh MJ, Usman A, Khattak S, *et al.* Rational use of antibiotics in an intensive care unit: A retrospective study of the impact on clinical outcomes and mortality rate. Infect Drug Resist 2019;12:493-9.
5. Thomas Z, Bandali F, Sankaranarayanan J, Reardon T, Olsen KM; Critical Care Pharmacotherapy Trials Network. A multicenter evaluation of prolonged empiric antibiotic therapy in adult ICUs in the United States. Crit Care Med 2015;43:2527-34.
6. Zilahi G, McMahon MA, Povoa P, Martin-Loeches I. Duration of antibiotic therapy in the intensive care unit. J Thorac Dis 2016;8:3774-80.
7. Montravers P, Augustin P, Grall N, Desmard M, Allou N, Marmuse JP, *et al.* Characteristics and outcomes of anti-infective de-escalation during health care-associated intra-abdominal infections. Crit Care 2016;20:83.
8. Liu P, Ohl C, Johnson J, Williamson J, Beardsley J, Luther V. Frequency of empiric antibiotic de-escalation in an acute care hospital with an established Antimicrobial Stewardship Program. BMC Infect Dis 2016;16:751.
9. Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sánchez PJ, *et al.* Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 2009;123:58-66.
10. Claridge JA, Pang P, Leukhardt WH, Golob JF, Carter JW, Fadlalla AM. Critical analysis of empiric antibiotic utilization: Establishing benchmarks. Surg Infect (Larchmt) 2010;11:125-31.
11. Grant SS, Hung DT. Persistent bacterial infections, antibiotic tolerance, and the oxidative stress response. Virulence 2014;4:273-83.
12. MacLean RC, Vogwill T. Limits to compensatory adaptation and the persistence of antibiotic resistance in pathogenic bacteria. Evol Med Public Health 2014;2015:4-12.
13. Currie CJ, Berni E, Jenkins-Jones S, Poole CD, Ouwens M, Driessen S, *et al.* Antibiotic treatment failure in four common infections in UK primary care 1991-2012: Longitudinal analysis. BMJ 2014;349:g5493.
14. Gerber JS, Ross RK, Bryan M, Localio AR, Szymczak JE, Wasserman R, *et al.* Association of broad- vs. narrow-spectrum antibiotics with treatment failure, adverse events, and quality of life in children with acute respiratory tract infections. JAMA 2017;318:2325-36.
15. Bidell MR, Opraseuth MP, Yoon M, Mohr J, Lodise TP. Effect of prior receipt of antibiotics on the pathogen distribution and antibiotic resistance profile of key Gram-negative pathogens among patients with hospital-onset urinary tract infections. BMC Infect Dis 2017;17:176.
16. Pakyz AL. The utility of hospital antibiograms as tools for guiding empiric therapy and tracking resistance. Insights from the society of infectious diseases pharmacists. Pharmacotherapy 2007;27:1306-12.
17. Zilberberg MD, Shorr AF. Secular trends in gram-negative resistance among urinary tract infection hospitalizations in the United States, 2000-2009. Infect Control Hosp Epidemiol 2013;34:940-6.
18. Van den Bergh B, Fauvart M, Michiels J. Formation, physiology, ecology, evolution and clinical importance of bacterial persisters. FEMS Microbiol Rev 2017;41:219-51.
19. Barlam TF, Cosgrove SE, Abbo LM. Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51-77.
20. Alonso-Valle H, Fariñas-Alvarez C, García-Palomo JD, Bernal JM, Martín-Durán R, Gutiérrez Díez JF, *et al.* Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. J Thorac Cardiovasc Surg 2010;139:887-93.
21. Kester JC, Fortune SM. Persisters and beyond: Mechanisms of

phenotypic drug resistance and drug tolerance in bacteria. Crit Rev Biochem Mol Biol 2014;49:91-101.
22. Lewis K. Persister cells, dormancy and infectious disease. Nat Rev Microbiol 2007;5:48-56.
23. Defraine V, Fauvart M, Michiels J. Fighting bacterial persistence: Current and emerging anti-persister strategies and therapeutics. Drug Resist Updat 2018;38:12-26.
24. Cantón R, Morosini MI. Emergence and spread of antibiotic resistance following exposure to antibiotics. FEMS Microbiol Rev 2011;35:977-91.
25. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, *et al.* International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323-9.
26. Fagon JY, Novara A, Stephan F, Girou E, Safar M. Mortality attributable to nosocomial infections in the ICU. Infect Control Hosp Epidemiol 1994;15:428-34.
27. Doyle JS, Buising KL, Thursky KA, Worth LJ, Richards MJ. Epidemiology of infections acquired in intensive care units. Semin Respir Crit Care Med 2011;32:115-38.
28. Gillis A, Beil M, Halevi-Tobias K, van Heerden PV, Sviri S, Agur Z. Alleviation of exhaustion-induced immunosuppression and sepsis by immune checkpoint blockers sequentially administered with antibiotics-analysis of a new mathematical model. Intensive Care Med Exp 2019;7:32.
29. Morris AC, Anderson N, Brittan M. Combined dysfunctions of immune cells predicts nosocomial infection in critically ill patients. Br J Anaesth 2013;111:778-87.
30. Conway Morris A, Datta D, Shankar-Hari M, Weir CJ, Rennie J, Antonelli J, *et al.* Predictive value of cell-surface markers in infections in critically ill patients: Protocol for an observational study (ImmuNe FailurE in Critical Therapy (INFECT) Study). BMJ Open 2016;6:e011326.