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LETTER

De-escalation of pivotal beta-lactam in ventilator-associated pneumonia does not impact outcome and marginally affects MDR acquisition

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De-escalation (DE) consists in reappraisal of antimicrobial therapy as soon as microbiological susceptibility data are available. One of its aims is to limit the emergence and spread of multidrug-resistant (MDR) pathogens by reducing broad-spectrum antibiotic use [1].

Up until recently, a precise or consensual definition of DE was missing and DE in real-life practice remained unclear. A consensual definition of DE based on a six-rank classification of beta-lactams according to both their spectrum and their selective pressure on microbiota among beta-lactams that was elaborated using the Delphi method is now available [2].

Using this new consensual definition, we retrospectively evaluated DE effects on antibiotic consumption and on bacterial resistance emergence and assessed their impact on individual clinical outcome in a population of patients with gram-negative bacilli (GNB)-related ventilator-associated pneumonia (VAP) in whom DE was microbiologically possible. We included all adults admitted in two mixed ICUs from the OUTCOMEREA database. Inclusion and exclusion criteria are provided in Fig. S1 and in supplementary material.

DE was defined as a reduction in spectrum and ecological consequences of pivotal beta-lactam within 5 days following treatment initiation and evaluated using the recent six-rank consensual classification of beta-lactams (Table S1) [2]. Patient outcome, antimicrobial consumption and MDR strain carriage were analysed. More information about methods is provided in the supplementary material.

Among the 182 VAP episodes who received empirical adequate therapy (Fig. S1), DE of the pivotal beta-lactams was feasible in 131 (72 %) and actually performed in 70 (38 %). DE occurred during the first 72 h in 61 cases (87 %) but its intensity was as high as microbiologically achievable in only 61 % of cases. Antimicrobial molecules used as empirical therapy are provided in Table S2. Patient comorbidities and illness severities at admission or during the first 48 h were not associated with DE (Table S3). Conversely, *Enterobacteriaceae*-related VAP predicted DE and medical reason for ICU admission and empiric use if fluoroquinolones as companion-drug prevented DE (Table S4). After adjustment for these predictors, individual outcome did not differ between groups (Table 1). DE did not impact antibiotic- and carbapenem-free days, but increased the number of group 4 molecule-free days (Table 1). We found a marginal but clinically significant reduction in extended spectrum beta-lactamase-producing (ESBL) colonization acquisition (1.4 vs. 8.2 %, $p = 0.07$) in the DE group but no difference in rate of global MDR strain carriage acquisition (Table 1).

The main strength of our work is the use of a consensual definition of DE in a very specific population of VAP appropriately treated within 48 h. The limitations of our work are the absence of control of the companion drugs, elapse time of 5 days chosen for DE and lack of power to demonstrate a significant effect on MDR strain carriage given the low rate of MDR acquisitions in our

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Table 1 Effect of de-escalation on antimicrobial consumption, multiresistant strain carriage acquisition and individual outcomes

	No-de-escalation ($n = 61$)	De-escalation ($n = 70$)	*P* value*
Individual outcomes			
VAP[a] relapse[b]	17 (27.9)	19 (27.1)	0.69
Length of mechanical ventilation (days)[c]	12 (8; 21)	14 (8; 24)	0.26
ICU length of stay (censored at day 28)	28 (18; 21)	28 (16; 28)	0.62
28-day ICU mortality	16 (26)	22 (31)	0.53
Antimicrobial consumption during VAP treatment (7 days)			
ICU length of stay	7 (7; 7)	7 (7; 7)	0.60
Number of antibiotic-free days	0 (0; 0)	0 (0; 0)	0.16
Number of carbapenem-free days	7 (6; 7)	7 (5; 7)	0.22
Number of group 4 molecule-free days[d]	2 (0; 7)	5 (3; 6)	<0.01
Antimicrobial consumption during the time period within 21 days after VAP treatment initiation[e]			
ICU length of stay	16 (10; 21)	18 (12; 21)	0.82
Number of antibiotic-free days	1 (0; 5)	2 (0; 6)	0.75
Number of carbapenem-free days	12 (9; 19)	15 (10; 19)	0.65
Number of group 4 molecule-free days[d]	8 (3; 13)	11.5 (7; 18)	0.04
Acquisition of multi-drug resistant strains within 21 days after VAP treatment initiation[e]			
Multi-drug resistant strains	13 (21.3)	10 (14.3)	0.32
ESBL *Enterobacteriaceae*	5 (8.2)	1 (1.4)	0.07
Resistant *Pseudomonas aeruginosa*	3 (4.9)	5 (7.1)	0.75
AmpC-hyperproducing *Enterobacteriaceae*	2 (3.3)	3 (4.3)	0.56
Methicillin-resistant *S. aureus*	1 (1.6)	1 (1.4)	0.44

Variables are described as median [interquartile range (IQR)]. *P* values were computed by logistic or linear regressions adjusted for risk factors of de-escalation (see Table S4)

[a] VAP was defined as a persistent radiological pulmonary infiltrates combined with purulent tracheal aspirates and body temperature $\geq$38.5 or $\leq$36.5 °C and peripheral blood leukocyte count $\geq 10 \times 10^9$/L or $\leq 4 \times 10^9$/L. VAP diagnosis required systematic microbiological confirmation using quantitative culture from protected specimen brush ($\geq 10^3$ colony-forming unit (CFU)/mL), plugged telescopic catheter ($\geq 10^3$ CFU/mL), bronchoalveolar lavage fluid specimen ($\geq 10^4$ CFU/mL), or endotracheal aspirate ($\geq 10^5$ CFU/mL). Only the first microbiologically proven episode of VAP was taken into account for each patient

[b] VAP relapse was defined on the basis of a new suspicion of VAP and the isolation of any pathogen in microbiological respiratory sample occurring at least 4 days after the first episode of pneumonia

[c] Recorded length of mechanical ventilation starts from initiation of an appropriate antimicrobial treatment of VAP

[d] Group 4 molecules included: piperacilin + tazobactam, ticarcillin + clavulanic acid, 4th generation cephalosporin and antipseudomonal 3rd generation cephalosporin (see Table S1)

[e] Multidrug-resistant bacteria carriage (including extended spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE), methicillin-resistant *Staphylococcus aureus* but not carbapenemase-producing *Enterobacteriaceae*) was systematically screened on once weekly nasal and rectal samples. *Pseudomonas aeruginosa* resistant to ticarcillin or carbapenems and AmpC-hyperproducing *Enterobacteriaceae* obtained from clinical samples, whatever it was, were recorded

centres. Our results suggest a beneficial effect of pivotal antimicrobial DE on ESBL-PE but not on global multidrug-resistant acquisitions. As suggested before [3], even short-term exposure to empirical carbapenem therapy may have induced resistance. At least, after adjustment for factors associated with DE, this strategy did not seem to be harmful at the individual level.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4448-7) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

All authors declare they have no conflict of interest relevant to the present work.

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