EDITORIAL

Treatment and mortality of *Klebsiella pneumoniae* infections in critically ill patients: should we do and predict them better?

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The incidence of severe infections caused by Gram negative bacteria continues to increase, particularly with advances in medical care, and remains a major contributor to morbidity and mortality with variation between countries and between hospitals [1, 2]. The variable mortality rates of patients with severe infections caused by Gram negative bacteria depends largely on antibiotic resistance but also on differences involving the populations analyzed, including those related to age and underlying disease/comorbidity profiles [3]. Among Enterobacteriaceae, *Klebsiella pneumoniae* (Kp) is largely prevalent in patients admitted to acute and long-term care facilities, and has an outstanding propensity to develop antibiotic resistance [4]. The issue of Kp resistance, initially involving the class of cephalosporins due to the production of extended-spectrum β -lactamases (ESBL), has now been compounded by the emergence of strains that are also resistant to carbapenems [4, 5]. Kp is currently the most prevalent species among carbapenem-resistant (CR) Enterobacteriaceae, having become endemic in several countries so that the emergence of CR-Kp has been declared an ‘urgent’ and ‘critical’ threat by national and international organizations [6].

The dramatic increase of antibiotic resistance in Kp has been associated with high rates of treatment failure and increased mortality, especially when appropriate antimicrobial therapy is delayed. In addition to a delay in administration of appropriate therapy, septic shock, severity of

underlying disease, intensive care unit stay at infection onset, infection with ESBL or CR-KP strain are among the most common predictors of mortality reported in patients with severe infections caused by Kp. Conversely, infection source control and early appropriate antimicrobial treatment are associated with increased survival [4, 5, 7, 8]. Although earlier observations indicated that beta-lactam/beta-lactamase inhibitor combinations may be effectively used as carbapenem-sparing alternatives in treating infections with ESBL-producing Kp infections (provided that infecting strain is susceptible) [9, 10], a recent prospective randomized trial (MERINO) indicated a different, game-changing scenario. The study showed in a prospective, randomized fashion that in 378 patients with ceftriaxone resistant, piperacillin-tazobactam (pip-tazo) sensitive *Escherichia coli* and Kp bacteremia, pip-tazo failed to be non-inferior to meropenem for 30-day mortality [11]. The paper by Bertolini et al. [12] in this issue of *Intensive Care Medicine* provides interesting data that are very compelling and useful. Their prognostic model developed with 801 Kp-infected patients including multi-susceptible (MS, $n=451$), extended-spectrum cephalosporin-resistant but carbapenem-susceptible *Klebsiella* (ESCR-CS, $n=116$), and carbapenem-resistant *Klebsiella* (CR-Kp, $n=234$) correctly predicted deaths in MS-Kp and ESCR-CS-Kp subgroups, but not the in CR-Kp subgroup indicating that infection with the latter has a negative prognostic role for mortality (20% increase). Thus, appropriate antibiotic therapy is essential in the CR-Kp subgroup. Such therapy had no effect on mortality among the other groups (CS-Kp and ESCR-CS-Kp) with the exception of critically ill patients with ESCR-CS-Kp. In this group, pip-tazo treatment resulted in increased mortality, whereas empirical carbapenem

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therapy produced results similar to those infected with CS-Kp. Although it is tempting to conclude that results in the MERINO and Bertolini trials are overlapping, some caution should be exercised. In the MERINO trial, only 13.8% of patients had Kp bacteremia and, irrespective of the severity of infection, pip-tazo could not reach non-inferiority compared to meropenem. In the Bertolini trial, instead, only 7.4% of patients had primary bloodstream infections and pip-tazo fared worse only in the severely-ill. Overall, the practical message for clinicians from these two trials should be 'do not use pip-tazo in severely-ill patients infected (or at risk) with ESCR-CS-Kp'. The role of new inhibitor combinations in this indication remains to be elucidated, but recent reports are promising and support the effectiveness of carbapenem sparing regimens with ceftolozane/tazobactam and ceftazidime/avibactam for the treatment of ESCR-CS-Kp infections.

The Bertolini trial also underlines the importance of an urgent need for effective regimens for CR-Kp infections. Ceftazidime-avibactam has been a promising agent [13], but resistant KPC mutants have already emerged [14]. Meropenem-vaborbactam, plazomycin and eravacycline have been approved only for limited indications (e.g., complicated urinary tract and abdominal infections). There are several other molecules in the pipeline; however, none of them has yet reached the market [15, 16].

Attempts have been made to predict mortality associated with Kp infections, adjusting for risk factors using matched analysis, logistic regression, and propensity score. Most of the studies, however, based the analysis on comparison of crude mortality rates only, which does not allow reaching a strong conclusion, as it is impossible to rule out the greater probability of infection by these agents in patients with the highest risk of death. Furthermore, the retrospective design of many studies does not allow defining with certainty the mortality attributable to Kp infection as an outcome. In addition, the studies concerning bacteremic patients are generally more reliable since a positive blood culture for Kp clearly reflects an infection, while the isolation of Kp from clinical samples of non-bacteremic patients makes it difficult to distinguish a true infection from colonization in some cases. [4, 5, 7, 8].

The Italian study published in the present issue of ICM [12], despite some important limitations, demonstrated—by analysing a large sample of patients recruited in a prospective infection surveillance program [GiViTI (the Italian ICU network)]—that CR-Kp infections have a significant impact, increasing attributable mortality by 20%. Therefore, if CR-Kp infection in a severely ill patient is suspected based on risk factors (e.g., previous therapy with carbapenems or fluoroquinolones, or

patient coming from an environment with high prevalence of CR-K carriers) or rapid diagnostic tests, the empirical therapy should take CR-Kp into account. Thus, if a severely ill infected patient enters the ICU without a microbiological diagnosis, the specific risk factors for multidrug resistant germs should be immediately sought. In positive cases, carbapenem-sparing empirical therapy with piperacillin-tazobactam should be avoided and high dose carbapenems or the new options active against CR-KP (such as ceftazidime/avibactam or meropenem/vaborbactam) should be started as soon as possible.

In addition, the application of meticulous infection control measures along with other elements of antimicrobial stewardship remains the best approach for managing these highly resistant bacterial infections.

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Compliance with ethical standards

Conflicts of interest

Dr. Bassetti has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Gilead, Menarini, MSD, Pfizer, The Medicine Company, Tetrphase and Vifor. Dr. Akova has no conflict of interests. Dr. Tumbarello has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Gilead, MSD, Nordic Pharma and Pfizer.

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