Carbapenem-resistant *Klebsiella pneumoniae*—impact of infection-prevention and control interventions

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Over the last decades, carbapenem-resistant Enterobacteriaceae (CRE) have been increasingly reported from countries all over the world. CRE have emerged as a public health issue reaching a "critical" status according to the "global priority list of antibiotic-resistant bacteria to guide research, discovery and development of new antibiotics" provided by the World Health Organization (WHO) (1). CRE, mainly *Klebsiella pneumoniae* and *Escherichia coli*, cause a plethora of healthcare-associated infections, leading to high rates of adverse outcomes among hospitalized patients (2). Attempts to reduce the rapidly increasing incidence of CRE have mainly resulted in recommendations for infection control and prevention measures, active surveillance programs and enhanced antibiotic stewardship, as shown in guidelines provided by the WHO, the European Center for Disease Control (ECDC) and the Centers for Disease Control and Prevention (CDC) (3-5). A recently published systematic review on control of CRE, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in healthcare facilities concluded that multimodal infection control and prevention interventions consisting of three or more components are able to provide highly effective results regarding containment of spread of these pathogens although intervention strategies between the studies were highly variable (6).

A recent study by Li *et al.*, published in *Antimicrobial Resistance and Infection Control*, report the results of a 4-year quasi-experimental before-and-after study evaluating infection-prevention and control interventions to reduce colonization and infection with carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in an intensive care unit (ICU) setting in China (7). While they did not differentiate between carbapenemase-producing *K. pneumoniae* and *K. pneumoniae* harbouring other resistance mechanisms against carbapenems, carbapenemases have been recently shown to be the most frequent cause of carbapenem resistance in CRE in China, the New Delhi Metallo-beta-lactamase (NDM) and *Klebsiella pneumoniae* carbapenemase-2 (KPC-2) strain type ST11 representing the most commonly encountered carbapenemases (8). According to the surveillance of bacterial resistance in China, CRKP have reached rates of up to 13.4% until 2014 (9). The afore mentioned study by Li *et al.* was performed in a single tertiary care center in Shanghai and included 629 patients admitted to the ICU within the study period from January 1, 2013 until June 30, 2016. Four time periods with stepwise implementation of infection control measures were defined as shown in *Table 1*. The periods consisted of a 6-month baseline period (74 cases), followed by a 12-month intervention period (187 cases), within which standard infection prevention and control (IPC) measures such as active surveillance cultures

Table 1 Implementation of interventions within the different study periods (7)

Intervention	Baseline	Period 1	Period 2	Period 3
Active surveillance cultures		X	X	X
Target bundles interventions		X	X	X
Intravascular catheter-related infection		X	X	X
Ventilation-associated pneumonia		X	X	X
Catheter-associated urinary tract infection		X	X	X
Skin and soft tissue infections		X	X	X
Standard interventions		X	X	X
Contact precautions		X	X	X
Patient isolation: single room isolation/cohorting		X	X	X
Cohorting of medical care		X	X	X
Disinfection and sterilization		X	X	X
De-escalation strategy of interventions		X	X	X
Enhanced interventions			X	X
Medical staff education			X	X
Contact precautions of shared equipment			X	X
Enhanced terminal room disinfection			X	X

(ASC), de-escalation concepts, contact precautions, patient isolation or cohorting of medical staff, disinfection and sterilization, as well as targeted bundle interventions for intravascular catheter-related infections (ICRI), ventilator-associated pneumonia (VAP), catheter-associated urinary tract infections (CAUTI) and skin and soft tissue infections (SSTI) were introduced. Within the following 12-month period (222 cases), enhanced IPC interventions including additional external medical staff education, contact precautions of shared equipment and enhanced terminal room disinfection including irradiation with ultraviolet light were applied in addition to the interventions implemented within the first phase. The fourth period consisted of a 12-month follow up period (146 cases) in which all measures were sustained. During the study period, a total of 87 patients were colonized or infected with CRKP, most of which were classified as ICU-acquired. Incidence of overall and ICU-acquired CRKP colonization or infection decreased from 10.08 cases/1,000 ICU patient-days in the baseline period to 3.18 (overall) and 3.12 (ICU-acquired) cases/1,000 ICU patient-days in the early intervention period, yet an increase was observed by the end of the same period. Within the modified intervention period and the follow-up period, a slight decrease of incidence to 5.78 (overall) and 2.84 (ICU-acquired) cases, respectively, /1,000 ICU patient-days was observed again.

To our knowledge, this study is one of the first comparing the effects of IPC measures to a period within which IPC interventions for patients at high risk of colonization or infection with CRE were completely lacking, providing unique and valuable insights into the impact of IPC measures for control of CRE.

Implementation of IPC measures led to a significant reduction of overall and ICU-acquired CRKP cases within the first intervention period. Yet, no further significant effect in reduction was achieved when comparing the modified intervention period to standard IPC, implying a maintenance of a plateauing lower incidence of CRKP. In line, several studies conducted in countries with a higher prevalence of CRKP as compared to China similarly reported a decrease of CRKP-incidence when enhanced infection control measures in hospitals were introduced (10,11). Nevertheless, there seems to be a limitation in efficacy of IPC when CRKP-incidence has reached an endemic scope, wherein implementing more stringent measures in the in-hospital setting does not result in further decrease. Given the persisting rate of CRKP within the community and as well in long-term healthcare facilities (LTHF), a consecutive stable rate of hospital admissions of asymptomatic carriers of CRKP is being sustained (12,13). Schwaber *et al.* therefore even concluded that eradication of CRKP might not be achievable, suggesting to limit the efforts of IPC measures to containment of outbreaks (12). In a recently published review on the global spread of CRE in the community, a high variability in community-acquired infections or community-onset CRE ranging from 7.7% to 29.5% was reported, yet data was scarce and community-acquired infections were frequently healthcare-associated, limiting its validity (14). Community-based interventions such as improvement of hygiene, sanitation, wastewater management, farming and veterinary medication, as well as reasonable implementation of IPC interventions in LTHF seem to be needed to be introduced simultaneously to accomplish additional success in controlling CRE (15). Still it remains questionable whether in the study by Li *et al.*, CRKP were community- or hospital-acquired. Considering the similarity of the 13 collected and analysed CRKP bla_{KPC-2} ST11 strains within the follow-up period, in-hospital transmission seems to be more likely. Based on this assumption it might have been interesting to look into environmental transmission of CRKP, as establishment of silent reservoirs, such as cushions, mattresses, endoscopes, sinks and wastewater plumbing fixtures, has been proposed as an important driver of transmission of CRKP (16).

Li *et al.* combined a comprehensive list of interventions representing two different infection control "philosophies". On the one hand multiple components of standard infection control measures such as hand hygiene, patient isolation or cohorting and staff cohorting were initiated simultaneously in addition to ASC, which represent a targeted attempt specifically aiming to control CRKP-transmission. On the other hand, a wider based approach on infection control by targeted bundle interventions tackling ICRI, CAUTI, VAP and SSTI was applied, which regrettably were not described in detail. Accordingly, distinguishing effects of each individual intervention measure performed in this study is impossible, albeit a significant reduction of central line catheters and indwelling urinary catheters after implementation of the targeted bundle interventions suggests a certain contribution to the observed results. However, intervention bundles are a common method in infection control and prevention and the impact of each component might only be estimated by a stepwise approach as postulated in a review by Munoz-Price *et al.* (17), who found that ASC are more likely to contribute to control a CRE outbreak when the concomitant information is used to guide cohorting of affected patients and staff. No consensus on the adequate combination of IPC measures has yet been found and perhaps never will be due to differences in prevalence of CRE, underlying resistance mechanisms, environmental settings and available resources between healthcare institutions on national and international levels.

ASC are key for early detection of possible asymptomatic carriers. It is recommended by the WHO to screen patients at high risk of CRE colonization, such as patients with a history of CRE colonization, patients with contacts to CRE colonized or infected patients, patients with a history of recent hospitalization in endemic CRE settings or patients admitted to a ward with higher risk of CRE such as isolation wards or ICUs (3). In this study, screening sites included nasopharyngeal swabs, respiratory samples, urine and other possible infections sites, yet no data on frequency of positive results per site nor time point of positive screening results for CRKP on or after ICU-admission is reported. As for the guidelines by the WHO, the CDC and the ECDC, it is strongly recommended to perform testing of fecal material, which might be performed easier by rectal swabs (3-5). In this study, lack of rectal swabs as ASC might have resulted in missed cases of asymptomatic CRKP-carriers, maintaining the spread of CRKP within the ICU. Further interesting questions this study raises concern de-escalation interventions according to two consecutive negative ASC over at least one week; how frequent and at which time-point have they been able to de-escalate or had to re-escalate IPC interventions? To conduct this study, Li *et al.* put a lot of effort in collecting and analyzing a big amount of data. Further analyses of their dataset on the above-mentioned objectives could provide additional valuable contribution to so far still poorly investigated questions in CRE research and might help lead future recommendations on screening on behalf of de-escalation of IPC measures.

Furthermore, in line with the WHO guidelines for the prevention and control of CRE, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities, it is essential for multimodal strategies for infection control and prevention to undergo regular monitoring, auditing and feedback in order to succeed (3). Lack of the afore mentioned assessments might result in a higher rate of incompliance with IPC measures, which may present one of the main reasons causing the increase of incidence by the end of the first intervention period within the study by Li *et al.*, rather than a reappearance of a CRKP outbreak.

Decrease of incidence of CRKP after implementation of the modified interventions may have been caused by a regain of compliance, rather than due to the additional or enhanced interventions. Yet, keeping up with monitoring, audit and feedback might present a challenging task to accomplish since financial and human resources might not be available.

In conclusion, CRKP are an emerging global threat and with increasing antibiotic selective pressure, there is no end of spread in sight. The study by Li *et al.* underscores the efficacy of standard infection control and prevention measures for colonization or infection with CRKP but also reveals gaps in knowledge regarding ecologic reservoirs, sources and transmission chains raising important questions for further research.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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