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REFERENCES

1. Baker MA, Huang SS, Letourneau AR, et al. Lack of comprehensive outbreak detection in hospitals. *Infect Control Hosp Epidemiol* 2016;37:466–468.
2. Kanamori H, Weber DJ, Rutala WA. Healthcare outbreaks associated with a water reservoir and infection prevention strategies. *Clin Infect Dis* 2016;62:1423–1435.
3. Reuter S, Sigge A, Wiedeck H, Trautmann M. Analysis of transmission pathways of *Pseudomonas aeruginosa* between patients and tap water outlets. *Crit Care Med* 2002;30: 2222–2228.
4. Skally M, Duffy F, Burns K, et al. What may be lurking in the hospital undergrowth? Inapparent cross-transmission of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. *J Hosp Infect* 2014;88:156–161.
5. Harris SR, Cartwright EJP, Török ME, et al. Whole-genome sequencing for analysis of an outbreak of meticillin-resistant *Staphylococcus aureus*: a descriptive study. *Lancet Infect Dis* 2013;13:130–136.
6. Skally M, Donlon S, Finn C, et al. Outbreak surveillance: necessity is the mother of invention. Program and Abstracts of the 26th European Society of Clinical Microbiology and Infectious Diseases (ESCMID); April 09–12, 2016; Amsterdam. Abstract EV0876.

Necessity of a Competing Risk Approach in Risk Factor Analysis of Central Line–Associated Bloodstream Infection

To the Editor—With great interest we read the article by Carter et al[1] investigating risk factors for central line–associated bloodstream infections (CLABSI). For estimating the proportion without CLABSI depending on time, Kaplan-Meier (KM) curves were calculated to account for the at-risk time from insertion until the occurrence of CLABSI or removal of the catheter (which is treated as censoring in the model). If a bloodstream infection occurs during the use of a central venous catheter it is considered to be catheter associated and it is rather unlikely to develop a CLABSI 48 hours after removal of the catheter.[2] However, KM models assume that the hazard of CLABSI remains unchanged when a censoring event occurs. This censoring assumption is clearly not fulfilled in the case of removal of the catheter since removal leads to a reduction of risk. Hence, removal of the catheter without CLABSI should be considered as a competing event for CLABSI.[3]

Using standard KM models in the presence of competing events leads to overestimation of the cumulative risk.[3] This can be seen in figure 3 of Carter et al.[1] The KM curve lies at approximately 80% without CLABSI, which corresponds to a risk of CLABSI of approximately 20%. But considering the actual number of patients with CLABSI this leads to a risk of CLABSI $= \frac{385}{5648} = 6.8\,\%$.

To illustrate the bias in this setting, we analyzed simulated data of a simplified competing event setting based on values from the article of Carter et al[1] (code is available upon request). We consider 2 constant competing event hazards, λ_1 for CLABSI and λ_2 for removal without CLABSI. Hence, the cumulative incidence function (CIF) of CLABSI and the CIF of removal without CLABSI are given by this formula[4]:

$$CIF_1(t) = \frac{\lambda_1}{\lambda_1+\lambda_2} \times (1-\exp(-(\lambda_1+\lambda_2)\times t)) \qquad (1)$$

$$CIF_2(t) = \frac{\lambda_2}{\lambda_1+\lambda_2} \times (1-\exp(-(\lambda_1+\lambda_2)\times t)) \qquad (2)$$

With λ_i being the hazard for event i, i = 1; 2. Formulas 1 and 2 illustrate that the CIFs of the respective events depend on both the hazard for the event of interest and the hazard for the competing event. The right terms of formulas 1 and 2 represent the probabilities that any event occurs at time t. The left terms $\frac{\lambda_i}{(\lambda_1+\lambda_2)}, (i = 1; 2)$ display the probabilities that the occurring event at time t is event i.

As seen in the formulas above, there is a direct connection between the overall risk of CLABSI and the rates of both events[5]: $CIF_1(t)$ approximates the overall CLABSI risk $\frac{\lambda_1}{(\lambda_1+\lambda_2)}$ for large time points, which is estimated by $\frac{\#\text{CLABSI}}{\#\text{patients}} = \frac{385}{5648} = 6.8\%$. Analogously, the overall probability of removal without CLABSI is $\frac{5648-385}{5648} = 93.2\%$.

The constant hazard rate λ_1 is estimated by $\frac{\#\,\text{CLABSI}}{\#\text{line}-\text{days at risk}}$. Note that line-days at risk are line-days the patients are actually at risk—that is, line-days from insertion until removal without infection or until CLABSI. If D_i is the individual line-days contribution of patient i, λ_1 can also be written as

$$\lambda_1 = \frac{\#\,CLABSI}{\sum_{\{i=1\}}^{N} D_i} = \frac{\#\,CLABSI}{N \times \frac{1}{N}\sum_{\{i=1\}}^{N} D_i} = \frac{\#\,CLABSI}{N} \times \frac{1}{\overline{D}} \qquad (3)$$

with N being the number of patients and $\overline{D}$ being the mean line-days at risk. Similarly, the hazard for removal without

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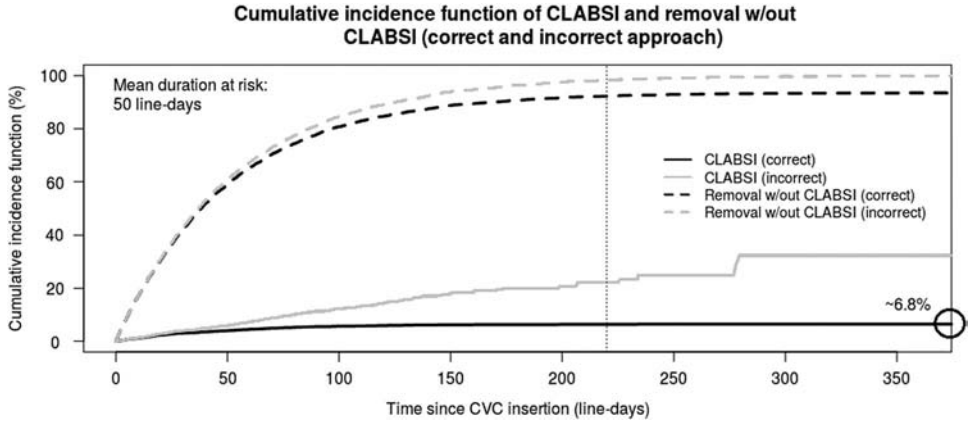

FIGURE 1. Cumulative incidence functions to study the bias caused by not accounting for the competing event (removal of central venous catheter [CVC] without central line–associated bloodstream infection [CLABSI]). Comparison of cumulative incidence functions (correct approach) with 1 minus the Kaplan-Meier curve (incorrect approach) for both events, CLABSI and removal without CLABSI.

CLABSI can be calculated by

$$\lambda_1 = \frac{\#removal\, w/o\ CLABSI}{N} \times \frac{1}{\overline{D}} \qquad (4)$$

Motivated by the data of Carter et al[1] we simulated data. The number of events (#CLABSI = 385) and number of patients (N = 5648) are given. For the formulas of the hazard rates 3 and 4 the mean line-days at risk is required. Since there is no information on the line-days of the first central venous catheter given in Carter et al[1] we considered $\overline{D} = 50$. This value lies somewhere in between the mean line-days considering either in-hospital line-days or total line-days as given by Carter et al[1]: $\left(\frac{\#\text{in hospital line} - \text{days}}{\#CVC} \approx 20 \text{ and } \frac{\#\text{total line} - \text{days}}{\#CVC} \approx 100\right)$. In Figure 1 we compare CIFs for the 2 events and 1 minus the KM curve in order to demonstrate the overestimation of the risk of developing an infection by using standard KM models mentioned above.

In Figure 1 the CIFs (correct approach) for each event, CLABSI and removal without CLABSI, are plotted. In addition, *1 minus the KM curve* for both events (incorrect approach, 1 − KM) is shown. At every time point the probabilities of CLABSI, removal without CLABSI, and remaining under risk should add up to 100%. Considering the curves of the KM approach at day 220 (dashed line) the probabilities of CLABSI (≈20%) and of removal without CLABSI (≈90%) already add up to more than 100% (≈110%). The incorrect approach ignoring the presence of competing events leads to an overestimation of the occurrence of the event of interest. Using the correct approach the CIF for CLABSI reaches 6.8%, which equals the actual risk of CLABSI as seen above.

In a further analysis Carter et al[1] used a Cox proportional hazards model in order to investigate the association between several covariates and CLABSI. This is a suitable approach but it is incomplete if it is performed only for the event of interest. Risk factors can be indirectly associated with the event of interest if they are associated with the competing event. Therefore, a Cox proportional hazards model for the competing events should be performed in addition in order to understand direct and indirect effects (cf. Wolkewitz et al[3]). Furthermore, investigation of the cumulative risk is necessary. This can be performed by the subdistribution hazard approach via a Fine and Gray model.[6]

We hope this letter provides a constructive contribution to future risk factor analyses in this kind of setting.

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REFERENCES

1. Carter JH, Langley JM, Kuhle S, Kirkland S. Risk factors for central venous catheter-associated bloodstream infection in pediatric patients: a cohort study [published online May 3, 2016]. *Infect Control Hosp Epidemiol* 2016;5:1–7.

https://doi.org/10.1017/ice.2016.166 Published online by Cambridge University Press

2. O'Grady NP, Alexander M, Dellinger EP, et al. Appendix A of Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2002;35:1281–1307.
3. Wolkewitz M, Cooper BS, Bonten MJM, Barnett AG, Schumacher M. Interpreting and comparing risks in the presence of competing events. *BMJ* 2014;349:g5060–g5060.
4. Grambauer N, Schumacher M, Dettenkofer M, Beyersmann J. Incidence densities in a competing events analysis. *Am J Epidemiol* 2010;172:1077–1084.
5. Beyersmann J, Gastmeier P, Schumacher M. Incidence in ICU populations: how to measure and report it? *Intensive Care Med* 2014;40:871–876.
6. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.

The Impact of Carbapenem-Resistant Enterobacteriaceae Type on Clinical Outcomes After the Recovery of This Organism From Urine of Critically Ill Patients

To the Editor—Carbapenem-resistant Enterobacteriaceae (CRE) are a leading cause of nosocomial infections. In the CRE group, the *Klebsiella pneumoniae* carbapenemase (KPC) producers stand out among the others and have been associated with serious infections and high mortality rates, mainly in intensive care units.[1] Apart from that, antimicrobial resistance among these isolates has increased worldwide, therefore limiting the therapeutic alternatives against KPC.[2]

Early detection of colonized or infected patients is crucial for the rapid management of patients and to establish infection control practices in order to avoid further dissemination and to curb the rise of antimicrobial resistance.[2]

We conducted a prospective survey from July 1, 2013, through November 30, 2015, to assess the impact of CRE type involved on the clinical outcomes and the emergence of antimicrobial resistance among CRE urinary or bloodstream isolates in a cohort of critically ill patients from an adult intensive care unit of a tertiary hospital in Porto Alegre, Southern Brazil.

Patients were included at the time of their first urine culture in which CRE were recovered. Isolates with reduced susceptibility to carbapenems (meropenem, imipenem, and/or ertapenem) were identified by MicroScan Walkaway automated system (Beckman Coulter) and confirmed by Etest (AB Biodisk). The presence of carbapenemase was detected by phenotypic testing and by gene detection using a polymerase chain reaction procedure, as previously described.[3]

The primary outcomes (or clinical outcomes) were determined by result of a subsequent urine culture (negative or recurrent/subsequent bacteriuria) and/or blood culture with the same CRE within 90 days and mortality at 30 days. Development of antimicrobial resistance (which was the microbiologic outcome in this study) was evaluated comparing results from the first CRE isolate with those obtained in a subsequent sample (urine or blood) for amikacin, gentamicin, polymyxin B, tigecycline, and fosfomycin.

During the study period, a total of 109 patients were included. In 85 patients, KPC-2-producers (mostly *Klebsiella pneumoniae* [*Kp*]) were recovered whereas, in the remaining 24, a culture with carbapenemase nonproducers was obtained. Of the 85 patients with KPC-2-*Kp* bacteriuria, 19 died during the 30-day period, 27 had a negative urine culture or were discharged, 14 had bacteriuria with a microorganism other than KPC-2-producers, and 25 had a recurrent KPC-2-*Kp* bacteriuria. Moreover, 15 patients, including 5 patients who also had a recurrent urinary isolate, had an episode of bacteremia due to KPC-2-*Kp* and the 30-day mortality for these patients was 47% (Table 1). Regarding carbapenemase nonproducers, no patients were bacteremic, and only 4 of them had recurrent bacteriuria.

In 35 patients, a KPC-2-*Kp* isolate was recovered in a subsequent bacteriuria/bacteremia case and a minor increase in resistance was observed for polymyxin B (34% vs 43%), gentamicin (57% vs 69%), amikacin and tigecycline (14% vs 26%). For fosfomycin, used more often nowadays as therapy to treat urinary tract infections due to KPC producers, a significant increase in resistance was detected (11% vs 34%; OR, 4.04 [95% CI, 1.1–14.2], $P = 0.03$), driven by prior fosfomycin use, as previously described.[4] On the other hand, no increase of antimicrobial resistance was observed among isolates of carbapenemase nonproducers.

In this study, the urine specimen was used as a starting point for surveillance for KPC-2-*Kp* isolated during hospitalization because KPC-2-*Kp* was found most commonly in urine

TABLE 1. Microbiologic Characteristics and Clinical Outcomes After CRE Bacteriuria

CRE bacteriuria (n/total n, %)	Carbapenemase	Urinary outcome (n/total n, %)	Bacteremia (n/total n, %)	30-Day mortality (n/total n, %)
Klebsiella pneumoniae (82/109, 75%)	KPC-2	Recurrence (25/82, 30%)	Yes (15/82, 18%)	Yes (7/15, 47%)
Enterobacter cloacae (18/109, 17%)	None	NSC (13/18, 72%)	No	NA
K. pneumoniae (6/109, 6%)	None	NSC (4/6, 67%)	No	NA
Escherichia coli (3/109, 3%)	KPC-2	NSC (3/3, 100%)	No	NA

NOTE. CRE, carbapenem-resistant Enterobacteriaceae; NA, not applied; NSC, negative subsequent culture.

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