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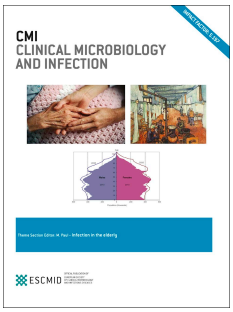

Distribution of pathogens and antimicrobial resistance in bacteremia according to hospitalization duration: A nationwide surveillance study in Switzerland

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Distribution of Pathogens and Antimicrobial Resistance in Bacteremia according to hospitalization duration: A Nationwide Surveillance Study in Switzerland

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Abstract

Objectives. Changing microorganism distributions and decreasing antibiotic susceptibility with increasing length of hospital stay have been demonstrated for the colonization or infection of selected organ systems. We wanted to describe microorganism distribution or antibiotic resistance in bacteremia according to duration of the hospitalization using a large national epidemiological/microbiological database (ANRESIS) in Switzerland.

Methods. We conducted a nationwide, observational study on bacteremia using ANRESIS data from 1st January 2008 to 31st December 2017. We analyzed data on bacteremia from those Swiss hospitals that sent information on a regular basis during the entire study period. We described the pathogen distribution and specific trends of resistance during the hospitalization for *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. marcescens* and *S. aureus*.

Results. We included 28,318 bacteremia isolates from 90 Swiss hospitals. The most common etiology was *E. coli* (33.4%, 9,459), followed by *S. aureus* (16.7%, 4,721), *K. pneumoniae* (7.1%, 2,005), *E. faecalis* (5.2%, 1,473), *P. aeruginosa* (4.3%, 1,228), *S. pneumoniae* (4.3%, 1,208) and *E. faecium* (3.9%, 1,101). We observed 489 (1.73%) *Serratia marcescens* isolates. We observed an increasing trend for *Enterococcus faecium* (from 1.5% at day 0 to 13.7% at day 30; p<0.001), *K. pneumoniae* (from 6.1% to 7.8%, p<0.001) and *P. aeruginosa* (from 2.9% to 13.7%, p<0.001) with increasing duration of hospitalization; and a decreasing trends for *E. coli* (from 41.6% at day 0 to 21.6% at day 30; p<0.001) and *S. aureus* (from 14.4% to 14.7%; p<0.001). Ceftriaxone resistance among *E. coli* remained stable for the first 15 days of hospitalization and then increased. Ceftriaxone resistance among *K. pneumoniae and S. marcescens* and oxacillin resistance among *S. aureus* increased linearly during the hospitalization. Cefepime resistance among *P. aeruginosa* remained stable during the hospitalization.

Conclusions. We showed that hospitalization duration is associated with a species- and antibiotic class-dependent pattern of antimicrobial resistance.

Introduction

Hospital-acquired bloodstream infection is a common and important healthcare-associated infection and is associated with high mortality [1]. Little is known on the impact of hospitalization duration on the epidemiology of hospital-acquired bloodstream infections. Decreasing antibiotic susceptibility with increasing length of hospital stay has been demonstrated for the colonization or infection of selected organ systems [2-4]. Only few investigators with modest numbers of isolates have scrutinized this question for bacteremia [5]. We suspected a systematic relationship between duration of hospitalization and distribution of microorganisms or increasing antimicrobial resistance. Our aim was therefore to describe distribution of pathogens and level of antimicrobial resistance in bacteremia according to the duration of the hospitalization using a large national epidemiological/microbiological database in Switzerland.

Material and methods

Study setting and design

We conducted a nationwide, retrospective observational study on bacteremia using the Swiss Antibiotic Resistance Surveillance System (ANRESIS) data from 1st January 2008 to 31st December 2017. The ANRESIS program receives information on all positive blood cultures from 20 Swiss microbiology laboratories, each of them collecting data from several hospitals distributed across the country. Accordingly, we analyzed data of patients from those Swiss hospitals that sent information on a regular basis during the entire study period without major fluctuations (at least 20 positive blood cultures during the study period). Only isolates from hospitals sending information on hospital length of stay at time of sampling were considered (see Table in the supplementary material). Isolates identified abroad were excluded. In order to remove any bias introduced by an individual patient's resistance evolution, only the first isolate of a species per patient was eligible for the study and duplicates (*i.e.*, the same microorganism detected in subsequent blood cultures during the hospitalization) were excluded. Moreover, we restricted the dataset to pathogens that occurred ≥50 times during the study period. Typical skin contaminants (*e.g.*, coagulase-negative Staphylococci [CoNS]) and fungemias were excluded. A comprehensive list of typical skin contaminant was described elsewhere [6].

Microbiological analyses

Species identification and antimicrobial susceptibility testing are performed at local laboratories according to European Committee on Antimicrobial Susceptibility Testing (EUCAST, https://eucast.org) or Clinical and Laboratory Standards Institute (CLSI, https://clsi.org) guidelines. Most of the participating laboratories switched from CLSI to EUCAST breakpoints between 2011 and 2013. All laboratories are participating in at least one external quality program of either National External Quality Assessment Service (NEQAS; www.uknegas.org.uk) or the Swiss quality control program by the Institute for Medical Microbiology, University of Zürich (http://www.imm.uzh.ch/services/qc.html).

Resistant isolates were defined as those who were resistant or displayed intermediate susceptibility against the antibiotic tested. Resistance against *first-line* antibiotics was defined as resistance against ceftriaxone or amoxicillin- clavulanic acid for gram-negative microorganisms, amoxicillin for enterococci, and oxacillin for *Staphylococcus aureus*. All non-fermenting gram-negative bacteria were considered as resistant to *first-line* antibiotics as detailed above. Resistance against *second-line* antibiotics was defined as carbapenem resistance for gram-negative, and vancomycin resistance for gram-positive microorganisms. Specific analyses of resistance data were performed for selected frequently detected microorganisms: *Escherichia coli* (ceftriaxone), *Klebsiella pneumoniae* (ceftriaxone), *Staphylococcus aureus* (oxacillin), *Serratia marcescens* (ceftriaxone) and *Pseudomonas aeruginosa* (cefepime).

Variables routinely collected

Epidemiological data allowed stratification by sex, age group, hospital type (university *vs* community), department (ICU *vs* non-ICU), region (southwest *vs* northeast) and year of detection (2008–2017). “Early hospital-acquired” was defined as bacteremias between 2 and 5 days after hospitalization, whereas “late hospital-acquired” bacteremias were those occurring >5 days after hospitalization. The remaining bacteremias were considered “community-acquired”.

Statistical analysis

The statistical plan had four steps: 1) to describe characteristics of bacteremia in different hospital acquisition setting; 2) to describe trends in pathogen distribution and resistance during the

hospitalization using graphical descriptions, 3) to quantify daily increase in proportion of microorganisms or resistance during the hospitalization and, finally, 4) to describe potentially non-linear antibiotic resistance proportion relative to hospitalization duration.

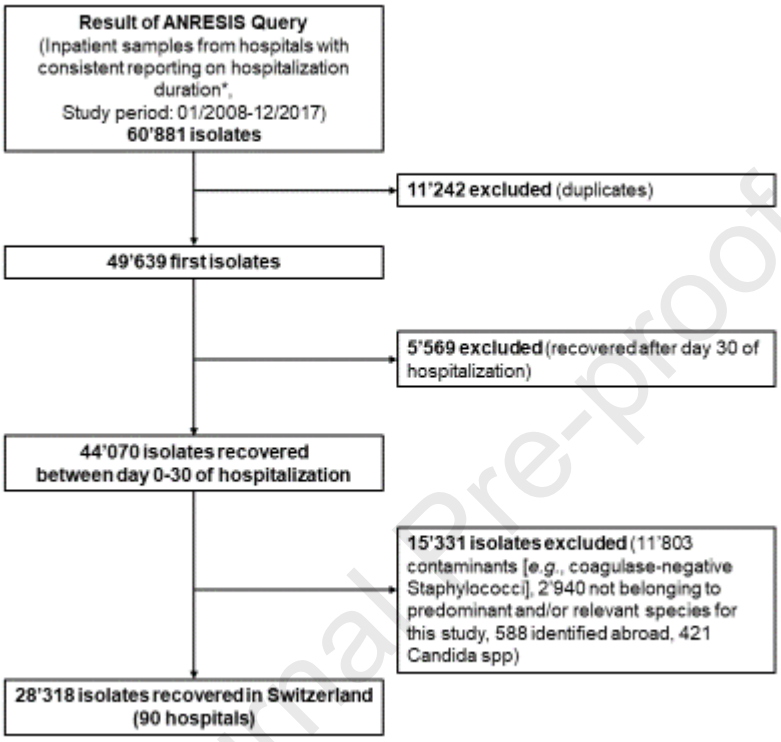
We used individual bacteremia data for all statistical analyses. Characteristics depending of hospitalization duration were compared with chi-square, Fisher- and Kruskal-Wallis test, as appropriate. The prevalence of specific microorganism was calculated as the number of this microorganism over the total number of isolates. The prevalence of specific resistance was calculated as the number of resistant strains over the total number of this isolate. Changes in the percentage were assessed using the Cochrane– Armitage test. In order to quantify daily increase in proportion of microorganisms and resistance, we applied multivariate logistic regression models: the prevalence of a specific microorganism (or a specific resistance against an antibiotic) was modelized and the interest variable (duration of hospitalization) was forced in the model. We adjusted for age, sex, hospital type, department and year of detection and we stratified our models by hospital (*i.e.*, center; PROC logistic of SAS with STRATA statement). To describe potentially non-linear antibiotic resistance effects relative to hospitalization duration we fitted unadjusted generalized additive models (PROC GAM of SAS). All statistical analyses were performed with R (version 3.6.1) and SAS (version 9.4). As the analysis was performed on anonymized non-genetic surveillance data, ethical consent was not required according to the Swiss law for research on humans. This study complied with the STROBE guidelines for observational studies.

Results

Epidemiological characteristics of bacteremias, 2008-2017

We screened 199 hospitals in the entire ANRESIS database. Among them, 44 hospitals (22%) reported less than 20 positive blood cultures during the study period and were therefore excluded. In the remaining 155 hospitals, 56 did not report information on length of stay and were therefore excluded. Overall, among the 137’592 positive blood cultures isolates, 76’711 were excluded (55.8% of positive blood cultures isolated, Table in Supplementary Material). From 1 January 2008 to 31 December 2017, data on 28,318 bacteremias were included (Figure 1).

Figure 1: Flowchart of isolates included in the study



Legend. *hospital reporting at least 20 positive blood cultures during the study period and hospitals reporting admission date.

Bacteremias were early hospital-acquired (day 2-5) in 4,457 episodes (15.7%) and late hospital-acquired (>5 days) in 9,039 (31.9%). Late hospital-acquired bacteremia occurred more frequently in university hospitals, males, patients <60 years, and in the ICU setting (see Table).

Table: Baseline epidemiological characteristics associated with the isolates included, stratified by acquisition.

	Community-acquired	Early hospital-acquired	Late hospital-acquired	p-value
Episodes, n	14822	4457	9039	
Sex, male n (%)	8336 (56.3)	2788 (62.6)	5835 (64.6)	<0.001
Age, >= 60y n (%)	10728 (72.4)	3178 (71.3)	6399 (70.8)	0,025

Region, Southwest n (%)	3763 (25.6)	1124 (25.7)	2626 (29.7)	<0.001
Hospital type, university hospital n (%)	2336 (15.8)	1161 (26.0)	3164 (35.0)	<0.001
Department, non-ICU n (%)	13108 (88.4)	3700 (83.0)	7533 (83.3)	<0.001
Year of detection, 2008-2012* n (%)	6626 (44.7)	1985 (44.5)	4358 (48.2)	<0.001

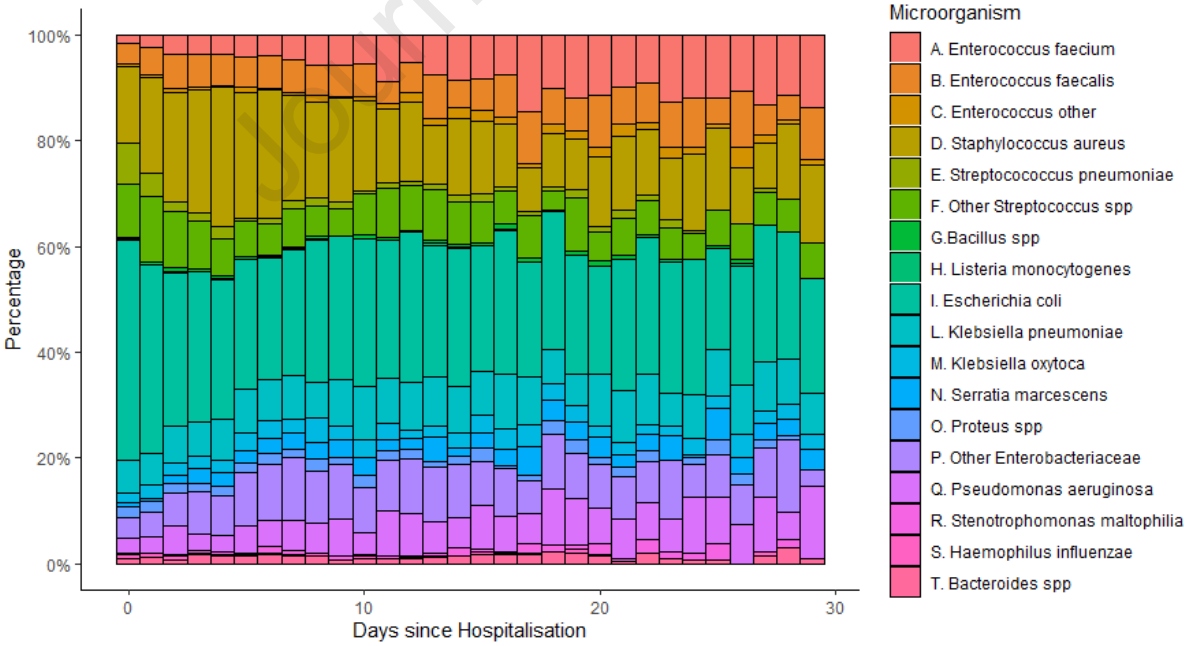
Notes. Community acquired: 0-2 days after hospital admission. Early hospital-acquired: 2-5 days after the hospitalization. Late hospital-acquired: >5 days after the hospitalization. ICU: Intensive Care Unit. y: years old. n: number. * versus 2013-2017

The most common etiology was *E. coli* (33.4%, 9,459), followed by *S. aureus* (16.7%, 4,721), *K. pneumoniae* (7.1%, 2,005), *E. faecalis* (5.2%, 1,473), *P. aeruginosa* (4.3%, 1,228), *S. pneumoniae* (4.3%, 1,208) and *E. faecium* (3.9%, 1,101). We observed 489 (1.73%) *Serratia marcescens* isolates.

Trends in microorganism distribution relative to hospitalization duration

The number of microorganism observed during the study period were illustrated in the supplementary Figure 1. The distribution of microorganism during the hospitalization is shown in Figure 2.

Figure 2: Distribution of microorganism during the hospitalization.



Notes. spp: species. A-H: Gram positives. I-P: *Enterobacteriaceae* (Gram negatives). Q/R: Non-fermenters (Gram negatives). S/T: Others.

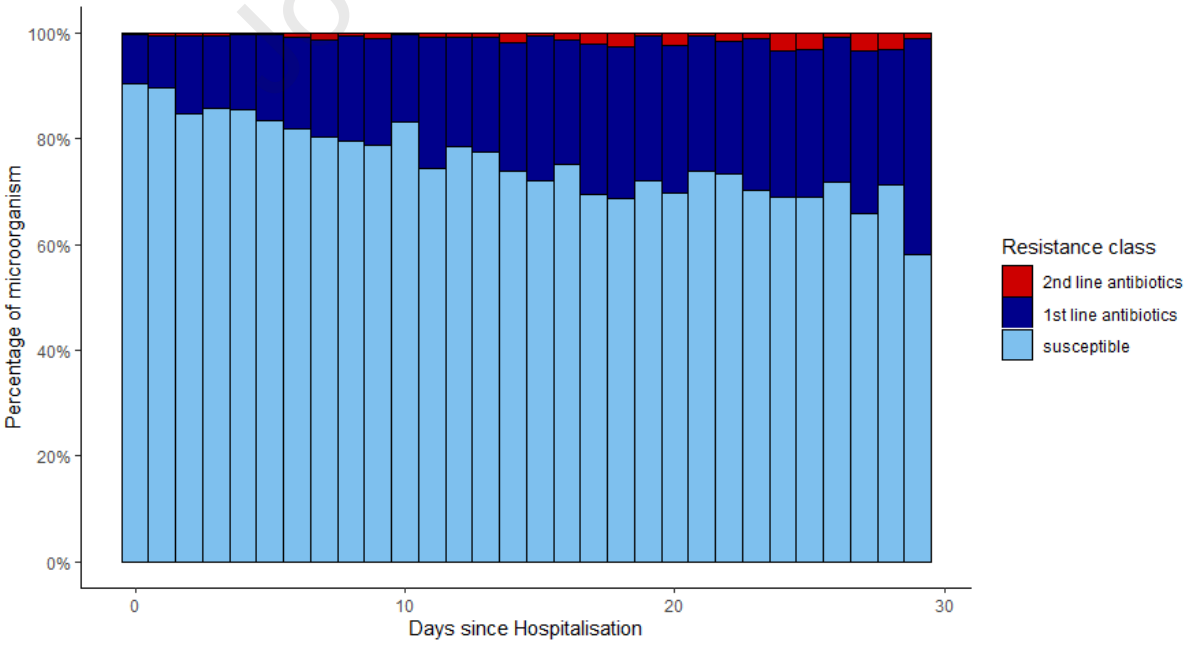
We observed an increasing trend for *Enterococcus faecium* (from 1.5% at day 0 to 13.7% at day 30, $p_{for\ trend}<0.001$), *K. pneumoniae* (from 6.1% to 7.8%, $p_{for\ trend}<0.001$) and *P. aeruginosa* (from 2.9% to 13.7%, $p_{for\ trend}<0.001$) with increasing duration of hospitalization. The adjusted distribution of microorganism proportion relative to hospitalization duration (starting with day 0) yielded increasing *Enterococcus faecium* and *K. pneumoniae* bacteremias at a relative daily rate of 7.5% (CI 95% 6.7-8.2, p<0.001) and 1.8% (CI 95% 1.1-2.5, p<0.001), respectively. The relative daily rate increase of *P. aeruginosa* was 4.6% (CI 95% 3.8-5.3, p<0.01). We observed a change in proportion from *E. faecalis* to *E. faecium* during the hospital stay (see Supplementary Material, Figure 2).

In contrast, decreasing trends for *E. coli* (from 41.6% at day 0 to 21.6% at day 30, $p_{for\ trend}<0.001$) and *S. aureus* (from 14.4% at day 0 to 14.7% at day 30, $p_{for\ trend}<0.001$) were observed. The daily decreasing rate was 3.1% for *E. coli* (95% CI 2.7-3.5, p<0.0001) and 1.4% for *S. aureus* (95% CI 0.9-1.8, p<0.0001), respectively.

Resistance trends

Antimicrobial resistance to first-line antibiotics was 9.3% at day zero and then increased continuously ($p_{for\ trend}<0.001$, Figure 3) at an adjusted relative rate of 5.5% per day (95% CI 5.0-6.0, p<0.001).

Figure 3: Antimicrobial resistance to first- and second-line antibiotics across all species.

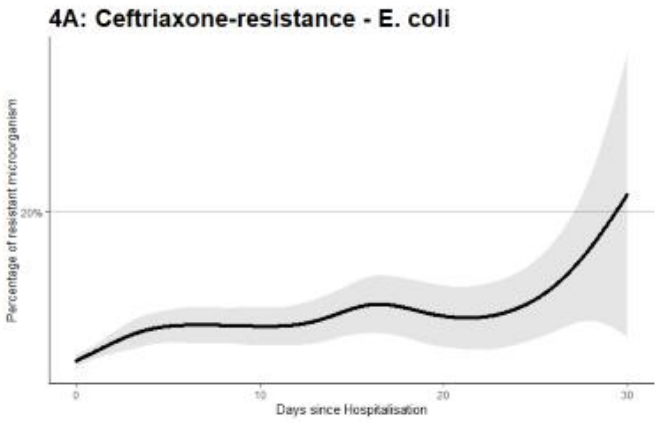


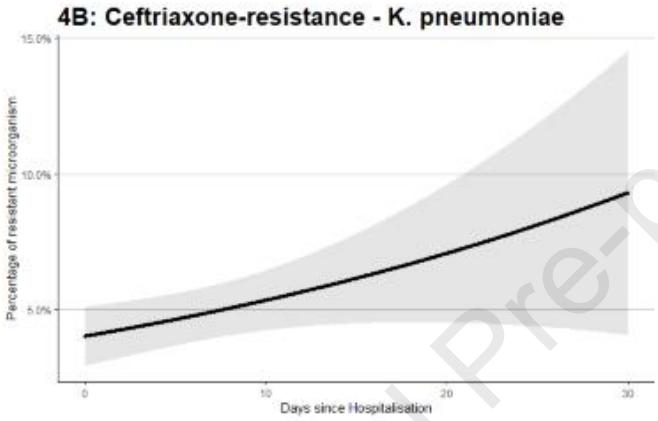
Notes. First-line antibiotic resistance (dark blue): ceftriaxone and amoxicillin- clavulanic acid for gram-negative microorganisms, amoxicillin for Enterococci or oxacillin for *S. aureus*. Second-line antibiotic resistance (red): Carbapenem for Gram-negative and vancomycin for Gram-positive microorganisms.

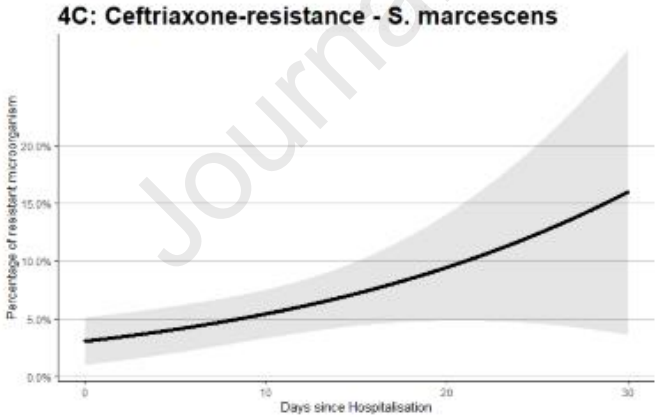
In contrast, antimicrobial resistance against second line antibiotics was rarely observed (0.7% of isolates), thus precluding a trend's analysis.

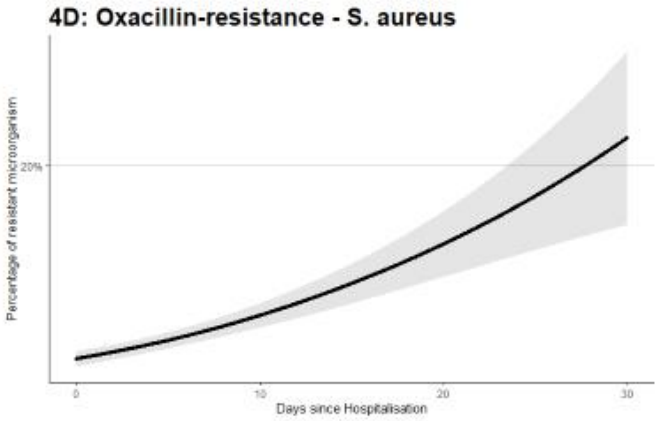
Our graphical descriptions showed that resistance patterns relative to hospitalization duration were pathogen-specific (Figure 3). Among *E coli* isolates, 670 (7.1%) were ceftriaxone resistant. Ceftriaxone resistance among *E. coli* remained stable for the first 15 days of hospitalization and then increased (non-linear relationship, p=0.016). Among *K. pneumoniae* isolates, 93 (4.6%) were ceftriaxon resistant and ceftriaxone resistance increased linearly during the hospitalization (p=0.21). Similarly, among *S. aureus* isolates, 263 isolates (5.6%) were oxacillin resistant and oxacillin resistance increased linearly during the hospitalization (p=0.13). Ceftriaxone resistance among *S. marcescens* increased linearly during the hospitalization (Figure 4). Interestingly, cefepime resistance among *P. aeruginosa* remained stable during the hospitalization (supplementary Figure 3).

Figure 4: Resistance proportions of *Escherichia coli*, *Klebsiella pneumoniae, Serratia marcescens* and *Staphylococcus aureus* – relative to hospitalization duration.









Legend. 95% confidence intervals highlighted in grey.

Discussion

Here we report a total 28,318 bacteremia microorganisms in a large dataset of 90 Swiss hospitals. Our goal was to describe the influence of hospital length of stay on pathogen distribution and antimicrobial resistance in bacteremia isolates. To our knowledge, our study is the most thorough analysis to date to address this research question. We observed that 1) the hospitalization duration was associated with the pathogen distribution in bacteremic episodes, with proportions of enterococcal bacteremia being more pronounced in the course of hospitalization, 2) the resistance against first-line antibiotics was characterized by a steady increase during the hospitalization duration and 3) antibiotic specific trends differed for the different bacteria analyzed.

The role enterococcal bacteremias appear to be more pronounced in the course of hospitalization. Unfortunately, we cannot provide rational explanations for his finding. It is conceivable that an increasing use of cephalosporins (*e.g.*, ceftriaxone and cefepime) in Switzerland may play a major role [7]. Although our epidemiological analysis did not allow firm clinical conclusions, enterococcal treatment should be considered for therapy of very *late* severe infections.

The decision between narrow versus broad-spectrum antimicrobial therapy in severe sepsis is often based on a time cut-off between community-acquired or early hospital-acquired and late hospital-acquired (or “healthcare-associated”) presentation. Considering for example the acquisition of multi-drug resistant gram-negative bacteremia, some authors have chosen a time cut-off of 5 days for comparisons between early and late onset following hospital admission [8]. For surveillance purposes, the Centers for Disease Control and Prevention defined “healthcare-associated” infections as those that occurred after the third hospital day [9]. We found that overall resistance against first-line antibiotics increased *linearly* during the hospitalization duration, however, the detailed view of individual species shows a much more complicated picture. Our data therefore provides evidence that simplistic recommendations based on a specific time cut-off may not properly reflect the complex epidemiological situation. Rather, the increasing duration of hospitalization should be included in the consideration of empirical therapy as a continuous and interacting risk factor along with other parameters.[10].

The linear increase of ceftriaxone resistance among *K. pneumoniae* and oxacillin resistance among *S. aureus* probably reflected a predominantly time-dependent dynamic. These findings suggested an important role of the hospital environment for the acquisition and subsequent infection with these specific resistant microorganisms [11-13]. In contrast, selection by antimicrobial therapy may better explain ceftriaxone resistance among *E. coli* [13, 14]: This assumption is based on the relatively stable resistance proportion for *E. coli* ceftriaxone resistance in the first 15 days of hospitalization, followed by a late increase.

Our study has several limitations. First, similarly to other resistance surveillance databases, relevant clinical data was unavailable (*e.g.*, patient-based antimicrobial treatment, comorbidities, complication during the hospitalization, information on invasive devices, specific data on wards of admission). Second, Switzerland is considered a country of low prevalence of multidrug resistant microorganisms. The generalization to other geographical settings requires caution; further studies are necessary in countries where high rates of resistance against first- and second class antibiotics are currently observed. Third, no information on molecular resistance mechanisms (*e.g.*, extended-spectrum beta lactamase-producing bacteria). Fourth, we excluded all CoNS from our analysis and, therefore, first and second line antibiotic resistance should be interpreted with caution, especially the low vancomycin resistance. Fifth, due to the low numbers of bacteremias in some small centers, we could not introduce a random effect for the different centers in our models and our analyses were only stratified by geographical region. Sixth, no baseline data on the number of hospital admissions was available and we used only the total number of bacteremias as denominator. Finally, a selection bias could have been introduced when restricting the analysis to bacteremias with known acquisition relative to hospitalization duration, but we consider this bias to be negligible.

In conclusion, we illustrated that hospitalization duration exerts a species- and antibiotic class-dependent effect on antimicrobial resistance. Further clinical studies and/or recommendations may be based on these findings.

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Transparency declaration

Conflict of interest. The authors have disclosed that they do not have conflict of interest. JFT received fees for lectures to 3M, MSD, Pfizer, and Biomerieux. JFT received research grants from Astellas, 3M, MSD, and Pfizer. JFT participated to advisory boards of 3M, MSD,

Bayer Pharma, Nabriva, and Pfizer. ANRESIS is co-financed by the Institute for Infectious Diseases, University of Bern and the Swiss Federal Office of Public Health (SFOPH). AK has received travel grant and meeting expenses from Gilead, Viofor and the World Health Organisation (WHO). AK provides not interpreted annual resistance data to LEO pharmaceutic company and the Swiss government. AK is advisor of the SFOPH concerning antibiotic resistance epidemiology in Switzerland.

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Contributions. NB and RS designed the study. AK acquired the data. NB, RS and AA did the statistical analysis. NB, AA and RS analyzed and interpreted the data. NB, JM, JFT and

RS drafted the manuscript. All authors critically reviewed the manuscript and approved the final report.

Preliminary results were presented at the ECCMID conference, Amsterdam 2019 (abstract number: O0293).