Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

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

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ARTICLE INFO

Article history:
Received 17 December 2020
Received in revised form
8 April 2021
Accepted 21 April 2021
Available online xxx

Editor: J. Rodriguez-Baño

Keywords:
Bacteraemia
Bloodstream infection
Hospitalization duration
Microorganism
Resistance
Length of stay

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 bacteraemia according to duration of the hospitalization using a large national epidemiological/microbiological database (ANRESIS) in Switzerland.

Methods: We conducted a nationwide, observational study on bacteraemia using ANRESIS data from 1 January 2008 to 31 December 2017. We analysed data on bacteraemia 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 hospitalization for *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia marcescens* and *Staphylococcus aureus*.

Results: We included 28 318 bacteraemia isolates from 90 Swiss hospitals. The most common aetiology was *E. coli* (33.4%, 9459), followed by *S. aureus* (16.7%, 4721), *K. pneumoniae* (7.1%, 2005), *Enterococcus faecalis* (5.2%, 1473), *P. aeruginosa* (4.3%, 1228), *Streptococcus pneumoniae* (4.3%, 1208) and *Enterococcus faecium* (3.9%, 1101). We observed 489 (1.73%) *S. marcescens* isolates. We observed an increasing trend for *E. 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 decreasing trends for *E. coli* (from 41.6% to 21.6%; $p < 0.001$) and *S. aureus* ($p < 0.001$). 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.

Discussion: We showed that hospitalization duration is associated with a species- and antibiotic class-dependent pattern of antimicrobial resistance. **Niccolò Buetti, Clin Microbiol Infect 2021;▪:1**

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

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https://doi.org/10.1016/j.cmi.2021.04.025

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 bacteraemia [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 bacteraemia 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 bacteraemia using the Swiss Antibiotic Resistance Surveillance System (ANRESIS) data from 1 January 2008 to 31 December 2017. The ANRESIS programme 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 analysed 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 S1). 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 pathogen species that occurred $\geq$50 times during the study period. Typical skin contaminants (e.g. coagulase-negative staphylococci (CoNS)) and fungaemias were excluded. A comprehensive list of typical skin contaminants 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 programme of either National External Quality Assessment Service (NEQAS; www.uknegas.org.uk) or the Swiss quality control programme 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. 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 (2008–2012 vs 2013–2017). 'Early hospital acquired' was defined as bacteraemias between 2 and 5 days after hospitalization, whereas 'late hospital-acquired' bacteraemias were those occurring >5 days after hospitalization. The remaining bacteraemias were considered 'community acquired'.

Statistical analysis

The statistical plan had four steps: (a) to describe characteristics of bacteraemia in different hospital acquisition setting; (b) to describe trends in pathogen distribution and resistance during the hospitalization using graphical descriptions, (c) to quantify daily increase in proportion of microorganisms or resistance during the hospitalization and, finally, (d) to describe potentially non-linear antibiotic resistance proportion relative to hospitalization duration.

We used individual bacteraemia data for all statistical analyses. Characteristics depending on hospitalization duration were compared with chi-square, Fisher and Kruskal–Wallis tests, 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. centre; 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, ethics 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 bacteraemias, 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 S1). From 1 January 2008 to 31 December 2017, data on 28 318 bacteraemias were included (Fig. 1).

Bacteraemias were early hospital acquired (days 2–5) in 4457 episodes (15.7%) and late hospital-acquired (>5 days) in 9039 (31.9%). Late hospital-acquired bacteraemia occurred more frequently in university hospitals, males, patients <60 years, and in the ICU setting (Table 1).

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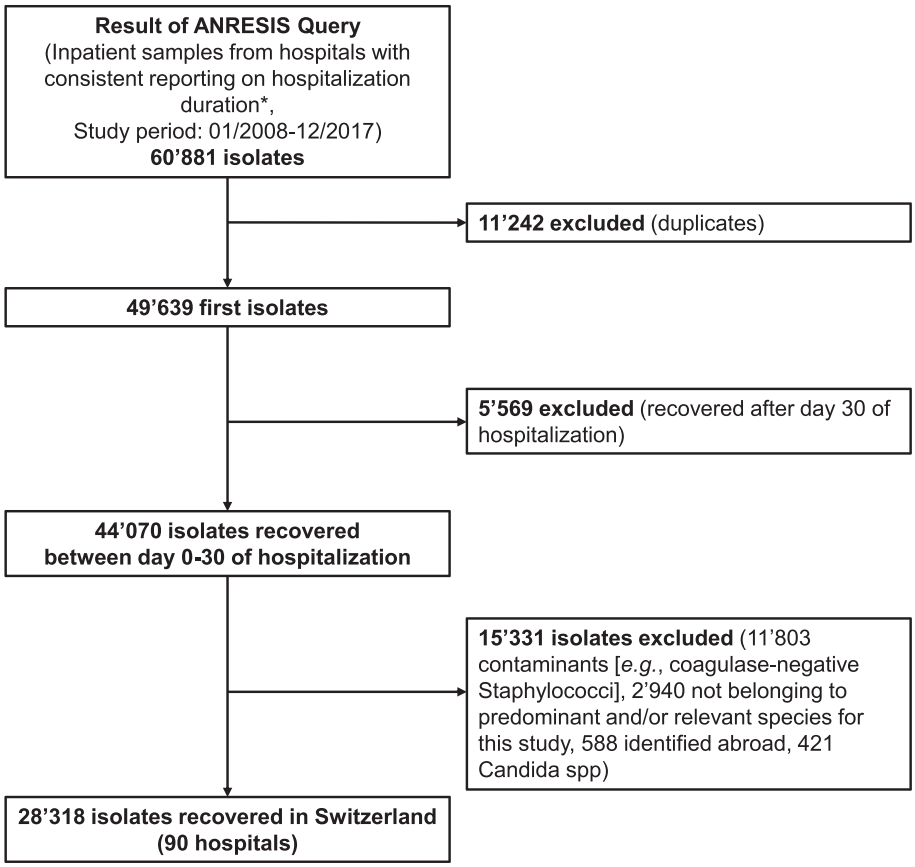

Fig. 1. Flowchart of isolates included in the study. *Hospital reporting at least 20 positive blood cultures during the study period and hospitals reporting admission date.

Table 1
Baseline epidemiological characteristics associated with the isolates included, stratified by acquisition

	Community acquired	Early hospital acquired	Late hospital acquired	p
Episodes, *n*	14 822	4457	9039	
Sex, male *n* (%)	8336 (56.3)	2788 (62.6)	5835 (64.6)	<0.001
Age, ≥ 60 y *n* (%)	10 728 (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* (%)	13 108 (88.4)	3700 (83.0)	7533 (83.3)	<0.001
Year of detection, 2008–2012[a] *n* (%)	6626 (44.7)	1985 (44.5)	4358 (48.2)	<0.001

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.
[a] Versus 2013–2017.

The most common aetiology was *E. coli* (33.4%, 9459), followed by *S. aureus* (16.7%, 4721), *K. pneumoniae* (7.1%, 2005), *E. faecalis* (5.2%, 1473), *P. aeruginosa* (4.3%, 1228), *S. pneumoniae* (4.3%, 1208) and *E. faecium* (3.9%, 1101). We observed 489 (1.73%) *S. marcescens* isolates.

Trends in microorganism distribution relative to hospitalization duration

The numbers of microorganisms observed during the study period are illustrated in Fig. S1. The distribution of microorganisms during hospitalization is shown in Fig. 2.

We observed an increasing trend for *E. 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* bacteraemias at a relative daily rate of 7.5% (95% CI 6.7-8.2, $p < 0.001$) and 1.8% (95% CI 1.1–2.5, $p < 0.001$), respectively. The relative daily rate increase of *P. aeruginosa* was 4.6% (95% CI 3.8–5.3, $p < 0.01$). We observed a change in proportion from *E. faecalis* to *E. faecium* during the hospital stay (Fig. S2).

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, Fig. 3) at an adjusted relative rate of 5.5% per day (95% CI 5.0–6.0, $p < 0.001$).

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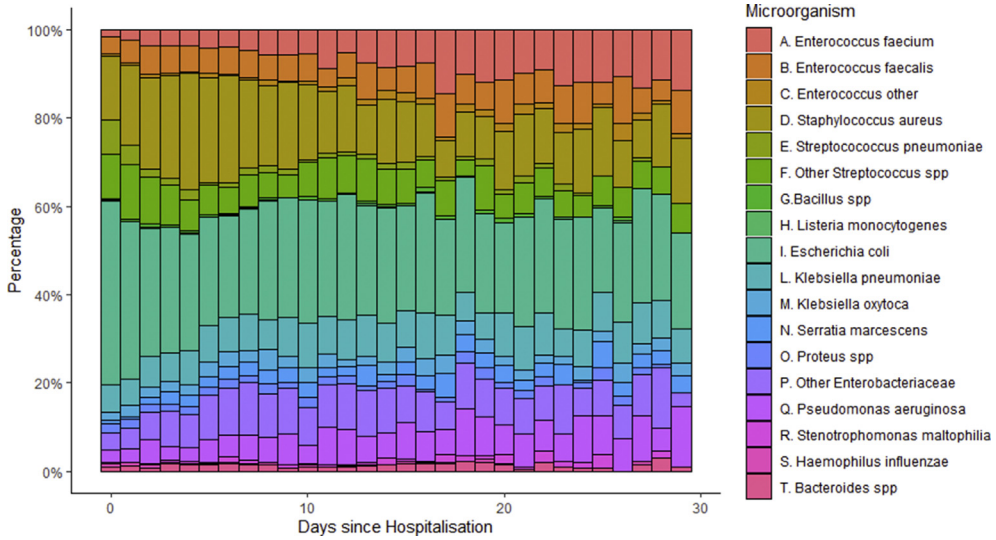

Fig. 2. Distribution of microorganisms during the hospitalization. Spp, species; A–H, Gram positives; I–P, Enterobacteriaceae (Gram negatives); Q/R, non-fermenters (Gram negatives); S/T, others.

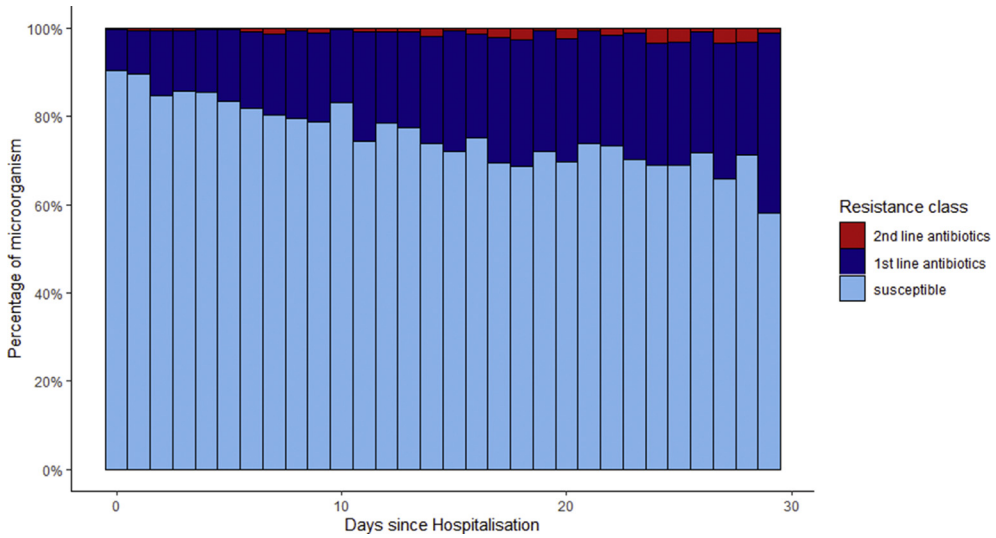

Fig. 3. Antimicrobial resistance to first- and second-line antibiotics across all species. Notes. First-line antibiotic resistance (dark blue): ceftriaxone and amoxicillin–clavulanic acid for Gram-negative microorganisms, amoxicillin for enterococci or oxacillin for *S. aureus*. Second-line antibiotic 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 analysis of a trend.

Our graphical descriptions showed that resistance patterns relative to hospitalization duration were pathogen-specific (Fig. 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 ceftriaxone 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 (Fig. 4). Interestingly, cefepime resistance among *P. aeruginosa* remained stable during the hospitalization (Fig. S3).

Discussion

Here we report a total 28 318 bacteraemia 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 bacteraemia isolates. To our knowledge, our study is the most thorough analysis to date to address this research question. We observed that (a) hospitalization duration was associated with the pathogen distribution in bacteraemic episodes, with proportions of enterococcal bacteraemia being more pronounced in the course of hospitalization, (b) the resistance against first-line antibiotics was characterized by a steady increase during hospitalization duration and (c) antibiotic specific trends differed for the different bacteria analysed.

The role of enterococcal bacteraemias appears to be more pronounced over the course of hospitalization. Unfortunately, we cannot provide rational explanations for this finding. It is conceivable that an

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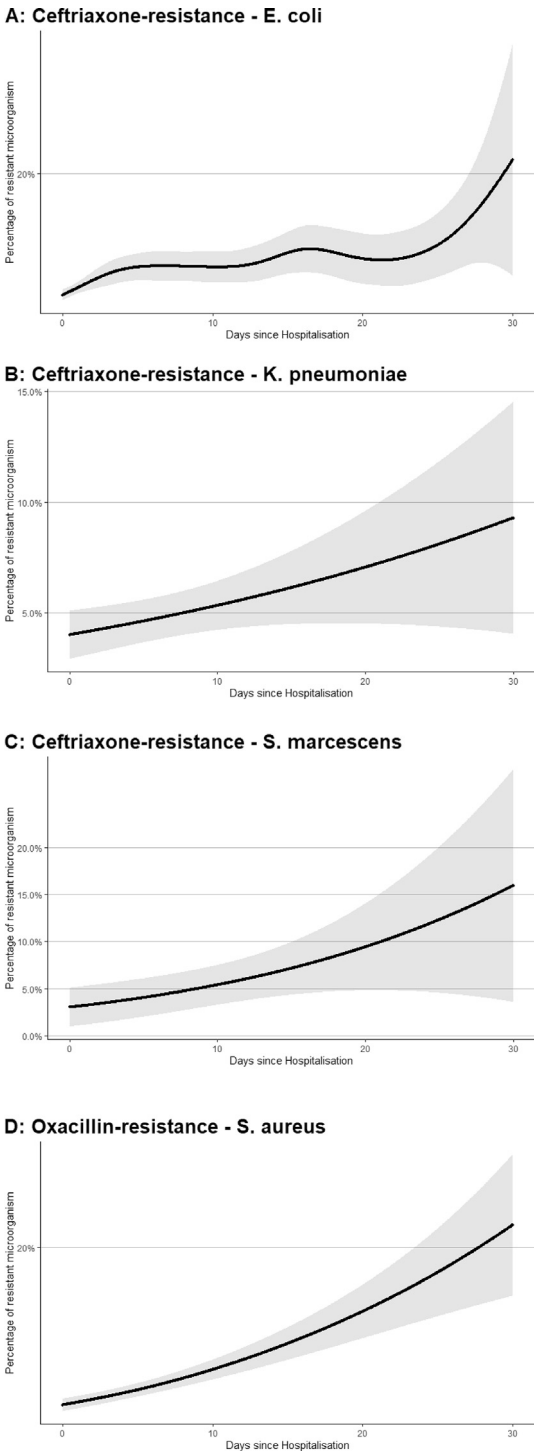

Fig. 4. Resistance proportions of *Escherichia coli, Klebsiella pneumoniae, Serratia marcescens* and *Staphylococcus aureus* relative to hospitalization duration; 95% confidence intervals are displayed in grey.

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 multidrug resistant Gram-negative bacteraemia, 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 provide 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 in 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) was available. 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, no baseline data on the number of hospital admissions was available and we used only the total number of bacteraemias as denominator. Finally, a selection bias could have been introduced when restricting the analysis to bacteraemias 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.

Transparency declaration

The authors declare that they have no conflicts of interest. J.F.T. received fees for lectures to 3M, MSD, Pfizer, and Biomerieux. J.F.T. received research grants from Astellas, 3M, MSD and Pfizer. J.F.T. 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). A.K. has received travel grant and meeting expenses from Gilead, Viofor and the World Health Organization (WHO). A.K. provides not interpreted annual resistance data to LEO pharmaceutic company and the Swiss government. A.K. is advisor of the SFOPH concerning antibiotic resistance epidemiology in Switzerland. This work was supported by the Swiss National

Science Foundation. NB is currently receiving a post doc Mobility grant from the Swiss National Science Foundation (grant number: P4P4PM_194449).

Contributions

N.B. and R.S. designed the study. A.K. acquired the data. N.B., R.S., and A.A. did the statistical analysis. N.B. and R.S. analysed and interpreted the data. N.B., J.M., J.F.T. and R.S. 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).

Acknowledgements

We thank all ANRESIS laboratories for sharing their data: ADMED Microbiology, La Chaux-de-Fonds; Bacteriology Laboratory, Geneva University Hospitals, Geneva; Central Institute, Hôpitaux Valaisans (ICHV), Sitten; Central Laboratory, Cantonal Hospital Graubünden; Central Laboratory, Microbiology Section, Cantonal Hospital Baden; Centre for Laboratory Medicine, Cantonal Hospital Luzern; Centre for Laboratory Medicine, Cantonal Hospital Schaffhausen; Centre for Laboratory Medicine Dr Risch, Schaan; Centre for Laboratory Medicine St. Gallen; Clinical Microbiology, University Hospital, Basel; Hôpital du Jura, Laboratoire; Institute for Infectious Diseases, University Bern; Institute for Laboratory Medicine, Cantonal Hospital Aarau; Institute for Medical Microbiology, University Hospital Zürich; Institute for Microbiology, Université de Lausanne; Laboratoire et analyses médicales, Etablissements Hospitaliers du Nord Vaudois, eHnv; Laboratory for Infectious Diseases, University Children's Hospital Zürich; Laboratory Medicine EOLAB, Department of Microbiology, Bellinzona; Labormedizin, Kantonsspital Winterthur; Microbiology Laboratory Hôpital Fribourgeois, Fribourg; Microbiology Laboratory, Hospital Thurgau; Microbiology Laboratory, Unilabs, Coppet; Promed SA, Laboratoire medical, Marly; Viollier AG, Basel.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.04.025.

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