ORIGINAL ARTICLE

National Bloodstream Infection Surveillance in Switzerland 2008–2014: Different Patterns and Trends for University and Community Hospitals

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OBJECTIVE. To characterize the epidemiology of bloodstream infections in Switzerland, comparing selected pathogens in community and university hospitals.

DESIGN. Observational, retrospective, multicenter laboratory surveillance study.

METHODS. Data on bloodstream infections from 2008 through 2014 were obtained from the Swiss infection surveillance system, which is part of the Swiss Centre for Antibiotic Resistance (ANRESIS). We compared pathogen prevalences across 26 acute care hospitals. A subanalysis for community-acquired and hospital-acquired bloodstream infections in community and university hospitals was performed.

RESULTS. A total of 42,802 bloodstream infection episodes were analyzed. The most common etiologies were *Escherichia coli* (28.3%), *Staphylococcus aureus* (12.4%), and polymicrobial bloodstream infections (11.4%). The proportion of *E. coli* increased from 27.5% in 2008 to 29.6% in 2014 ($P = .04$). *E. coli* and *S. aureus* were more commonly reported in community than university hospitals (34.3% vs 22.7%, $P < .001$ and 13.9% vs 11.1%, $P < .001$, respectively). Fifty percent of episodes were community-acquired, with *E. coli* again being more common in community hospitals (41.0% vs 32.4%, $P < .001$). The proportion of *E. coli* in community-acquired bloodstream infections increased in community hospitals only. Community-acquired polymicrobial infections (9.9% vs 5.6%, $P < .001$) and community-acquired coagulase-negative staphylococci (6.7% vs 3.4%, $P < 0.001$) were more prevalent in university hospitals.

CONCLUSIONS. The role of *E. coli* as predominant pathogen in bloodstream infections has become more pronounced. There are distinct patterns in community and university hospitals, potentially influencing empirical antibiotic treatment.

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Bloodstream infections (BSI) are a major healthcare issue with a disease burden comparable with that caused by myocardial infarction, trauma, and major strokes.[1] BSI represent a significant cause of mortality worldwide,[2] leading to approximately 157,000 deaths per year in Northern Europe and more than 79,000 deaths per year in North America.[3]

Demographic changes and advances in medical technology have changed the epidemiology of BSI in recent decades, and resulted in a shift in the pathogen spectrum. Although gram-positive bacteria were the predominant agents in BSI from 1987–2000,[4] gram-negative bacteria have constantly increased since then, with *Escherichia coli* reemerging as the most prevalent pathogen.[5] Because changes in the spectrum and antimicrobial resistance patterns have a direct impact on the choice of empirical antimicrobial therapy, experts have recommended that the epidemiology of BSI be reassessed periodically on a national scale.[6] Hence, the assessment of this evolution in Switzerland was the primary goal of the study.

Moreover, since 2002 a new category of healthcare-associated bloodstream infection has been introduced[7] and validated that distinguishes between "true" community-acquired (CA) infections and those with previous healthcare exposure.[2,8] However, the distinction between BSI encountered in university hospitals (UH) versus community hospitals (CH) has garnered less attention.[9–11]

We hypothesized that the epidemiology of BSI differs markedly between UH and CH when analyzed on a national scale. A study specifically addressing these differences therefore provides valuable additional insights into recent trends and patterns of BSI. With the present study we intended to elucidate the epidemiology, etiology, and temporal changes of BSI episodes in CH and UH in Switzerland from 2008 through 2014.

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METHODS

Design and Setting

We conducted a longitudinal, observational, retrospective, multicenter study on BSI in Switzerland from 2008 through 2014. Data on BSI were obtained from the national bloodstream infection surveillance database, which is part of the Swiss Centre for Antibiotic Resistance (ANRESIS).[12] Since 2004 the ANRESIS program has collected all routine microbiologic data from a representative group of microbiology laboratories located across Switzerland, with blood culture surveillance introduced in 2006. Each participating laboratory sends bacteremia results on a regular basis to a central database located at the Institute for Infectious Diseases in Bern, Switzerland. Most laboratories collect microbiologic data from different hospitals, including UH and CH from a wide geographic area covering the most densely populated regions.

A few major features differentiate UH from CH in Switzerland. UH perform specific and difficult surgical interventions (eg, cardiac surgery, neurosurgery, and organ transplantation surgery) and manage difficult-to-treat patients that are often transferred from CH. Additionally, the number of beds in UH (>800 beds/hospital) is higher than in CH. CH are characterized by rather small intensive care units (ICU) but play an important role in the Swiss healthcare system by initially stabilizing septic patients and providing treatment for most cases.[13,14]

We restricted the dataset to acute care hospitals that continually reported at least 5 BSIs per year without fluctuations from 2008 through 2014. We obtained BSI data from 26 hospitals (Figure A, Supplementary Appendix); the number of acute beds from this sample of hospitals remained stable in relation to the Swiss population over the study period and represented 33.7 % of the acute care beds in Switzerland in 2014.[13] Two hospitals merged in 2011 and were analyzed as 1 hospital throughout the entire study period.

Definitions

We considered only positive blood cultures in the analysis; cultures from intravascular tips were interpreted as blood cultures. Organisms were isolated and speciated according to the Clinical Laboratory Standards Institute guidelines.[15] Positive cultures were grouped as a BSI episode if they occurred within a 7-day window in the same patient. If another set of cultures was obtained more than 7 days after the most recent positive blood culture result, it was considered a separate episode.

Contaminant episodes were excluded from the analysis, being defined as episodes including only 1 positive culture of a typical contaminant (namely coagulase-negative staphylococci [CoNS], anaerobes such as *Bacillus* spp., *Corynebacterium* spp., *Propionibacterium* spp., oral streptococci, and others [see Supplementary Appendix]). If the same contaminant occurred at least twice (specifically, from 2 blood cultures or from a catheter tip and 1 blood culture) in a 7-day window, the episode was considered to be a true BSI. A BSI was defined as *polymicrobial* if different microbial species were isolated from 1 or more cultures within the same episode.

The following pathogen categories were selected for more detailed analysis: *Staphylococcus aureus*, CoNS, *Enterococcus* spp., *E. coli*, Enterobacteriaceae other than *E. coli*, gram-negative nonfermenters, anaerobes, polymicrobial infection, fungi, and "others." Descriptive statistics were used to compare pathogen prevalence over time. The analyses were stratified by gender, age groups, linguistic region (ie, Southwest vs Northeast), season (winter, defined as October 1 to March 30, vs summer), hospital type (CH vs UH), hospital department (outpatient department, ICU, general wards), and year of detection (2008 to 2014). Patterns and temporal trends were calculated for the 4 major microorganism groups (*E. coli*, *S. aureus*, CoNS, and polymicrobial). BSI for which the hospitalization date was available were grouped into *hospital-acquired* (HA; positive blood culture >2 days after admission) and CA. Both HA and CA BSI were further differentiated into infections occurring in CH and UH.

Statistical Analysis

Group comparisons were performed using the χ^2 test.[16] The Bonferroni correction was used to correct for multiple comparisons on a family-wise basis, where appropriate. A critical P value for testing at the 5% level of significance was accordingly set at .005 for tests, otherwise at the level of .05. For linear time trends, tests of significant difference between the gradients of regression curves were based on standard analysis of variance techniques. All analyses were conducted with the statistical package R (R Foundation for Statistical Computing).[17]

RESULTS

Etiology of BSIs

From 2008 through 2014, a total of 57,544 BSI episodes were identified after considering 118,224 individual positive blood cultures. Of these, 42,802 episodes (74.4%) were classified as true infections. Most of the 14,742 contaminant episodes were from CoNS (79.3%, 11,696). Fifty-eight percent $^{(25,017)}$ of BSIs occurred in male patients, more than half (57%) of episodes occurred in people at least 65 years of age, and 52% were detected in UH (Table 1).

E. coli was the most frequent agent (28%), followed by Enterobacteriaceae other than *E. coli* (13%) and *S. aureus* (12%). Polymicrobial BSIs accounted for 11% of all episodes (Figure 1). A review of the following 4 microorganism (*E. coli*, *S. aureus*, CoNS, polymicrobial) groups is provided in Table 1.

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TABLE 1. Epidemiology of 42,802 BSIs in Switzerland, 2008–2014

Variable	*E. coli*		*S. aureus*		CoNS		Polymicrobial		Totals
Sex	$P < .001$[a]		$P < .001$		$P < .001$		$P < .001$		
Female	6,475	36.4%	1,914	10.8%	1,380	7.8%	1,730	9.7%	17,777
Male	5,626	22.5%	3,402	13.6%	2,494	10.0%	3,160	12.6%	25,017
Season	$P = .002$		$P > .99$		$P > .99$		$P = .7$		
Summer	6,342	29.1%	2,682	12.3%	1,974	9.1%	2,554	11.7%	21,810
Winter	5,761	27.4%	2,635	12.6%	1,900	9.1%	2,339	11.1%	20,992
Age, y	$P < .001$		$P < .001$		$P < .001$		$P < .001$		
<65	4,129	22.4%	2,470	13.4%	2,097	11.4%	2,349	12.7%	18,448
≥65	7,973	32.8%	2,846	11.7%	1,773	7.3%	2,540	10.4%	24,333
Region	$P < .001$		$P = .2$		$P < .001$		$P < .001$		
Northeast	6,350	24.5%	3,298	12.7%	3,088	11.9%	3,324	12.8%	25,937
Southwest	5,753	34.1%	2,019	12.0%	786	4.7%	1,569	9.3%	16,865
Department	$P < .001$		$P = .2$		$P < .001$		$P < .001$		
ICU	679	13.5%	632	12.6%	792	15.8%	936	18.6%	5,026
General wards[b]	5,193	23.7%	3,041	13.9%	2,427	11.1%	2,793	12.7%	21,918
Site of acquisition[c]	$P < .001$		$P < .001$		$P < .001$		$P < .001$		
CA	7,954	37.3%	2,530	11.9%	1,015	4.8%	1,580	7.4%	21,308
HA	1,508	16.9%	1,211	13.6%	1,315	14.8%	1,359	15.3%	8,900
Hospital type	$P < .001$		$P < .001$		$P < .001$		$P < .001$		
CH	7,026	34.3%	2,839	13.9%	1,164	5.7%	1,560	7.6%	20,478
UH	5,077	22.7%	2,478	11.1%	2,710	12.1%	3,333	14.9%	22,324

NOTE. Data are no. (%) of microorganisms unless otherwise indicated. BSI, bloodstream infection; CA, community-acquired; CH, community hospital; CoNS, coagulase-negative staphylococci; *E. coli*, *Escherichia coli*; HA, hospital-acquired; ICU, intensive care unit; *S. aureus*, *Staphylococcus aureus*; UH, university hospital.

[a]χ^2 test on equal proportions, adjusted for column marginal totals, Bonferroni corrected.

[b]General wards excluding outpatients.

[c]Acquisition: Excluding 29% of BSIs that were not attributable to either category.

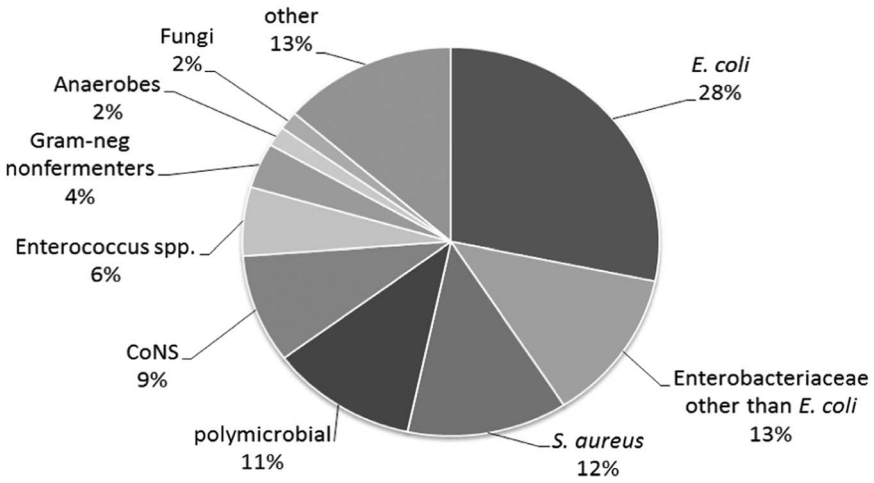

FIGURE 1. Distribution of microorganisms encountered in bloodstream infections, Switzerland, 2008-2014. *E. coli*, *Escherichia coli*; CoNS, coagulase-negative staphylococci; *S. aureus*, *Staphylococcus aureus*.

E. coli was more prevalent in females than males (36% vs 23%, $P < .001$) and in older patients (33% in >65 years vs 22% in 15-45-year-olds, $P < .001$). *E. coli* was more common during summertime (29% vs 27%, $P = .002$), in general wards (24% vs 14%, $P < .001$), and in Southwest Switzerland (34% vs 25%, $P < .001$). Furthermore, *E. coli* was more frequently detected in CA vs HA episodes (37% vs 17%, $P < .001$), and in CH compared with UH (34% vs 23%, $P < .001$).

S. aureus was found to be more common in male patients (14% vs 11%, $P < .001$) and among patients aged at least

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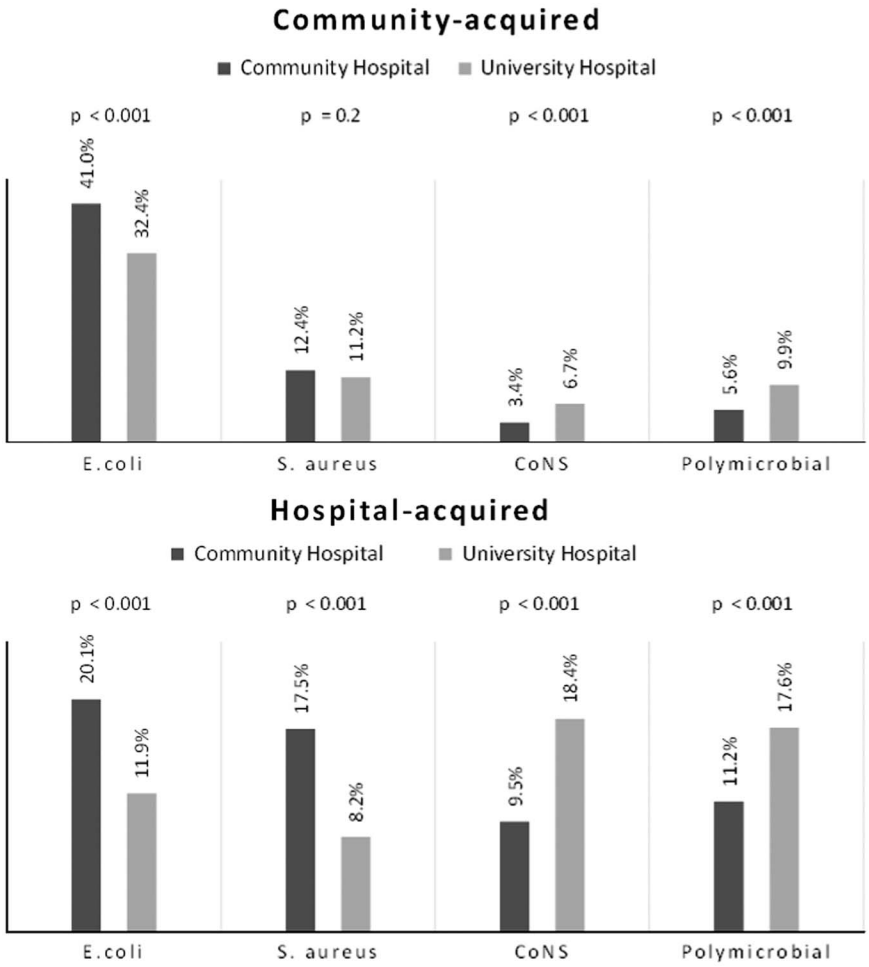

FIGURE 2. Proportion (%) of *Escherichia coli*, *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and polymicrobial sources in community-acquired (top) and hospital-acquired (bottom) bloodstream infections, Switzerland 2008–2014.

65 years. However, there were no significant seasonal or regional differences, and no differences between ICU and general wards. *S. aureus* was more frequently detected in HA episodes (14% vs 12%, $P < .001$) and in CH (14% vs 11%, $P < .001$).

CoNS occurred more frequently in males (10% vs 8%, $P < .001$), in patients younger than 65 years (11% vs 7%, $P < .001$), and in the Northeast region (12% vs 5%, $P < .001$). In addition, ICU departments (16% vs 11%, $P < .001$), hospital acquisition (15% vs 5%, $P < .001$), and UH (12% vs 6%, $P < .001$) were associated with a higher proportion of CoNS BSIs.

Polymicrobial BSIs were more common in male patients (13% vs 10%, $P < .001$), Northeast Switzerland (13% vs 9%, $P < .001$), ICU departments (19% vs 13%, $P < .001$), in HA episodes (15% vs 7.4%, $P < .001$), and in UH (15% vs 8%, $P < .001$).

Pattern of Microorganisms by Site of Acquisition and Hospital Type

The following analyses were restricted to 30,208 episodes (70.6%) with known hospitalization date. Of these, 21,308 (70.5%) were CA-BSI. Among CA-BSIs, CH-onset BSIs were more frequent in those more than 65 years of age (64% vs 55%, $P < .001$), and in non-ICU departments (85% vs 79%, $P = .002$). Moreover, *E. coli* was observed more often in CH, whereas polymicrobial BSIs and CoNS were more frequent in the university setting (Figure 2).

For HA infections, the proportion of elderly patients was greater in CH-onset BSIs (60%) vs in UH-onset BSIs (47%) ($P < .001$). There was a similar picture with *E. coli* and *S. aureus* being more frequent in CH, whereas UH saw more CoNS and polymicrobial BSI (Figure 2). Focusing on larger CH (>500 beds), we found the same patterns as in the CH group as a whole (data not shown).

Time Trends 2008 Through 2014

The annual total of reported episodes increased over time from 5,754 in 2008 to 6,694 in 2014. In terms of microorganisms, the proportion of *E. coli* BSI increased from 1,582 (28%) in 2008 to 1,978 (30%) in 2014 ($P = .04$), whereas there was a

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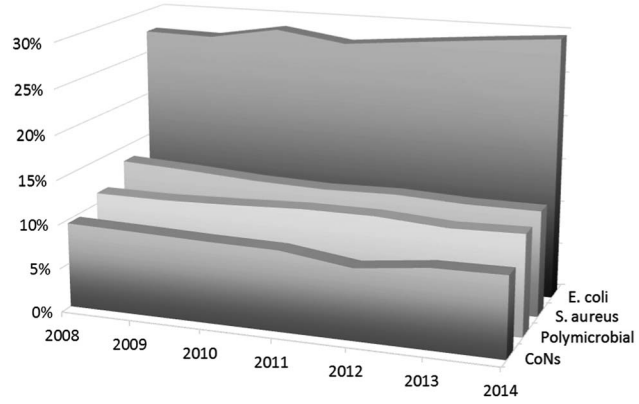

FIGURE 3. Trends of *Escherichia coli*, *Staphylococcus aureus*, polymicrobial sources, and coagulase-negative staphylococci (CoNS) in bloodstream infections, Switzerland 2008–2014.

decreasing trend in the proportion of *S. aureus* from 765 (13%) to 803 (12%) during the same period ($P = .05$; Figure 3).

Trends by Site of Acquisition and Hospital Type

No increase in the identification of the site of acquisition was detected over the study period. As noted previously, *E. coli* was more prevalent in CA infections and even more so in CH. Moreover, in the CH setting, the trend increased over time from a prevalence of 39% in 2008 to 45% in 2014 ($P = .05$), differing significantly from the stable prevalence encountered in CA *E. coli* infections in UH (33% in 2008 vs 30% in 2014, $P = .16$, P for divergence $= .02$; Figure 4). For HA infections, we observed a stable proportion of *E. coli* in both CH and UH. Moreover, we observed a significant decrease for HA *S. aureus* BSI in UH (12% in 2008 vs 7.1% in 2014, $P = 0.04$) and for HA CoNS in CH (12% in 2008 vs 6.6% in 2014, $P = .04$). Trends for other microorganism groups are shown in Figure 4.

DISCUSSION

To our knowledge, this is the first report on the national bacteremia surveillance in Switzerland. Including approximately one-third of BSIs nationwide, the database can be considered as representative for the entire country. In addition, given the geographic location at the crossroads of Europe, our findings may be useful for benchmarking purposes with other European countries. The analysis incorporated data on 9 microorganism groups from 26 hospitals reporting data consistently, comprising both CH and UH, and included 7 years of data.

As in other countries, *E. coli* was the predominant cause of BSI.[5,18] *E. coli*, which is usually considered as a pathogen acquired in the community, was also the most common cause of HA-BSI and the most detected across all hospital disciplines. The increasing trend in bacteremia caused by *E. coli* until 2014 is noteworthy and consistent with European trends, as reported by de Kraker et al[19] and others.[5] One possible explanation for this trend is the earlier discharge of patients to the community (reflected in a decreasing average length-of-stay over the study period[13]), where they are at greater risk of developing *E. coli* BSI.[20,21] Furthermore, the increase in bacteremia due to *E. coli* should be considered particularly alarming because third-generation cephalosporin resistance among *E. coli* is increasing in Switzerland[22] and surrounding countries.[6]

Consistent with the findings of most population-based studies, *S. aureus* was the second most frequent pathogen identified.[18,23] In most European countries, decreasing incidences of *S. aureus* BSI have been described up to 2008,[5,19,24] whereas more recent data are not yet available. Our study confirmed this ongoing trend for Switzerland, including the years up to 2014. In some European countries this decrease could be explained by a decline in methicillin-resistant *S. aureus* infections, and may be the result of national initiatives aimed at reducing such infections.[5,6,25,26] In addition, improving standards in hospital infection prevention may concurrently have led to fewer methicillin-susceptible *S. aureus* bacteremias.[27]

Polymicrobial BSIs are of particular concern because they are often associated with increased mortality.[18,28] However, the lack of a generally accepted definition for what constitutes polymicrobial complicates the evaluation of patterns and trends of polymicrobial BSI. Most authors define polymicrobial as being a sequence of episodes of bacteremia occurring within a time frame varying between 24 hours and 1 week.[2,18,29–31] In contrast, Chowers et al[32] consider an episode as being polymicrobial if multiple microorganisms were isolated in the same patient within 1 month. In our study we considered an episode as being polymicrobial if multiple pathogens were isolated within 1 week. According to this definition 11.4% of all BSIs from 2008 through 2014 were polymicrobial, which is comparable to the observations of other studies relying on the same definition.[30,31] As expected, a higher frequency of polymicrobial BSI was detected in nosocomial BSI, in ICU and in UH,[28,33] with a stable proportion observed over the past 7 years.[24] Of particular note, polymicrobial BSIs often include significant proportions of *Enterococcus* spp. and *Pseudomonas* spp.[28,30,31] and, consequently, standard empirical therapies in Switzerland (eg, amoxicillin/clavulanate or a third-generation cephalosporin) may not always be adequate.

To our knowledge, this is also the first nationwide study describing differences in BSI between CH and UH. Only few studies, with a limited number of hospitals, have performed a comparison between the community and the academic setting up to now,[9–11] with the latter often being overrepresented in large-scale surveillances.[6] This might be considered somewhat surprising because CH contribute a significant percentage of positive blood cultures, with CH representing 83% of all patients admitted to acute care

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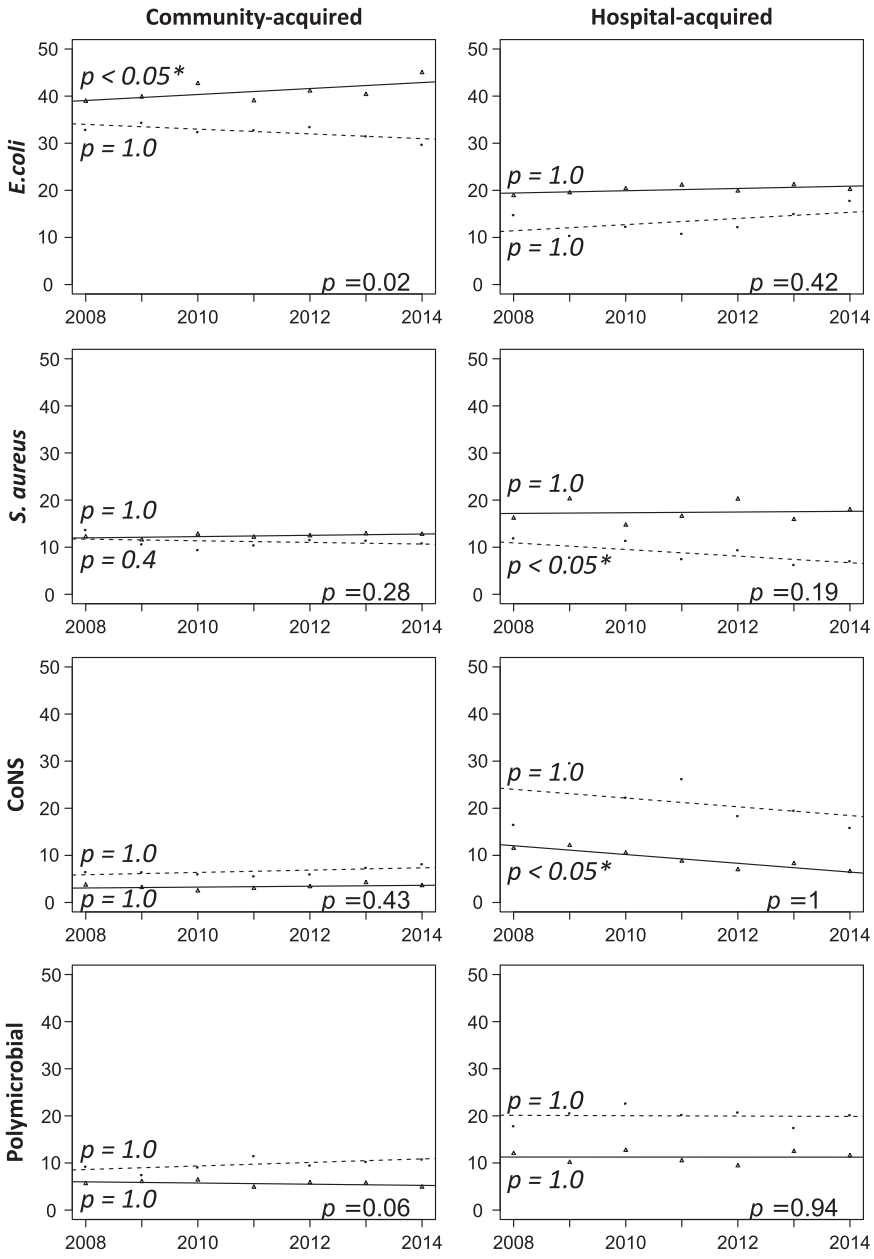

FIGURE 4. Trends in community hospitals and university hospitals by site of acquisition for *Escherichia coli*, *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and polymicrobial bloodstream infections. Linear regression denoted by solid line for community hospitals, and by dotted line for university hospitals. *P* values on the regression lines pertain to the gradient, those at the bottom right refer to the divergence of these lines. Asterisks indicate a significant effect at the 5% level.

hospitals in Switzerland.[13] Similar healthcare systems characterize other European countries[34,35] or the United States—for example, in 2009 69% of all hospitals in the United States were nonteaching CH and, in 2010, 51% (19.9 million) of patient discharges were from nonteaching facilities.[36,37]

The hypothesis that the patterns and trends of BSI differ between UH and CH was confirmed. *E. coli* and *S. aureus* were identified more frequently in CH, whereas polymicrobial BSIs and CoNS were more commonly observed in the university setting. Interestingly, this difference was not only observed in HA infections but, with the exception of *S. aureus*, in CA-BSI too. Our findings were further confirmed by the divergent trend for CA-*E. coli* BSI in the 2 hospital types in the 2008–2014 period: *E. coli* increased in CH to 45% of all CA episodes and decreased in UH. This trend and the observed patterns among CA-BSI probably reflect the differences between the 2 hospital settings, with elderly patients and a different mix of clinical presentations (eg, more pneumonia,

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abdominal infections, cutaneous ulcers, fewer chronic renal failures) being more often observed in CH.[9,10] Furthermore, HA-BSIs are often associated with hematologic cancer, neutropenic patients, venous catheter infections, and less commonly with urinary tract infections or abdominal infections in tertiary care centers.[9] Our results provide the first microbiologic description on a national scale for the clinical manifestation witnessed in other, smaller clinical studies.[9–11]

The significant differences in the distribution of microorganisms causing BSI in CH and UH affect clinical care. Empirical antibiotic treatment guidelines in Switzerland are often produced by academic centers and distributed to networks of smaller centers. Such protocols are mostly based on the local epidemiology observed in the academic setting, and application to community centers may be less appropriate. For example, a reduced use of broad-spectrum antimicrobial agents (eg, antibiotics against oxacillin-resistant strains usually found in polymicrobial and CoNS BSIs) could be envisioned for the treatment of CA infections in community centers.

Our study has several limitations. Although the initial selection of hospitals was representative, selection bias could have been introduced when restricting the analysis to BSIs with known acquisition (71% of included episodes). In this context, inaccurate documentation of the date of sampling might be a source of uncertainty. Furthermore, possible "healthcare-associated" infections were not identified among CA infections because we had no access to pertinent clinical data. Prospective observational studies are needed to better delineate differences in site of acquisition and the role of hospital setting. Moreover, because we did not distinguish between catheter and peripheral culture results, we may have overestimated the number of BSIs due to "noncontaminant" organisms. Finally, we did not provide data on resistance of microorganisms, which are essential for decision-making about empirical antimicrobial therapies.

In conclusion, this study documents a very timely picture of the BSI epidemiology in Switzerland over a 7-year period. *E. coli* maintains a predominant role in BSIs and its importance has become even more pronounced, especially in CH. Difficult-to-treat infections—for example, CoNS and polymicrobial BSIs—remain important, especially in HA infections and UH. CH and UH show divergent BSI epidemiology, with *E. coli* representing almost half of CA-BSIs in CH in 2014. The choice of empirical antibiotic treatment should follow the local epidemiology, in particular taking the type of hospital into consideration, especially in countries with a similar healthcare system.

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SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/ice.2016.137

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