ISSN 2277 - 5730

AN INTERNATIONAL MULTIDISCIPLINARY
QUARTERLY RESEARCH JOURNAL

# AJANTA

Volume - VII Issue - IV October - December - 2018

English Part - XIV / XV

## Peer Reviewed Refereed and UGC Listed Journal

Journal No. 40776

ज्ञान-विज्ञान विमुक्तये

**IMPACT FACTOR / INDEXING**
**2018 - 5.505**
**www.sjifactor.com**

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**Ajanta Prakashan**
Aurangabad. (M.S.)

**Printed by**

Ajanta Computer, Near University Gate, Jaisingpura, Aurangabad. (M.S.)

**Published by :**

Ajanta Prakashan, Near University Gate, Jaisingpura, Aurangabad. (M.S.)

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**AJANTA - ISSN 2277 - 5730 - Impact Factor - 5.505** (www.sjifactor.com)

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# 7. A Nationwide Surveillance Study Looked at the Distribution of Microorganisms and Antibiotic Resistance in ICU-Bloodstream Infections during Hospitalisation

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**Abstract**

For the colonisation or infection of selected organ systems, changing microbe distributions and decreasing antibiotic susceptibility have been described over the course of hospitalisation. In the intensive care unit (ICU), there are few statistics on bacteremias. Using data from the Swiss Centre for Antibiotic Resistance, we conducted a nationwide study on bloodstream infection (BSI) (ANRESIS). During the whole study period (2008–2017), we reviewed data on BSI found in the ICU from hospitals that supplied information on a regular basis. During the course of the hospitalisation, we observed specific trends in pathogen spread and resistance. 6505 ICU-BSI isolates from 35 Swiss hospitals were included in the study. A total of 2587 potential skin pollutants, 3788 bacteremias, and 130 fungemias were discovered. Escherichia coli was the most frequent microorganism (23.2 percent, 910), followed by Staphylococcus aureus (18.7%, 734) and enterococci (13.1 percent , 515). During hospitalisation, the proportions of Enterococcus spp (p 0.0001) and Candida spp (p 0.0001) increased, while the proportions of E. coli (p 0.0001) and S. aureus (p 0.0001) declined. During hospitalisation, resistance to first- and second-line antibiotics rose linearly. The distribution of pathogens and antibiotic resistance in ICU-BSI is affected by the length of stay. During hospitalisation, the proportion of enterococcal BSI, candidemia, and resistant bacteria to first- and second-line antibiotics rose.

**Introduction**

ICU-BSI (intensive care unit-acquired bloodstream infection) is a prevalent healthcare-associated infection. It's linked to infection and has a high fatality rate. The association between

the length of stay in the hospital and the epidemiology of ICU-BSI is poorly understood. For infection of specific organ systems, decreasing antibiotic susceptibility with increasing period of hospital stay has already been demonstrated. To our knowledge, the influence of length of hospital stay on ICU-BSI epidemiology has never been studied in a large multi-centric cohort. Only a few authors have looked into this subject in the non-ICU context for bacteremia. Using a comprehensive national microbiological database, we set out to explain the distribution of infections and antibiotic resistance in ICU-BSI based on the length of stay.

**Design and Data Collection**

From January 1, 2008, to December 31, 2017, we conducted a statewide observational study on BSI using data from the Swiss Centre for Antibiotic Resistance (ANRESIS). ANRESIS gets data on all positive blood cultures on a regular basis from 30 Swiss microbiology laboratories, some of which collect data from multiple institutions. Hospitals are located throughout the country and account for at least 80% of yearly hospitalisation days. As a result, we reviewed data from BSIs from Swiss hospitals that supplied data on a consistent basis (i.e., without large reporting fluctuations) during the study period. Only ICU isolates from Swiss hospitals that provided information on hospital length of stay at the time of sampling were included. Only the first isolate of a species per patient was suitable for this research, in order to eliminate any bias induced by an individual patient's resistance evolution: duplicates (i.e., the same bacterium discovered in later collected blood samples) were removed. Furthermore, we limited the dataset to infections that appeared more than 10 times during the research period (i.e., those belonging to prevalent and/or relevant species).

**Microbiological Data and Resistance**

Local laboratories use the European Committee on Antibiotic Susceptibility Testing (EUCAST, https://eucast.org) or Clinical and Laboratory Standards Institute (CLSI, https://clsi.org) criteria for species identification and antimicrobial susceptibility testing. At least one external quality programme, such as the Swiss quality control programme issued by the Institute for Medical Microbiology, University of Zürich (http://www.imm.uzh.ch/services/qc.html) or the National External Quality Assessment Service (NEQAS; www.uknegas.org.uk), is used by all laboratories. Resistant isolates were classified as those that were resistant to the antibiotic tested or showed intermediate susceptibility to it. Resistance to amoxicillin for enterococci, ceftriaxone and/or amoxicillin/clavulanic acid for

Gram-negative bacteria, and oxacillin for Staphylococcus aureus8 were designated as first-line antibiotic resistance. As previously stated, all non-fermenting Gram-negative bacteria were considered resistant to first-line antibiotics. Vancomycin resistance in Gram-positive bacteria and carbapenem resistance in Gram-negative bacteria were used to characterise resistance to second-line antibiotics. Fungal pathogens were categorised as first- and second-line antimicrobial resistance. We looked at coagulase-negative Staphylococci, Corynebacterium sp, Micrococcus spp, and Cutibacterium acnes individually as probable skin pollutants. The bacteria Staphylococcus lugdunensis was left out.

**Variables Collected**

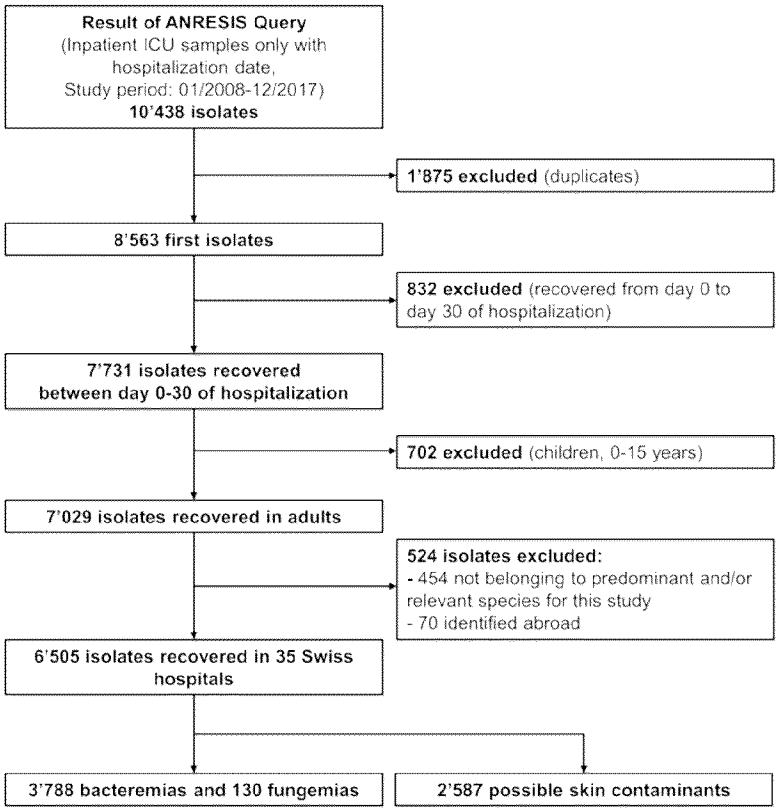
Epidemiological data permitted stratification by age group, gender, hospital type (community vs. university), and detection year. Early hospital-acquired BSI occurred between 2 and 5 days following hospitalisation, while late hospital-acquired BSI occurred more than 5 days after admission. The remaining BSIs were classified as acquired in the community. Using the hospital admission date and the BSI date, the length of stay was computed. A date for ICU admission was not available.

**Statistical Analysis**

The analytical plan had two steps: (1) describe characteristics of BSI in different hospital acquisition scenarios (i.e., community versus early hospital-acquired versus late hospital-acquired); and (2) use graphical descriptions and descriptive statistics to describe trends in pathogen distribution and resistance during the hospitalisation. Characteristics were compared using the chi-square or Fisher test, depending on the length of the hospitalisation. The number of isolates of a certain microbe was divided by the total number of isolates to calculate the prevalence of that pathogen. The number of resistant strains divided by the total number of isolates was used to calculate the prevalence of resistance (i.e., against first or second line antibiotics). The Cochrane–Armitage test was used to assess changes in prevalence during the hospitalisation. A fungi-free sensitivity analysis was added. SAS software version 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.6.1 (R Core Team) were used to create the data analysis for this paper (2020). R is a statistical computing language and environment. Vienna, Austria: R Foundation for Statistical Computing (https://www.R-project.org/). Statistical significance was defined as p values less than 0.05. According to Swiss law, ethical consent for

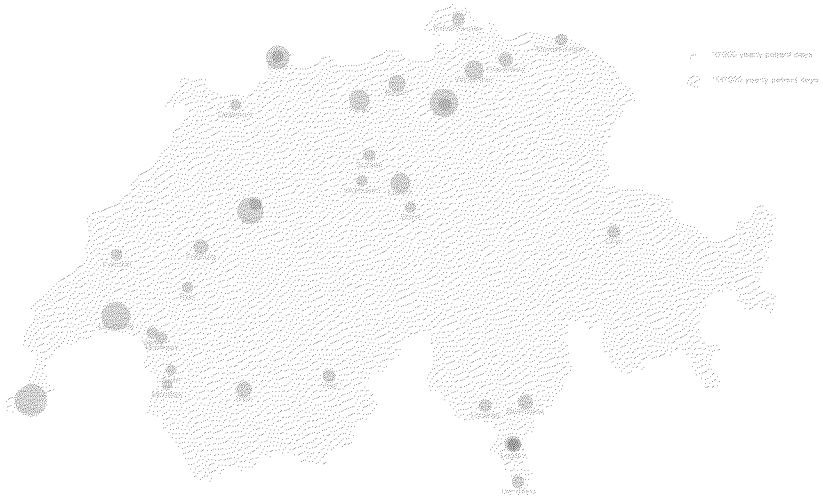
human research is not required because the analysis was performed on anonymized non-genetic surveillance data.

**Figure 1**

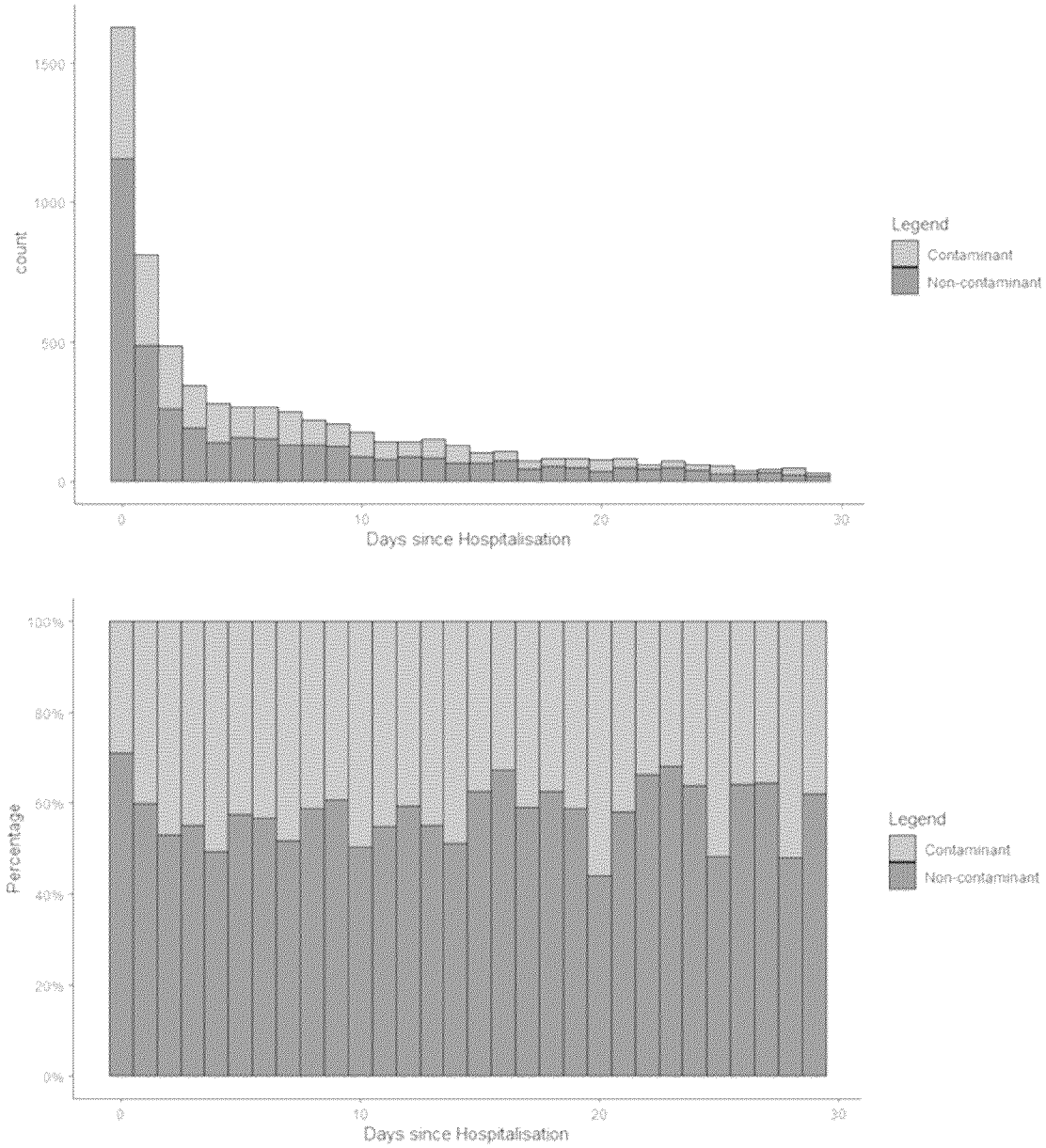



Flowchart of ICU-BSI included.

**Figure 2**



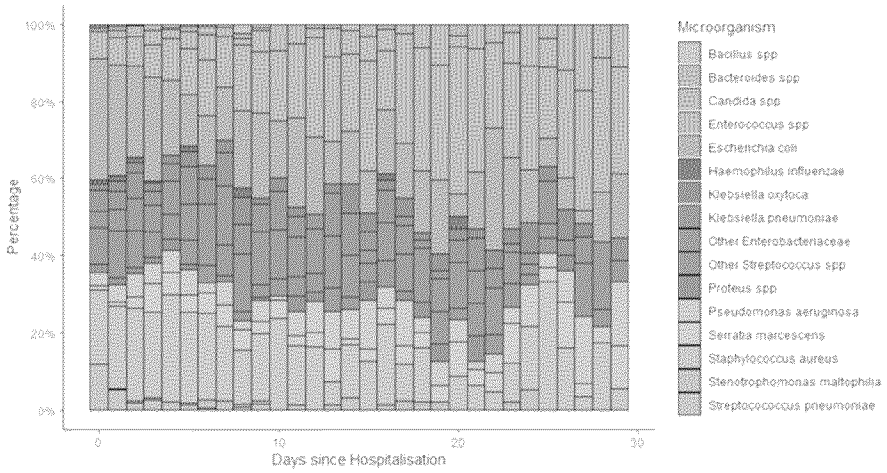
The study involved Swiss hospitals. The disc sizes are related to the number of annual patient days at the hospitals. R 3.5.2 and the raster package (https://cran.r-project.org/web/packages/raster/index.html) were used to create the map.




In relation to the length of hospitalisation, the number and proportion of bacteria and probable skin pollutants. Bacteria and fungus were among the microorganisms studied.

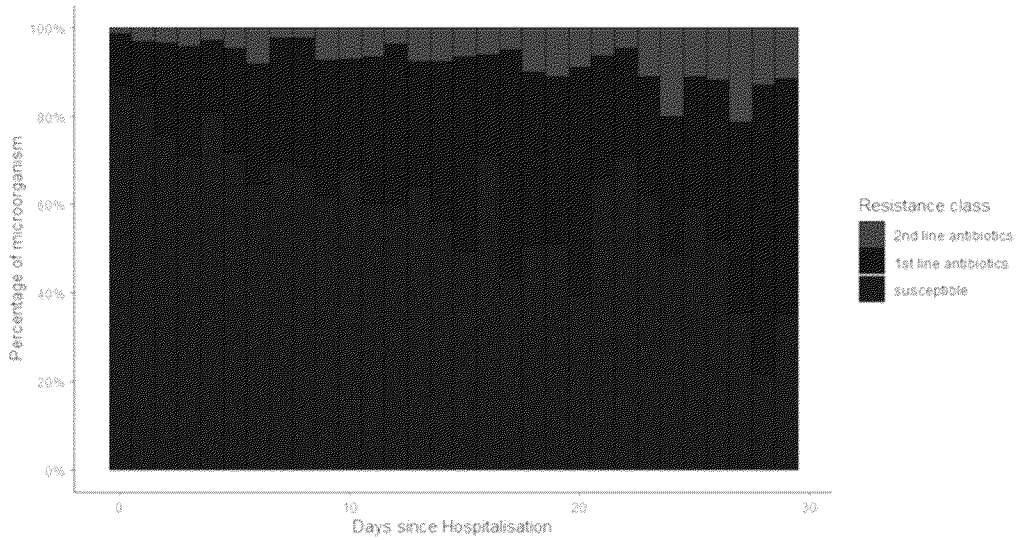
Figure 4 depicts the dispersion of bacteria during the hospitalisation.

**Figure 4**




Distribution of microorganism observed in the ICU relative to the hospitalization duration. *spp* species. Enterococci increased from 7.1 percent on day zero to 28 percent on day 30 (p 0.001), whereas Candida spp. increased from 0.7 to 11.1 percent (p 0.001). S. aureus reduced from 19 to 5.6 percent (p 0.0001). E. coli decreased from 31.4 percent on day zero to 16.7 percent on day 30 (p 0.0001). There was no significant trend in Klebsiella pneumoniae (p = 0.41). Antimicrobial resistance to first-line antibiotics was 13.1% on day zero and subsequently steadily grew to more than 60% on days 28–30 (p 0.001, Fig. 5). When fungi were excluded from the analysis, similar patterns were seen (p 0.001, Supplementary Figure S1). Resistance to second-line antibiotics has also been seen to be on the rise (p 0.001).

**Figure 5**



Antimicrobial resistance to first- and second-line antibiotics as a function of the length of stay in the hospital. Antibiotic resistance in the first line (dark blue): ceftriaxone for gram-negative bacteria, amoxicillin for Enterococci, and oxacillin for Staphylococcus aureus. Antibiotic resistance in the second line (red): carbapenem for Gram-negative bacteria and vancomycin for Gram-positive bacteria. Fungi are shown (or included) here as resistant to 2nd line antibiotics since antifungal drugs were not empirically provided.

**Discussion**

We studied data from 6505 BSI events from 35 Swiss ICUs using a comprehensive microbiological database. There is a scarcity of information in the literature about the length of hospitalisation and the distribution of diseases. Only the EPIC I study, to our knowledge, has shown rates of chosen infections in the ICU environment based on the number of hospital days prior to the study day. However, this study (1) did not examine data throughout the entire hospitalisation and (2) did not address this research topic specifically. During the stay, the proportion of enterococcal BSI and resistant bacteria to first- and second-line antibiotics grew significantly. Furthermore, we discovered that probable pollutants had the lowest proportion at hospital admission (i.e., day zero), but their proportions did not alter throughout the stay.

Surprisingly, the proportion of Enterococci rose throughout the hospitalisation, accounting for nearly 30% of all BSIs in late hospitalizations. It's possible that antibiotic exposure, notably the increasing use of cephalosporins in Switzerland, as well as the accumulation of comorbidities and often increasing case severity throughout hospitalisation, predispose individuals to enterococcal BSI. Despite the fact that we did not look at individual clinical patient data, our findings may aid doctors in picking empirical therapies for patients who have been in the hospital for a long time.

Similarly, during the stay, resistance to first or second line antibiotics rose linearly. When analysing the acquisition of BSIs, clinicians and intensivists frequently use a precise cut-off (i.e., community versus hospital-acquired). Antimicrobial medicines were routinely chosen based on these cut-offs. For comparisons between early and late start Gram-negative bacteremias following hospital admission, several investigators chose a time cut-off of 5 days. Simple recommendations based on a single time cut-off may not adequately reflect the complicated ICU-acquired BSI epidemiology, based on our findings. As a result, an oversimplified “community”

vs "hospital-acquired" classification based on length of hospitalisation should be avoided when choosing empirical antibiotic therapy.

On the first day, possible skin pollutants were low and thereafter stayed stable. This could be explained by the fact that emergency medicine workers (as opposed to those on wards) have a better skill level when it comes to obtaining blood cultures. Another reason for the increased proportion of probable contaminants during ICU stays (excluding day zero) could be the use of intravascular catheters, which are more prone to contamination. Probable contamination trends should be viewed with caution: we did not conduct a patient-based assessment for possible contamination, and possible contaminants should not be regarded as established blood culture contaminations.

There are a few flaws in our research. First, we analysed a microbiological database, but clinical data (e.g., baseline comorbidities, grounds for admission, ICU admission date and reason, source of BSI and antibiotic treatment) were not available, and we were unable to draw recommendations on BSI management from this information. Second, because Switzerland has a low frequency of multidrug-resistant bacteria, our findings are difficult to extrapolate to other countries. Third, we characterised fungemic BSI episodes as those that were resistant to first-generation antibiotics: officially, the epidemiology of fungemia and the epidemiology of bacteremia are not interchangeable. However, we ran a sensitivity analysis to rule out fungi that showed similar patterns. Fourth, we conducted simple descriptive analyses without adjusting for other variables, and we did not provide a more comprehensive risk prediction analysis or score. Fifth, by limiting the analysis to BSI with known acquisition relative to hospitalisation time, a selection bias may have been established. Finally, while the total number of ICU-BSI events fell during the stay, proportionate patterns should be taken with caution.

**Conclusions**

We describe pathogen distribution and bacterial resistance in ICU-BSI during hospitalisation using data from a large national microbiological database. During hospitalisation, the proportion of enterococcal BSI, candidemia, and resistant bacteria to first and second line antibiotics rose.

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