Sources of Primary Bloodstream Infections in Internal Medicine Patients – a Cohort Study

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Abstract

Objectives: To describe the sources of bloodstream infections (BSIs) in internal-medicine patients, on admission and during hospitalization, and to determine the proportion of BSIs in which no secondary cause could be defined (i.e. primary-BSI).

Methods: We analyzed all BSIs at the internal-medicine wards of the two campuses of the Hadassah Hebrew-University Medical Center, during 2017-2018. We defined the BSI source of each event (secondary, Central-line associated BSI (CLABSI) or primary non-CLABSI) and compared BSIs present on admission (POA) to hospital acquired (HA).

Results: There were 595 patient-unique BSI events, 316 (53.1%) POA-BSI and 279 (46.9%) HA-BSI. Overall, 309 (51.9%) were secondary, 194 (32.6%) primary non-CLABSI and 92 (15.5%) CLABSI. Primary non-CLABSI in the POA-BSI group was 20.6% vs. 46.2% in the HA-BSI group (p=0.001). The length of hospital stay (LOS) from culture to discharge of the HA-BSI group was longer than in the POA-BSI group (mean LOS, 19 days vs. 13.6 days, p=0.01) and the mortality rate was higher (48.7% vs. 19%, p=0.001). *Staphylococcus aureus* was more common in primary non-CLABSI than in CLABSI and secondary BSI (29.5%, 12.8% and 16.2%, respectively).

Interpretations: The proportion of primary non-CLABSI among HA-BSI events is very high (46.2%). The absence of any plausible source for these BSIs, and the fact that most patients in Internal-medicine wards have peripheral lines, suggests that the peripheral catheter is a probable source for primary non-CLABSI. Measures to prevent peripheral line associated BSI (PLABSI), similar to those implemented successfully for the prevention of CLABSI, should be considered.

Introduction

Bloodstream infection (BSI) is a common diagnosis in hospitalized patients causing significant morbidity and mortality (1−2). Its incidence rate has increased from 7.4 episodes per 1000 admissions in the 1950s to 31.2 episodes per 1000 admissions in 2006 (3). BSIs are divided into present on admission BSI (POA-BSI), where a positive blood culture (BC) occurs within two days of admission and hospital acquired BSI (HA-BSI) where the positive BC occurs later.

Hospital acquired BSIs have been extensively studied among patients in intensive-care units, (4, 5) especially central-line associated BSI (CLABSI) (6); however, there is a research gap regarding BSIs among patients hospitalized in other departments, especially internal medicine wards. Previous studies among hospitalized patients described the common pathogens causing BSI and their susceptibility pattern but did not relate to the possible source of the BSI (7−9).

BSI is usually secondary to an infection at another body site (e.g. urinary tract infection, intra-abdominal infection etc.). When there is no clear secondary source of infection, the term primary BSI is used. When the patient has primary BSI in the presence of a central line, the BSI is attributed to the line and defined as
CLABSI. If a patient with primary BSI has no central line, the BSI is defined as primary non-CLABSI (10). The common infection complicating peripheral venous catheters (PVC) is thrombophlebitis while BSIs secondary to the presence of PVCs are considered a rare complication (11–13). Nevertheless, given the large proportion of primary non-CLABSI among hospitalized patients with BSI, this assumption needs to be re-examined. If the peripheral line can be appointed as a significant cause of BSI, then preventive measures should be taken in order to minimize it, similar to CLABSI prevention (14).

In our Medical Center, we perform routine surveillance of BSIs among patients hospitalized in the medical wards. We have noticed that in many cases of HA-BSI a secondary source cannot be defined; in most cases there is no central line either. In order to further investigate this group, we initiated a two-year study of BSIs in the medical wards.

**Methods**

**Design**

We preset a cohort study among patients admitted to internal medicine wards.

**Setting**

The Hadassah-Hebrew University Medical Center consists of two academic hospitals with 1075 in-patient beds, Jerusalem's largest. The Hadassah Ein-Kerem Campus is a 775-bed, academic tertiary care hospital with all facilities. The Mount-Scopus Campus is a 300-bed, community hospital. In total, there are six internal medicine departments with 170 beds.

A waiver of informed consent was granted by the institutional research ethics committee, as this was considered a quality control initiative, and there were no patients identified or treatments given.

**Blood cultures**

Blood cultures are obtained when BSI is suspected, either in the emergency department or during hospitalization, at the discretion of the attending physician. It is recommended to obtain two sets of BCs when BSI is suspected, but this is not always carried out. Each BC set includes both aerobic and anaerobic bottles. Bottles are used according to the manufacturer's instructions. Blood cultures are usually obtained from peripheral venipuncture following skin prep with 70% isopropyl alcohol or 0.5% chlorhexidine in 70% alcohol.

**Microbiologic Methods**

Becton-Dickinson BACTEC Plus aerobic and anaerobic bottles (Becton, Dickinson & co., Sparks, MD, USA) were used for all blood cultures and were processed using the BACTEC 9240 system. Bacteria were identified using standard microbiological techniques (15).
Data collection and Analysis of Bloodstream infection events

The study population included patients aged 18 years or above, hospitalized in an internal medicine department, from January 1, 2017 to December 31, 2018, and had at least one positive blood culture, upon admission or during hospitalization. Analysis of positive BCs was done at the end of each month. Data was obtained from the Information Systems Division using a dedicated computerized system, including demographics, admission date, department, culture date and the pathogen. Clinical data (i.e. past medical history, vital signs, physical examination, laboratory) and clinical course (i.e. length of hospitalization, intensive-care unit admission, mortality) were further collected from the electronic medical chart.

An infectious disease specialist assessed the data: The first step in every BC analysis was to exclude contaminants according to Centers for Disease Control surveillance guidelines (10, 16); Blood cultures with true pathogens were further analyzed. Each BSI was classified either as POA-BSI if the culture was obtained within two calendar days since admission, or as HA-BSI if the culture was obtained later. When more than one positive BC were related to the same clinical event they were counted as one BSI. If a patient had more than one BSI event during the study period, only the first was included in the analysis. Every BSI was further categorized to one of three groups: 1) secondary BSI, a BSI that is thought to be seeded from a specific infection at another body site (unique bacteria, e.g. Brucella species, which are endemic in Israel (17), were classified as secondary BSI); 2) CLABSI, a BSI that is not secondary and the patient has a central line for at least two days prior to the date of the positive BC; 3) primary non-CLABSI, a BSI that is not secondary and the patient doesn't have a central line (3). In the secondary BSI group the source of infection was defined according to CDC definitions (e.g. catheter-associated UTI, intra-abdominal infection etc.).

Statistical analysis

Categorical variable distributions are presented with absolute count and percentages, continuous variables with mean and standard deviation. We compared variable distribution between clinical events that were defined as POA and HA. Additionally, we compared variable distribution between secondary BSI, CLABSI and primary non-CLABSI events. Categorical variables were compared with the chi-square test and continuous variables with the Student t-test and ANOVA (between three groups). We considered p-values below 0.05 statistically significant. In order to assess the association of BSI group (CLABSI, primary non-CLABSI and secondary infection) and community/hospital source with in-hospital mortality, we generated a logistic regression model including age and sex variables as well as co-morbidities, which were unevenly distributed between the groups of interest. The associations are described with odds ratio and a 95% confidence interval.

Results
During the two-year period (2017-2018), there were 2084 positive blood cultures among patients hospitalized at the internal medicine wards (Figure 1). After excluding contaminants and recurrent BSI events in the same patient, 595 patient-unique events were included in the final analysis. Overall, 309 (51.9%) were secondary, 194 (32.6%) primary non-CLABSI and 92 (15.5%) CLABSI. The classification into POA-BSI and HA-BSI, and the source of the BSI, are presented in the Figure 1.

Baseline and clinical patients’ characteristics according to the timing of the event are presented in Table 1. The patients with HA-BSI were older than those with POA-BSI (mean age 71.3 vs. 66.6, p=0.001) and the proportion of nursing home residence among them was higher (25.1% vs. 16.8%, p=0.027). The clinical characteristics of both groups were generally similar, with only minor differences. The length of hospital stay (LOS) from culture to discharge in the HA-BSI group was longer than in the POA-BSI group (mean LOS, 19 days vs. 13.6 days, p=0.01) and the mortality rate was higher (48.7% vs. 19%, p=0.001). This latter finding remained significant in the multivariate model, controlling for age, sex, hemodialysis, chronic obstructive pulmonary disease and nursing home residency, where we found that HA-BSIs were associated with an increased OR of mortality of 3.76 (95%CI, 2.46 - 5.74) compared to POA-BSIs.
Table 1
Patients characteristics, clinical outcome and source of bloodstream infection according to the timing of the event (N=595)

| Present on admission (POA) | Hospital acquired (HA) | p-value |
|---------------------------|------------------------|---------|
| N=316                     | N=279                  |         |
| N (%) / mean ± SD         |                        |         |
| Female gender             | 113 (35.8%)            | 121 (43.4%) | 0.1 |
| Age                       | 66.6 (18.5)            | 71.3 (16.3) | 0.001 |
| Nursing-home residence    | 53 (16.8%)             | 70 (25.1%) | 0.027 |

Medical conditions

| Hypertension              | 186 (58.9%)            | 172 (61.6%) | 0.38 |
| COPD                      | 25 (7.9%)              | 36 (12.9%)  | 0.09 |
| Cirrhosis                 | 13 (4.1%)              | 24 (8.6%)   | 0.55 |
| Diabetes mellitus         | 158 (50%)              | 158 (56.6%) | 0.15 |
| Chronic renal failure     | 115 (36.4%)            | 105 (37.6%) | 0.69 |
| Dialysis                  | 93 (19.9%)             | 30 (10.8%)  | 0.008 |
| Needs assistance in ADL   | 232 (73.4%)            | 246 (88.2%) | 0.001 |

Clinical characteristics on the day of bloodstream infection (BSI)

| Highest temperature (°C) | 37.7 (1.0) | 37.5 (1.2) | 0.03 |
| Lowest systolic blood-pressure | 100 (21.6) | 97 (23) | 0.1 |
| C-reactive protein (mg/dl) | 14.8 (11.7) | 12.8 (11.3) | 0.03 |
| WBC (10^9/L)              | 12.6 (8.8)  | 15.4 (16.1) | 0.01 |
| %PMN                      | 84.7 (12.1) | 86.5 (11.5) | 0.08 |
| Creatinine (mmol/L)       | 241.6 (236) | 230 (197) | 0.52 |

Clinical outcome

| LOS from culture to discharge | 13.6 (14.4) | 19 (21.4) | 0.01 |
| In hospital death            | 60 (19.0%)  | 136 (48.7%) | 0.001 |
| LOS from culture to death (days) | 7.8 (13.2) | 12.2 (21) | 0.1 |

Source of bloodstream infection
|                             | Present on admission (POA) | Hospital acquired (HA) | p-value |
|-----------------------------|---------------------------|------------------------|---------|
|                             | N=316                     | N=279                  |         |
| Secondary bloodstream infection | 213 (67.4%)               | 96 (34.4%)             | 0.001   |
| Primary non-CLABSI          | 65 (20.6%)                | 129* (46.2%)           | 0.001   |
| CLABSI                      | 38# (12.0%)               | 54 (19.4%)             | 0.001   |

COPD, chronic obstructive pulmonary disease; ADL, activity of daily living; WBC, white blood cell count; PMN, polymorphonuclear; LOS, length of stay; CLABSI, central-line associated bloodstream infection

* 3/129 had documented thrombophlebitis

# CLABSI present on admission was found in patients with long term central lines, most for hemodialysis

The source of BSI differed significantly between the two groups: among the POA-BSI group 67% were secondary BSIs and 20.6% were primary non-CLABSIs. Among the HA-BSI group 34.4% were secondary BSI and 46.2% were primary non-CLABSI (p=0.001) (Figure 1, Table 1).

We compared patients’ characteristics and clinical outcomes according to the source of the BSI (Table 2). Chronic renal failure and the need for dialysis were more common among patients with CLABSI than in patients with primary non-CLABSI or secondary BSI (p=0.001). In addition, in-hospital death rate was significantly higher in the CLABSI and primary non-CLABSI groups (43.5% and 39.7% respectively) than in the secondary BSI group (25.6%, p=0.001). However, in the multi-variate analysis the difference in mortality stayed significant only for CLABSI. Compared to secondary BSI, CLABSI was associated with an increase OR of mortality of 2.1 (95% CI, 1.1 to 3.8) while the OR of mortality among primary non-CLABSI was 1.2 (95% CI, 0.78-1.79).
Table 2
Patients characteristics and clinical outcome, according to the source of bloodstream infection (N=595)

| Source of bloodstream infection | CLABSI N=92 | Primary non-CLABSI N=194 | Secondary BSI N=309 | p-value |
|---------------------------------|-------------|--------------------------|---------------------|---------|
|                                 | N (%) / mean ± SD |                          |                     |         |
| Female gender                   |             |                          |                     | 0.7     |
| Age                             | 63.5 (18.5) | 71.4 (15.6)              | 68.9 (18.3)         | 0.002   |
| Nursing-home residence          | 23 (25%)    | 46 (23.7%)               | 54 (17.5%)          | 0.2     |
| Medical conditions              |             |                          |                     |         |
| Hypertension                    | 59 (64.1%)  | 122 (62.3%)              | 177 (57.3%)         | 0.34    |
| COPD                            | 8 (8.7%)    | 24 (12.4%)               | 29 (9.4%)           | 0.51    |
| Cirrhosis                       | 6 (6.5%)    | 14 (7.2%)                | 17 (5.5%)           | 0.63    |
| Diabetes mellitus               | 52 (56.5%)  | 103 (53.1%)              | 161 (52.1%)         | 0.58    |
| Chronic renal failure           | 61 (66.3%)  | 74 (38.1%)               | 85 (27.5%)          | 0.001   |
| Dialysis                        | 41 (44.6%)  | 24 (12.4%)               | 28 (9.1%)           | 0.001   |
| Needs assistance in ADL         | 75 (81.5%)  | 163 (84%)                | 240 (77.7%)         | 0.5     |
| Clinical characteristics on the day of bloodstream infection (BSI) | | | | |
| Highest temperature (°C)        | 37.6 (1.2)  | 37.4 (1.0)               | 37.7 (1.1)          | 0.02    |
| Lowest systolic blood pressure  | 99.0 (25.8) | 99.6 (22)                | 98.4 (21.4)         | 0.83    |
| C-reactive protein (mg/dl)      | 10.6 (10.2) | 13.3 (12.0)              | 15.3 (11.5)         | 0.002   |
| WBC (10^9/L)                    | 10.9 (9.6)  | 15.6 (17.1)              | 13.7 (10.1)         | 0.014   |
| Source of bloodstream infection | CLABSI N=92 | Primary non-CLABSI N=194 | Secondary BSI N=309 | p-value |
|--------------------------------|-------------|--------------------------|---------------------|---------|
| %PMN                           | 85.4 (10.3) | 86.2 (11.2)              | 85.2 (12.7)         | 0.65    |
| Creatinine (mmol/L)            | 415 (295)   | 227 (213)                | 188 (161)           | 0.001   |

**Clinical outcome**

|                           |             |             |             |         |
|--------------------------|-------------|-------------|-------------|---------|
| LOS from culture to discharge | 17 (18.3)  | 15.2 (18.2) | 15.3 (16.6) | 0.84    |
| In hospital death         | 40 (43.5%)  | 77 (39.7%)  | 79 (25.6%)  | 0.001   |
| LOS from culture to death (days) | 10 (17.1)  | 10.8 (19.1) | 11.3 (20.2) | 0.94    |

CLABSI, central-line associated bloodstream infection; BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; ADL, activity of daily living; WBC, white blood cell count; PMN, polymorphonuclear; LOS, length of stay

The secondary BSI source of infection according to the timing of the event (POA or HA) are presented in Table 3. The most common secondary sources were urinary tract infections (44.1% and 26.0% respectively) followed by skin and soft tissue infections (13.6% and 18.8% respectively) and lower respiratory tract infections (7.5% and 27.1% respectively). Unique bacteria (i.e. *Brucella sp.*, *Salmonella enterica*) were found only in the POA-BSI group.
Table 3
Secondary bacteremia source of infection according to the timing of the event

| Secondary bacteremia source                  | Present on admission (POA) N=213 | Hospital acquired (HA) N=96 |
|---------------------------------------------|----------------------------------|-----------------------------|
| Urinary tract infection (UTI)               | 94 (44.1%)                       | 25 (26.0%)                  |
| Skin & soft tissue infection                | 29 (13.6%)                       | 18 (18.8%)                  |
| Lower respiratory tract infection           | 16 (7.5%)                        | 26 (27.1%)                  |
| Endocarditis                                | 33 (15.5%)                       | 4 (4.2%)                    |
| Intra-abdominal infection                   | 19 (8.9%)                        | 18 (18.8%)                  |
| Unique bacteria*                            | 14 (6.6%)                        | 0 (0.0%)                    |
| Mucosal barrier infection (MBI)             | 0 (0.0%)                         | 2 (2.1%)                    |
| Other                                       | 8 (3.8%)                         | 3 (3.1%)                    |

* Unique bacteria, *Brucella species* and *Salmonella enterica*

The bacteria isolated according to the timing of the event (POA or HA) and according to the source of infection are presented in Table 4. In POA events, the most common bacteria belonged to Enterobacteriaceae followed by *Staphylococcus aureus, Enterococcus species* and *Pseudomonas aeruginosa*. In HA events the findings were quite similar: Enterobacteriaceae were the most common bacteria followed by *S. aureus* (Table 4a). Among CLABSI events, Gram-negative bacilli account for most events followed by *S. aureus* and coagulase-negative Staphylococcus. In contrast, in primary non-CLABSI, *S. aureus* was much more dominant and accounted for about a third of cases (Table 4b).
**Table 4**
Pathogen classification

**Table 4a: Pathogen classification according to the timing of the event**

| Pathogen Classification | Present on admission (POA) | Hospital acquired (HA) |
|-------------------------|-----------------------------|------------------------|
|                         | 316 cases (334 bacteria)    | 279 cases (316 bacteria) |
| Gram negative bacteria  | 164 (49.1%)                 | 170 (53.8%)            |
| Enterobacteriaceae      | 145 (43.5%)                 | 129 (40.8%)            |
| *Acinetobacter species* | 3 (0.9%)                    | 15 (4.7%)              |
| *Pseudomonas species*   | 16 (4.8%)                   | 26 (8.2%)              |
| Gram positive bacteria  | 120 (35.9%)                 | 106 (33.5%)            |
| *Staphylococcus aureus* | 71 (21.3%)                  | 58 (18.4%)             |
| Coagulase-negative Staphylococci | 8 (2.4%)         | 15 (4.7%)              |
| *Enterococcus species*  | 25 (7.5%)                   | 30 (4%)                |
| α-hemolytic streptococci| 7 (2.1%)                    | 2 (0.6%)               |
| β-hemolytic streptococci| 4 (1.2%)                    | 1 (0.3%)               |
| *Streptococcus pneumoniae* | 5 (1.5%)            | 0 (0.0%)               |
| Unique bacteria &       | 21 (6.3%)                   | 0 (0.0%)               |
| Candida                 | 4 (1.2%)                    | 16 (5.1%)              |
| Other                   | 25 (7.5%)                   | 24 (7.5%)              |
Table 4b: Pathogen classification according to the source of bloodstream infection

| Pathogen                        | CLABSI N=109 | Primary non-CLABSI N=207 | Secondary BSI N=334 |
|---------------------------------|--------------|--------------------------|---------------------|
| Gram negative bacteria          | 59 (54.1%)   | 81 (39.1%)               | 196 (58.6%)         |
| Enterobacteriaceae              | 38 (34.8%)   | 62 (29.9%)               | 176 (52.6%)         |
| *Acinetobacter species*         | 5 (4.6%)     | 6 (2.9%)                 | 7 (2.1%)            |
| *Pseudomonas species*           | 16 (14.7%)   | 13 (6.3%)                | 13 (3.9%)           |
| Gram positive bacteria          | 32 (29.3%)   | 98 (47.3%)               | 96 (28.7%)          |
| *Staphylococcal aureus*         | 14 (12.8%)   | 61 (29.5%)               | 54 (16.2%)          |
| Coagulase-negative staphylococci| 10 (9.2%)    | 7 (3.4%)                 | 6 (1.8%)            |
| *Enterococcus species*          | 7 (6.4%)     | 23 (11.2%)               | 25 (7.5%)           |
| α-hemolytic streptococci        | 1 (0.9%)     | 1 (0.5%)                 | 7 (2.1%)            |
| β-hemolytic streptococci        | 0 (0.0%)     | 3 (1.5%)                 | 2 (0.6%)            |
| *Streptococcus pneumoniae*      | 0 (0.0%)     | 3 (1.6%)                 | 2 (0.6%)            |
| Unique bacteria &               | 0 (0%)       | 0 (0%)                   | 21 (6.3%)           |
| Candida                         | 9 (8.3%)     | 9 (4.3%)                 | 2 (0.6%)            |
| Other                           | 9 (8.3%)     | 19 (9.1%)                | 19 (5.6%)           |

*16/18 (88.9%) *Acinetobacter baumannii*

# 38/42 (90.5%) *Pseudomonas aeruginosa*

& Unique bacteria, *Brucella species, Salmonella enterica*

**Discussion**

We present a two-year survey of BSI in six internal medicine wards in a tertiary medical center. The BSI source could be defined in 79.4% of the POA events (67.4% secondary BSI and 12.0% CLABSI) but only in 53.8% when the BSI was hospital acquired (34.4% secondary BSI and 19.4% CLABSI). Primary non-CLABSI events were over two times more common in the HA group compared to the POA group (46.2% vs. 20.6% respectively, p=0.001) (Figure 1, Table 1).

True BSI should always warrant clinicians to look for its source, in order to treat the patient properly. In clinical practice, many times such a source cannot be defined. Several reasons can be given for that, such
as lack of appropriate workup or previous antibiotic treatment. In addition, adherence to the strict CDC
criteria when analyzing a BSI event can sometimes diminish the ability to classify events as secondary.

We conducted a rigorous evaluation in each BSI event in order to identify the likely source. The finding of
lack of a source for HA-BSI in almost half of the cases requires explanation.

Over the last two decades, attention has been focused on central venous lines as an important and
common source of BSI. The same mechanisms leading to BSI secondary to the presence of a central
venous catheter (i.e. bacterial invasion through or around the catheter) (18), may apply also to PVCs.
Though peripheral lines are placed for a shorter duration than central lines (19), PVCs are much more
prevalent in the hospital setting. Practically, almost every hospitalized patient in the internal medicine
ward has a PVC (20). These lines are usually inserted and maintained without the strict precautions
applied for central lines (11). Hence, it is reasonable to conclude that PVCs can be an important source of
primary non-CLABSI.

The peripheral line is an obvious cause for primary non-CLABSI when thrombophlebitis is present (13,
21–23), however in our study, thrombophlebitis was found only in 3/129 (2.3%) cases of primary non-
CLABSI. Lack of local signs in primary non-CLABSI is not surprising, as patients with CLABSI also usually
have no local signs of infection. We propose that when there is a BSI without a secondary cause, in the
presence of a peripheral line (and without a central line), peripheral-line associated BSI (PLABSI) is the
presumed diagnosis. As in the CDC guidelines for the diagnosis of CLABSI, the PLABSI definition is also
not relied on tip of the line cultures (i.e. catheter-related BSI), since these are not feasible in everyday
clinical practice. In our opinion, PLABSI is the commonest hospital acquired cause for primary non-
CLABSI, and in most cases without local signs.

In a systematic review by Mermel (24) in most studies included, PLABSI was diagnosed by local signs of
infection (i.e. thrombophlebitis). According to our findings, those events of PLABSI with local signs
probably constitute only a small part of PLABSI cases.

Once the concept of PLABSI is defined, it should lead us to take appropriate preventive measures. There
is plenty of information regarding CLABSI prevention, on insertion of the catheter and during its use. It is
reasonable to assume that the proven practices for the prevention of CLABSI (25) can be effective as well
for PLABSI prevention. (26–29). Prevention of BSI as a complication of a PVC through appropriate
handling of insertion and maintenance of such lines could prevent a considerable number of deaths from
HA-BSIs (30). Moreover, when there is a BSI and no secondary cause can be identified, it may be prudent
to replace the peripheral line.

In our study, both in POA and HA, Gram-negative bacteria were the commonest pathogens identified
followed by *Staphylococcus aureus*. The same prevalence was found in primary non-CLABSI (39.1% and
29.5%, respectively) (Table 4b).
We found worse outcomes of HA-BSI vs. POA-BSI, with a prolonged length of stay since the positive culture (21.4 days vs. 14.4 days, p=0.01) and significantly higher mortality rate (48.7% vs. 19.0%; OR 3.76, 95% CI, 2.46 - 5.74) (Table 1). In our cohort, the patients with HA-BSI were older and had more comorbidities compared to the patients with POA-BSI; this might explain their worse outcomes.

Comparing the clinical outcomes according to the BSI source (Table 2), the mortality rates in CLABSI and primary non-CLABSI were similar and significantly higher than that in secondary BSI (43.5%, 39.7% and 25.6% respectively, p=0.001). However, in multi-variate analysis, only in CLABSI the mortality rate was significantly higher than in secondary BSI (OR 2.1, 95% CI, 1.1 to 3.8).

Our study has some limitations. We conducted analyses at the end of each month and not immediately on the date of the positive BC. This delay could have led to missing of some information. However, we conducted a thorough investigation in each case and the perspective nature of the analysis allowed us a better understanding of the disease course. Additionally, we could not record the presence of a peripheral line at the time of BSI, yet it is rare to find a patient in internal medicine wards without a line, as is known also from the literature (12). Finally, we did not prove microbiologically that the peripheral line is the cause of BSI in primary non-CLABSI. This would have been difficult to perform and was not part of this study. For the same reason, the CDC surveillance guidelines use the definition of CLABSI rather than the microbiologically proven catheter-related BSI (10).

In conclusion, we found that a large proportion (46.2%) of HA-BSI among internal medicine patients do not have a secondary cause. We suggest that the source for many of these BSIs is the peripheral line. Measures to prevent PLABSI, similar to those implemented for the prevention of CLABSI, should be applied.

Declarations

- Ethics approval and consent to participate - A waiver of informed consent was granted by the Hadassah hospital research ethics committee (HMO-12-0460), as this was considered a quality control initiative, and there were no patients identified or treatments given.
  - All methods were carried all methods were performed in accordance with the relevant guidelines and regulations.
  - The study was not experimental.
  - The Hadassah institutional research ethics committee granted waiver from the need for informed consent.
  - Hadassah institutional research ethics committee approved all the study methods.

- Consent for publication – not applicable

- Availability of data and materials - the datasets generated and/or analyzed during the current study are not publicly available due hospital policy but are available from the corresponding author on reasonable request.
Competing interests - None
Funding - none
Authors' contributions - SB initiated the study and raised the research question and strategies. YBY, YO, and SB collected and analyzed the data. CS reviewed and appraised collected data. MJC and YBY provided statistical expertise in data analysis. SB, YO, YBY and CS drafted the manuscript.

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References

1. Guidelines on Core Components of Infection Prevention and Control Programmes at the National and Acute Health Care Facility Level. Geneva: World Health Organization; 2016.

2. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1994;271(20):1598-1601. doi:10.1001/jama.271.20.1598

3. John EB, Raphael D, Martin JB. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, Vol. 1. 9th edn. 2019; chapter 194, pages 2393-2431

4. Timsit JF, Ruppé E, Barbier F, Tabah A, Bassetti M. Bloodstream infections in critically ill patients: an expert statement. Intensive Care Med. 2020;46(2):266-284. doi:10.1007/s00134-020-05950-6

5. Tabah A, Koulenti D, Laupland K, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med. 2012;38(12):1930-1945. doi:10.1007/s00134-012-2695-9

6. Nuckols TK, Keeler E, Morton SC, et al. Economic Evaluation of Quality Improvement Interventions for Bloodstream Infections Related to Central Catheters: A Systematic Review [published correction appears in JAMA Intern Med. 2016 Dec 1;176(12):1884]. JAMA Intern Med. 2016;176(12):1843-1854. doi:10.1001/jamainternmed.2016.6610

7. Kaye KS, Marchaim D, Chen TY, et al. Predictors of nosocomial bloodstream infections in older adults. J Am Geriatr Soc. 2011;59(4):622-627. doi:10.1111/j.1532-5415.2010.03289.x

8. Diekema DJ, Hsueh PR, Mendes RE, et al. The Microbiology of Bloodstream Infection: 20-Year Trends from the SENTRY Antimicrobial Surveillance Program. Antimicrob Agents Chemother. 2019;63(7):e00355-19. Published 2019 Jun 24. doi:10.1128/AAC.00355-19

9. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study [published correction appears in Clin Infect Dis. 2004 Oct 1;39(7):1093] [published correction appears in Clin Infect Dis. 2005 Apr 1;40(7):1077]. Clin Infect Dis. 2004;39(3):309-317. doi:10.1086/421946

10. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection) by the National Healthcare Safety Network, Centers for Disease
11. Webster J, Osborne S, Rickard CM, Marsh N. Clinically-indicated replacement versus routine replacement of peripheral venous catheters. *Cochrane Database Syst Rev*. 2019;1(1):CD007798. Published 2019 Jan 23. doi:10.1002/14651858.CD007798.pub5

12. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc*. 2006;81(9):1159-1171. doi:10.4065/81.9.1159

13. Ripa M, Morata L, Rodríguez-Núñez O, et al. Short-Term Peripheral Venous Catheter-Related Bloodstream Infections: Evidence for Increasing Prevalence of Gram-Negative Microorganisms from a 25-Year Prospective Observational Study. *Antimicrob Agents Chemother*. 2018;62(11):e00892-18. Published 2018 Oct 24. doi:10.1128/AAC.00892-18

14. Zingg W, Pittet D. Peripheral venous catheters: an under-evaluated problem. *Int J Antimicrob Agents*. 2009;34 Suppl 4: S38-S42. doi:10.1016/S0924-8579(09)70565-5

15. Lamy B, Sundqvist M, Idelevich EA; ESCMID Study Group for Bloodstream Infections, Endocarditis and Sepsis (ESGBIES). Bloodstream infections - Standard and progress in pathogen diagnostics. *Clin Microbiol Infect*. 2020;26(2):142-150. doi: 10.1016/j.cmi.2019.11.017

16. Organism List, updated 01/2021, by the National Healthcare Safety Network, Centers for Disease Control and Prevention, [https://www.cdc.gov/nhsn/xls/master-organism-com-commensals-lists.xlsx](https://www.cdc.gov/nhsn/xls/master-organism-com-commensals-lists.xlsx)

17. Glikman D. Human Brucellosis in Israel - The Saga Continues. *Isr Med Assoc J*. 2019 Jan;21(1):52-53. PMID: 30685907.

18. John EB, Raphael D, Martin JB. Mandell, Douglas, and Bennett’s principles and practice of infectious diseases, Vol. 1. 9th edn. 2019; chapter 300, pages 3560-3575

19. Timsit JF. Scheduled replacement of central venous catheters is not necessary. *Infect Control Hosp Epidemiol*. 2000 Jun;21(6):371-4. doi: 10.1086/501775. PMID: 10879566.

20. Guembe M, Pérez-Granda MJ, Capdevila JA, et al. Nationwide study on the use of intravascular catheters in internal medicine departments. *J Hosp Infect*. 2015;90(2):135-141. doi:10.1016/j.jhin.2015.01.024

21. Freixas N, Bella F, Limón E, Pujol M, Almirante B, Gudiol F. Impact of a multimodal intervention to reduce bloodstream infections related to vascular catheters in non-ICU wards: a multicentre study. *Clin Microbiol Infect*. 2013 Sep;19(9):838-44. doi: 10.1111/1469-0691.12049. Epub 2012 Nov 6. PMID: 23130638.

22. Trinh TT, Chan PA, Edwards O, et al. Peripheral venous catheter-related Staphylococcus aureus bacteremia [published correction appears in Infect Control Hosp Epidemiol. 2011 Jul;32(7):735]. *Infect Control Hosp Epidemiol*. 2011;32(6):579-583. doi:10.1086/660099

23. Stuart RL, Cameron DR, Scott C, et al. Peripheral intravenous catheter-associated Staphylococcus aureus bacteraemia: more than 5 years of prospective data from two tertiary health services. *Med J Aust*. 2013;198(10):551-553. doi:10.5694/mja12.11699
24. Mermel LA. Short-term Peripheral Venous Catheter-Related Bloodstream Infections: A Systematic Review. *Clin Infect Dis.* 2017 Oct 30;65(10):1757-1762. doi: 10.1093/cid/cix562. PMID: 29020252.

25. Xiong Z, Chen H. Interventions to reduce unnecessary central venous catheter use to prevent central-line-associated bloodstream infections in adults: A systematic review. *Infect Control Hosp Epidemiol.* 2018 Dec;39(12):1442-1448. doi: 10.1017/ice.2018.250. Epub 2018 Oct 11. PMID: 30305194.

26. Ray-Barruel G, Xu H, Marsh N, Cooke M, Rickard CM. Effectiveness of insertion and maintenance bundles in preventing peripheral intravenous catheter-related complications and bloodstream infection in hospital patients: A systematic review. *Infect Dis Health.* 2019;24(3):152-168. doi:10.1016/j.idh.2019.03.001

27. Austin ED, Sullivan SB, Whittier S, Lowy FD, Uhlemann AC. Peripheral Intravenous Catheter Placement Is an Underrecognized Source of Staphylococcus aureus Bloodstream Infection. *Open Forum Infect Dis.* 2016;3(2):ofw072. Published 2016 Apr 6. doi:10.1093/ofid/ofw072

28. Rhodes D, Cheng AC, McLellan S, et al. Reducing Staphylococcus aureus bloodstream infections associated with peripheral intravenous cannulae: successful implementation of a care bundle at a large Australian health service. *J Hosp Infect.* 2016;94(1):86-91. doi:10.1016/j.jhin.2016.05.020

29. Fakih MG, Jones K, Rey JE, et al. Sustained improvements in peripheral venous catheter care in non-intensive care units: a quasi-experimental controlled study of education and feedback. *Infect Control Hosp Epidemiol.* 2012;33(5):449-455. doi:10.1086/665322

30. Martínez JA, Piazuelo M, Almela M, et al. Evaluation of add-on devices for the prevention of phlebitis and other complications associated with the use of peripheral catheters in hospitalised adults: a randomised controlled study. *J Hosp Infect.* 2009;73(2):135-142. doi:10.1016/j.jhin.2009.06.031

**Figures**
Figure 1

Flow chart of the classification of bloodstream infection (BSI) events in the internal medicine wards 2017-2018. The analyses were done monthly by infectious diseases specialists.

BSI, bloodstream infection; CLABSI, central line associated blood stream infection