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ORIGINAL RESEARCH

Positive predictive values of the International Classification of Diseases, 10th revision diagnoses of Gram-negative septicemia/sepsis and urosepsis for presence of Gram-negative bacteremia

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Background: Health care databases are a valuable resource for infectious disease epidemiology if diagnoses are accurately coded. We examined the ability of diagnostic coding to accurately identify Gram-negative bacteremia.

Methods: We randomly selected 100 patients among 1,703 patients recorded in the Danish National Patient Register with a diagnosis of either "septicemia/sepsis due to other Gram-negative organisms" (International Classification of Diseases, 10th revision [ICD-10] code A41.5) or "urosepsis" (ICD-10 code A41.9B) who had been admitted at Aalborg University Hospital, Denmark between 1994 and 2012. We estimated the positive predictive value (PPV) of these diagnoses for presence of Gram-negative bacteremia, using microbiological results from blood cultures as standard reference. Complementary clinical information was obtained from the medical records.

Results: Of the 100 patients registered with Gram-negative septicemia/sepsis or urosepsis, 72 had blood culture confirmed Gram-negative bacteremia, four patients had monomicrobial Gram-positive bacteremia, 21 patients had a negative blood culture, and three had no blood culture taken. The overall PPV of a blood culture confirmed Gram-negative bacteremia diagnosis was 72% (95% confidence interval [CI]: 62%–81%); for ICD-10 code A41.5 it was 86% (95% CI: 74%–94%) and for ICD-10 code A41.9B it was 55% (95% CI: 39%–70%). The highest PPV was achieved for diagnoses registered in the most recent calendar period (2009–2012) and for secondary discharge diagnoses.

Conclusion: Our findings indicated good agreement between ICD-10 code A41.5 "septicemia/sepsis due to other Gram-negative organisms" and Gram-negative bacteremia, whereas ICD-10 code A41.9B "urosepsis" was not suited for identification of Gram-negative bacteremia.

Keywords: validation studies, Danish National Patient Register

Introduction

Gram-negative bacteremia is a serious infection with high mortality,[1] and therefore often a central issue in intensive care research. The information recorded in hospital discharge registries is readily available at low cost and usually covers large and unselected populations.[2] Accordingly, there may be a great potential in using hospital discharge diagnosis codes to identify patients with bacteremia in infectious disease epidemiology. The Danish National Patient Register (NPR) has recorded more than 99% of all hospital discharges in Denmark since 1977, and generally has a documented high validity and completeness of many diseases registered,[3] including community-acquired infections.[4]

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Several studies have validated diagnosis codes of sepsis in administrative databases, but only a few studies examined the potential of using septicemia or sepsis diagnosis codes to identify patients with documented bacteremia. In a Danish study, diagnoses of septicemia registered in the NPR (1994, N=83) were validated against a microbiological registry, and accuracy was poor both in terms of positive predictive value (PPV) and sensitivity for bacteremia (22% and 4%, respectively).[5] However, these results are 20 years old and based on registrations made during the first year after introduction of the Danish version of International Classification of Diseases, 10th revision (ICD-10) diagnosis codes in 1994.[5] A US study validated International Classification of Diseases, ninth revision, Clinical Modifications (ICD-9-CM) discharge diagnoses of septicemia or bacteremia (2001–2004, N=22) and found a PPV of 86%.[6]

We therefore examined the ability of diagnosis codes for Gram-negative septicemia/sepsis and urosepsis to accurately identify patients with Gram-negative bacteremia, validating ICD-10 diagnoses in the NPR against results of blood cultures.

Materials and methods

Danish National Patient Register

The NPR records the civil registration number of the patient, dates of admission and discharge, surgical procedures performed, and up to 20 discharge diagnoses coded by treating physicians according to the Danish version of the International Classification of Diseases, eighth revision (ICD-8) until the end of 1993 and the 10th revision (ICD-10) thereafter, on each hospital admission since 1977.[3] The primary diagnosis refers to the condition that prompted patient admission and the main condition responsible for the completed diagnosis and treatment course. The secondary diagnoses refer to conditions that affected the diagnosis and treatment course. For this validation study, we used diagnoses recorded at Aalborg University Hospital, Denmark from January 1, 1994 to December 31, 2012 (with a catchment area of 580,000 inhabitants in 2012).[7] All clinical specialties are represented at this hospital, with the exception of dermatology. We used both primary and secondary diagnosis codes and included only inpatient hospitalization diagnoses. The study was approved by the Central Region of Denmark (Journal no 1-16-02-1-08) and the National Board of Health.

Terminology and ICD-10 codes used

The terminology referring to bacteremia, septicemia, and sepsis has been subject to some ambiguity. Bacteremia refers to detection of bacteria or other microorganism in the blood, septicemia requires presence of a systemic inflammatory response to microorganisms or toxins in the blood, and sepsis demands that the criteria for a systemic inflammatory response are fulfilled together with clinical evidence of infection (not necessarily bacteremia).[8]

The majority of infectious and parasitic diseases are coded in the ICD-10 system chapters A00–B99, while a number of frequent, localized infections are coded in other body system-related chapters (eg, J12–J18 pneumonia, N30 cystitis). Most codes targeting bacteremia or sepsis in ICD-10 are placed in chapters A40 (streptococcal/pneumococcal sepsis) and A41 (other sepsis). An international consensus was reached to abandon the terminology "septicemia" in the 1990s. Still, it remained in the Danish version of the ICD-10 until the end of 2011, and was only thereafter replaced with "sepsis."

To identify patients with possible Gram-negative bacteremia in the NPR, we used diagnoses of "septicemia/sepsis due to other Gram-negative organisms" (ICD-10 code A41.5). We also used the frequently recorded diagnostic code for "urosepsis" (ICD-10 code A41.9B), assuming that the majority of urosepsis would be caused by a detectable Gram-negative microorganism.

Validation: microbiological diagnostics and medical journals

Blood culture data were obtained from the laboratory information system (ADBakt; Autonik, Ramsta, Sweden) maintained by the Department of Clinical Microbiology at Aalborg University Hospital. Blood culture sets included three bottles (two aerobic and one anaerobic).[9] Information on number of blood cultures (number taken/number positive), microorganism, and acquisition of bacteremia (community-acquired, ie, present or incubating at admission to the hospital/health care associated, ie, occurred in patients with a hospital admission within 30 days or regular hospital visits)[9] was evaluated for each individual by the first author (KKS). Thereafter, this information was validated against results in the laboratory information system by a skilled laboratory technician. Using the laboratory information system, we identified all urine cultures taken on the same day (±1 day) as the blood culture. The medical journals were reviewed only by KKS to retrieve additional information about source of bacteremia.

Statistical analyses

During the study period, 1,703 patients (73% with A41.5 and 27% with A41.9B) were registered at Aalborg University

Hospital with a code for septicemia/sepsis potentially covering incident Gram-negative bacteremia diagnosis in the NPR. The distribution of the codes was more equal using nationwide data (57% with A41.5, 43% with A41.9B). Using the SAS RANUNI function (SAS Institute, Cary, NC, USA), we randomly sampled 100 patients (range 9–93 years) after weighing the number of patients diagnosed in the different calendar periods and the distribution of the two ICD-10 codes (based on the distribution in the nationwide cohort). As a measure of accuracy, we estimated the PPV as the proportion of patients with blood culture confirmed Gram-negative bacteremia. For each PPV, we estimated the corresponding 95% confidence intervals (CIs) using the method for binominal proportions. The PPV was calculated for patients registered by ICD-10 codes A41.5, A41.9B, and combined. As we hypothesized that the PPV may have improved over the years, given the increasing focus on bacteremia and sepsis through actions like Surviving Sepsis Campaign guidelines, we stratified by calendar period (1994–1998, 1999–2003, 2004–2008, and 2009–2012). We also stratified by type of diagnosis (primary and secondary diagnosis) as we expected the PPV to be higher for bacteremia coded as primary reason for admission.

Results

Descriptive data

We were able to retrieve medical journals for all 100 patients. The sample included 64 men, and median age was 76 years (interquartile range 64–82 years). Among the patients, 56 were registered with "septicemia/sepsis due to other Gram-negative organisms" (ICD-10 code A41.5) and 44 with "urosepsis" (ICD-10 code A41.9B). The diagnosis was registered as the primary reason for admission among 74 patients, and as a secondary diagnosis for the remaining 26 patients.

In total, 72 had a blood culture confirmed Gram-negative bacteremia (overall, 129 blood culture sets including 385 bottles were drawn). Among the remaining patients, four patients had monomicrobial Gram-positive bacteremia (*Staphylococcus aureus, Staphylococcus epidermidis*, *Enterococcus faecalis,* and *Clostridium perfringens*), 21 patients had a negative blood culture, and three had no blood culture taken.

Blood culture confirmed Gram-negative bacteremia

Among the 72 patients with a blood culture confirmed diagnosis, 48 (67%) were recorded with "septicemia/sepsis due to other Gram-negative organisms" and 24 (33%) with "urosepsis."

The most frequent isolated pathogen was *Escherichia coli* (48/72, 67%) followed by *Klebsiella* spp. (16/72, 22%) and *Pseudomonas* spp. (6/72, 8%) (Table 1). A total of 61 patients had monomicrobial Gram-negative bacteremia, eight patients had polymicrobial Gram-negative bacteremia, and three patients had mixed Gram-negative and Gram-positive bacteremia. The source of the bacteremia was urinary tract infection in 45 of the 72 patients (63%). Among 21 patients (44%) with "septicemia/sepsis due to other Gram-negative organisms" and 21 patients (88%) with "urosepsis", the same organism was also detected in a urine sample. Among the remaining patients, the source of the bacteremia was gastrointestinal (N=4), pneumonia (N=2), central venous line (N=1), soft tissue (N=1), and unknown (N=19). In 32 (44%) patients with confirmed Gram-negative bacteremia, the bacteremia was community-acquired, and in 40 (56%) it was health care-associated.

Positive predictive values

The overall PPV of a blood culture confirmed Gram-negative bacteremia diagnosis was 72% (95% CI: 62%–81%).

Table 1 Bacteria specimens in 72 patients with verified Gram-negative bacteremia, diagnosed at Aalborg University Hospital, Denmark, 1994–2012

	International Classification of Diseases codes, 10th revision		
	Septicemia/sepsis due to other Gram-negative organisms (A41.5) N=48	**Urosepsis (A41.9B) N=24**	**Combined (A41.5 and A41.9B) N=72**
Bacteria, N			
Escherichia coli	30	18	48
Klebsiella pneumoniae	7	2	9
Klebsiella oxytoca	5	2	7
Citrobacter koseri[a]	2	0	2
Enterobacter cloacae	2	0	2
Proteus vulgaris	0	1	1
Proteus mirabilis	1	0	1
Morganella morganii	1	0	1
Serratia marcescens	1	0	1
Kingella denitrificans	1	0	1
Leclercia adecarboxylata	1	0	1
Pseudomonas aeruginosa	3	2	5
Pseudomonas species (not *P. aeruginosa*)	1	0	1

Notes: A total of 61 patients had monomicrobial Gram-negative bacteremia (one patient had two episodes of bacteremia with different Gram-negative bacteremia during admission); Eight patients had polymicrobial Gram-negative bacteremia, and three patients had mixed Gram-negative and Gram-positive bacteremia (including *Enterococcus faecalis,* nonhemolytic streptococci, and *Staphylococcus epidermidis)*; [a]Synonymous with *Citrobacter diversus*.

The overall PPV for diagnosis code A41.5 was 86% (95% CI: 74%–94%), but even higher for the period 2009–2012 (100% [95% CI: 74%–100%]) and for diagnoses recorded as secondary diagnoses (95% [95% CI: 76%–100%]). The overall PPV for diagnoses registered by ICD-10 code A41.9B was 55% (95% CI: 39%–70%). For the period 2009–2012 the PPV was 67% (95% CI: 46%–83%), but for other periods the PPVs were both lower and more imprecise (due to low numbers). For ICD-10 code A41.9B, stratification by type of diagnosis (primary versus secondary) gave almost similar results (Table 2).

Discussion

In this study, we document the PPV of two ICD-10 diagnosis codes potentially covering Gram-negative bacteremia. We found that diagnoses of "septicemia/sepsis due to other Gram-negative organisms" (ICD-10 code A41.5) accurately identified patients with Gram-negative bacteremia, whereas "urosepsis" (ICD-10 code A41.9B) did not identify Gram-negative bacteremia with sufficient certainty.

Only a few studies examined the potential of using septicemia or sepsis diagnosis codes to identify patients with documented bacteremia, and no study examined the PPV specifically for Gram-negative bacteremia. A Danish study validated ICD-10 codes of septicemia among 83 patients registered in 1994 against a microbiological registry. This study found a low PPV of septicemia for presence of bacteremia. However, the results were based on registrations made during the first year after introduction of the new coding system in Denmark.[5] A more recent cross-sectional study from the US validated ICD-9-CM discharge diagnoses of septicemia (038.×) and bacteremia (790.7) among 22 patients registered between 2001 and 2004 in the Department of Veterans Affairs administrative database. The diagnoses were validated against blood culture results and resulted in a PPV of 86%,[6] similar to our PPV.

We evaluated diagnoses only at one Danish university hospital, covering medical departments, surgical departments, and intensive care units. The Department of Clinical Microbiology at Aalborg University Hospital provides diagnostic microbiology to all public hospitals in the local region, with a mean annual prevalence of Gram-negative bacteremia of 447 episodes among hospitalized individuals, corresponding to 718 Gram-negative bacteremias per 100,000 hospitalized persons.[7,9] All Danish residents have free access (tax-funded) to medical care, including hospital admission and treatment, which minimizes risk of selection bias. Data in the registry are recorded by the treating physician and collected mainly for administrative use and is therefore unrelated to research purposes. Therefore, the risk of recall and nonresponse bias is reduced, whereas the risk of misclassification still exists. Of note, we did not examine if the patients fulfilled the criteria for sepsis. We found a low PPV of urosepsis for presence of Gram-negative bacteremia, but this does not transfer into serious miscoding of urosepsis. Some of the patients may indeed have had systemic inflammatory response and a urinary tract infection; however, it was not the purpose of our study to examine the validity of urosepsis diagnosis. We believe our PPV of diagnosis code A41.5 for presence of Gram-negative bacteremia may also be applicable in a US setting (using either 038.4 [septicemia due to other Gram-negative organisms] or A41.5 [sepsis due to other Gram-negative organisms]), in addition to other member states of the World Health Organization that use

Table 2 Descriptive and validity of ICD-10 codes for presence of Gram-negative bacteremia among 100 selected patients at Aalborg University Hospital, Denmark, 1994–2012

	International Classification of Diseases codes, 10th revision				
	Septicemia/sepsis due to other Gram-negative organisms (A41.5) N=56		Urosepsis (A41.9B) N=44		Combined (A41.5 and A41.9B) N=100
	Confirmed, N (%)	PPV (95% CI)	Confirmed, N (%)	PPV (95% CI)	PPV (95% CI)
Total	48 (86)	86 (74–94)	24 (55)	55 (39–70)	72 (62–81)
Period					
1994–1998	9 (19)	82 (48–98)	–	–	82 (48–98)
1999–2003	13 (27)	81 (54–96)	1 (4)	33 (8–91)	74 (49–91)
2004–2008	14 (29)	82 (57–96)	5 (21)	36 (13–65)	61 (42–78)
2009–2012	12 (25)	100 (74–100[a])	18 (75)	67 (46–83)	77 (61–89)
Type of diagnosis					
Primary	28 (58)	80 (63–92)	21 (88)	55 (37–70)	67 (54–77)
Secondary	20 (42)	95 (76–100)	3 (12)	60 (15–95)	88 (70–98)

Note: [a]One-sided, 97.5% CI.

Abbreviations: CI, confidence interval; ICD-10, International Classification of Disease, 10th revision; PPV, positive predictive value.

ICD codes. Even though urosepsis is an unspecific term, it has a specific code in the Danish ICD coding system. In contrast, there is no exclusive code for urosepsis in the US coding system, but the condition may be captured by combining codes for urinary tract infection and septicemia or sepsis. However, because of the different coding praxis of urosepsis, our PPV for urosepsis is probably not transferable to other countries.

The results from the blood culture tests were validated against information from the laboratory information system by two persons. However, we did not evaluate the proportion of patients with Gram-negative bacteremia not registered in the NPR (ie, the sensitivity and completeness). Potentially, a low capture rate would make hospital discharge diagnoses covering bacteremia less appropriate for surveillance and incidence studies. Nevertheless, when the prevalence is low the PPV is a good approximation of specificity; and a high specificity leads to unbiased relative measures of risk even if the sensitivity is low.[2]

In conclusion, we found that the diagnosis code "septicemia/sepsis due to other Gram-negative organisms" (ICD-10 code A41.5) may be used to identify patients with Gram-negative bacteremia in the NPR, and may accordingly be useful in epidemiological research. In contrast, the diagnosis code "urosepsis" (ICD-10 code A41.9B) was not well suited for identification of Gram-negative bacteremia.

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Disclosure

The authors report no conflicts of interest in this work.

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