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Increasing Bacteremia Due to Coagulase-Negative Staphylococci: Fiction or Reality?

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ABSTRACT

BACKGROUND: The role of coagulase-negative staphylococci (CNS) in bacteremias continues to be controversial. Until the 1970s, CNS were mostly recognized as contaminants, being part of the cutaneous flora. Since then, several studies have reported increasing incidence and severity of infections due to CNS.

PURPOSE: To review the literature concerning the epidemiology of CNS bacteremia in the United States and Europe with reference to the multiple definitions of infection versus contamination, considering the effect of potential biases influencing the validity of the reported results.

METHODS: Literature search of the MEDLINE database from January 1980 to February 1998. Studies with fewer than 500 episodes of bloodstream infections or fewer than 100 episodes of CNS bacteremia were not included in the pooled analysis.

RESULTS: (1) CNS remain the most frequent contaminants (58%-83% of positive blood cultures); (2) the proportion of all bloodstream infections caused by CNS is increasing (R=.51); (3) the overall incidence of true CNS bacteremia is increasing (R=.54, *P*=.0014); (4) comparing the United States to Europe, there is an increasing trend in the incidence of nosocomial bacteremia due to CNS in the United States (R=.82, *P*=.0006), but no trend is seen in European studies; (5) the mortality associated with true CNS bacteremia varies between 4.9% and 28%.

DISCUSSION: This review confirms the increasing importance of CNS bacteremias, measured both as a proportion and as an incidence of bloodstream infections. The contributions of several possible explanations for the incidence increase and the difference between the United States and Europe need further evaluation: (1) increased recognition and awareness of CNS infections among clinicians; (2) a gradual change in the definition of true bacteremia from an obligatory two positive blood cultures to one positive blood culture associated with a clinical picture compatible with infection; (3) a change in blood culture practices and techniques; (4) an increase in the numbers of blood cultures performed, which is reported both in the United States and in Europe; (5) a shift toward more elderly patients with increasingly severe underlying illnesses; and (6) increasing use of intravascular devices.

CONCLUSIONS: The apparent trend of increasing CNS bacteremia seems to be valid. Whether there is a real difference between the United States and Europe concerning the increase of CNS bacteremia is difficult to establish due to the large number of confounding factors. Few studies take into account the number of blood cultures performed or the use of intravascular devices to adjust for the observed trends. Further on-site surveillance studies are needed to investigate the phenomenon more extensively (*Infect Control Hosp Epidemiol* 1998;19:581-589).

The role and importance of coagulase-negative staphylococci (CNS) in bloodstream infections (BSIs) continues to be controversial. They were first described as pathogens in the 1950s, in the context of cardiovascular surgery, as techniques for implantation of prosthetic devices were developed.[1] The reporting of CNS was very low until the 1970s, as they were almost exclusively regarded as contaminants arising from the cutaneous flora.[2] Since then, several studies have reported trends of increasing incidence and severity of CNS bacteremia both in the United States [3-6] and in Europe.[7-11]

It is a well-established observation that CNS bacteremias are associated with the use of indwelling devices such as central venous, peripheral venous, or hemodialysis catheters and prosthetic material.[12,13] Two properties of CNS may explain this: the ability to adhere to foreign bodies and artificial surfaces due to adhesins, and the production of extracellular glycocalyx (slime).[12,13]

The purpose of this article is to review the literature concerning the epidemiology of CNS bacteremia in the United States and in Europe with reference to the multiple definitions of infection versus contamination and the effect of potential biases on the validity of the reported results.

METHODS

Data Sources

From the Infection Control Program, the University of Geneva Hospitals, Geneva, Switzerland.

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TABLE 1
STUDIES RETAINED FOR ANALYSIS OF TRENDED ESTIMATES, MEDLINE SEARCH 1980 TO 1998

Author	Reference	Setting	Study Period	Definitions	No. in Study
United States					
Weinstein	14	Duke UMC, Robert Wood Johnson UH, Salt Lake City VAMC	Feb 1992-Jan 1993	All positive blood cultures assessed. Only patients >18 y included. Classified as HA according to CDC guidelines.[73]	1,585 episodes
Jarvis	15	NNIS hospitals	Oct 1986-Dec 1990	CDC definitions.[73]	138,925 pathogens
Banerjee	4	124 NNIS hospitals	Only 1989 data used	CDC definitions.[73]	25,269 BSI (1980-1989)
Cockerill	16	Mayo Clinic Rochester, microbiology laboratory	Nov 1984-Nov 1992	Two positive blood cultures required.	20,456 pathogens
Pittet	6	University of Iowa	Jul 1980-Jun 1992	All positive blood cultures assessed through prospective surveillance. HA 72 h after admission.	3,461 HA BSIs
Roberts	17	Vancouver General Hospital, Vancouver Clinic of the British Columbia Cancer Agency	1984-1987	One positive culture and clinical signs of infection.	1,244 episodes
Morrison	3	State of Virginia	1978-1984	All positive blood cultures assessed through prospective surveillance. HA 48 h after admission.	4,617 HA BSIs
Martin	18	University of Iowa	Only 1980 included	All positive blood cultures assessed through prospective surveillance.	NA
Stillman	19	University of Virginia	1975-1982	Clinical signs of infection + treatment for CNS. HA 48 h after admission.	1,843 HA BSIs
Kirchhoff	20	University of Michigan Medical Center	Jan 1978-Feb 1980	Two positive blood cultures required.	4,733 isolates
Scheckler	5	Community hospital, St Mary's Hospital Medical Center	1970-1973, 1982, 1987	Two positive blood cultures required.	585 episodes
Weinstein	21	University of Colorado, Denver, VAH	Jul 1975-Mar 1977	All positive blood cultures assessed. HA 48 h after admission.	500 episodes
Europe					
Jensen	22	Copenhagen county	Oct 1992-Apr 1993	Each positive blood culture evaluated. HA 48 h after admission.	590 episodes
Rubio	23	The Hospital University, San Carlos, Spain	1990-1992	Two positive blood cultures required.	2,166 BSIs
Elhanan	25	University Hospital, Tel-Aviv, Israel	Jan 1990-Jun 1991	Two positive blood cultures required.	1,048 cases

(continued on page 585)

Abbreviations: BSI, bloodstream infection; CDC, Centers for Disease Control and Prevention; CNS, coagulase-negative staphylococci; HA, hospital-acquired infection; NA, not available; NNIS, National Nosocomial Infection Surveillance System; UH, university hospital; UMC, university medical center; VA, Veteran's Affairs; VAH, Veterans' Affairs Hospital; VAMC, Veterans' Affairs Medical Center.

We searched the MEDLINE database from January 1980 to February 1998 using Knowledge finder (Aries System Corp, North Andover, MA). The following key words were used: *coagulase-negative staphylococci,* Staphylococcus epidermidis, *staphylococci, epidemiology, bloodstream infection, bacteremia, sepsis,* and *septicemia*. Frequently cited articles also were identified.

Study Selection

This literature review generally concentrates on large tertiary-care centers, but studies from community hospitals, intensive-care units (ICUs), high-risk nurseries, and wards with immunosuppressed patients also were considered to allow for a cross-sectional analysis. We excluded studies with fewer than 500 episodes of BSI or fewer than 100 episodes of CNS bacteremia. Articles written in English, French, or German were retained for analysis.

Data Extraction

We abstracted data from the studies concerning the description of the population, definitions of bacteremia and nosocomial infection, and the incidence of community- and hospital-acquired CNS bacteremia per 1,000 admissions. We also calculated the percentage of all BSI episodes due to CNS. Contamination was calculated both as a proportion of all CNS-positive blood cultures and as a proportion of all positive

TABLE 1 *(continued)*
STUDIES RETAINED FOR ANALYSIS OF TRENDED ESTIMATES, MEDLINE SEARCH 1980 TO 1998

Author	Reference	Setting	Study Period	Definitions	No. in Study
Geerdes	7	University Hospital Klinikum, Steglitz in Berlinfour	1979, 1982, 1986, 1992	One positive blood culture for CNS and criteria for septicemia. HA 48 h after admission.	980 episodes
Arpi	10	Fredriksberg Hospital, UH, Copenhagen	1968-1992	Each positive blood culture evaluated. HA 72 h after admission. No pediatric service.	3,491 episodes
Leibovici	26	Beilinson Medical Centre, Israel and St Thomas's Hospital, London, UK	Mar 1988-Sep 1990 and 1987-1990	Two positive blood cultures required or 1 positive blood culture and 1 positive blood culture from another source. HA 48 h after admission.	1,410 and 1,040 episodes
Maniatis	27	Dept. of Infectious Diseases, Hellenic Air Force and VA General Hospital	1986-1994	Two positive blood cultures required.	993 isolates
Rosenthal	28	13 microbiology institutes in Germany and Austria	1983-1985, Aug 1991-Jul 1992	Two positive blood cultures required.	12,880 episodes
Haug	9	Bergen University Hospital, Norway	1974-1979, 1988-1989	For CNS, at least two biochemically identical isolates. HA 24 h after admission.	648+799 episodes
Dornbusch	29	37 laboratories in Europe	1987-1988	Isolates considered to be contaminants were excluded.	3,440 isolates
French	30	Prince of Wales Hospital, Hong Kong	May 1984-Jun 1989	Definitions of Weinstein et al.[21]	2,211 episodes
Gatell	24	University of Barcelona, Spain	Mar 1983-Feb 1986	All positive blood cultures evaluated. HA 48 h after admission.	1,366 episodes
Vazquez	31	Hospital Covadonga of Oviedo, Spain	1981-1984	Two positive blood cultures required.	43,63 episodes
Müller	32	University of Berlin, Germany	1979-1986	All positive blood cultures evaluated.	691 patients
Ispahani	33	University Hospital of Nottingham and three local hospitals	Jan 1980-Dec 1983	Number of positive cultures and clinical findings, but CNS regarded as highly improbable cause of infection.	933 episodes
Bruun	34	Statens seruminstitut, Denmark	1977-1978	Two positive blood cultures required.	3,170 isolates
Michel	35	University Hospital Rotterdam, The Netherlands	1972-1977	Two positive blood cultures required.	1,289 BSIs

Abbreviations: BSI, bloodstream infection; CDC, Centers for Disease Control and Prevention; CNS, coagulase-negative staphylococci; HA, hospital-acquired infection; NA, not available; NNIS, National Nosocomial Infection Surveillance System; UH, university hospital; UMC, university medical center; VA, Veterans' Affairs; VAH, Veterans' Affairs Hospital; VAMC, Veterans' Affairs Medical Center.

blood cultures. CNS bacteremia was defined as either one positive blood culture plus a clinical picture compatible with infection or as two positive blood cultures (Table 1).[3-7,9,10,14-35]

Statistical Analysis

The sum of all BSIs (episodes), or of all bloodstream isolates documented in each study period, was considered for statistical analysis.[6] Incidence rates per 1,000 discharges or admissions were calculated. Linear trends were analyzed using linear regression, with study years or the median year of the study period considered as an independent variable and numbers of BSI episodes or isolates, respectively, as dependent variables. Statistical analysis was performed using SPSS software (SPSS Inc, Chicago, IL).

RESULTS

Coagulase-negative staphylococci remain the most important contaminants of blood cultures, accounting for an average of 75% (range, 58%-85%) of all contaminated blood cultures.[9,10,14,17,22,24,36] The percentage of blood cultures positive for CNS and representing true bacteremia was very constant and similar both in time and numbers between the United States and Europe (mean, 18%; range, 6%-31%).[7,9,14,17,22,36,37]

Global Trends

A global trend of increasing CNS bacteremia as a proportion of all BSIs can be observed when combining all hospitalwide studies retained for analysis (R=.51, Figure 1). There is however a large spread, reflecting the heteroge-

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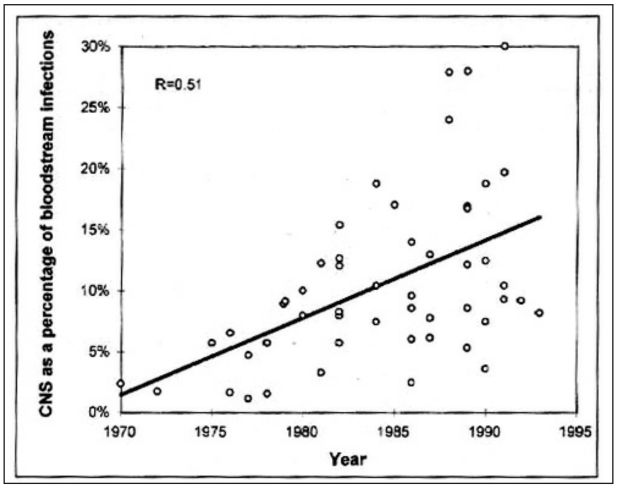

FIGURE 1. Proportion of all bloodstream infections caused by coagulase-negative staphylococci, secular trend, 1970 to 1993. Hospitalwide studies, university and community hospitals.[3-7,9,10,14,16-19,21-31,33-35,74] Abbreviation: CNS, coagulase-negative staphylococci.

neous hospital mix. Table 1 summarizes all the studies kept for analysis.

Not only is the proportion of CNS increasing but also the incidence of CNS bacteremia (Figure 2a; R=.54, *P*=.0014). The analysis of incidence data was possible only for teaching hospitals, this group being the most readily compared.

Comparison of the United States Versus Europe

The incidence of nosocomial CNS BSIs increased significantly in the United States over the study period (R=.82, *P*=.0006; Figure 2b). In Europe, no significant trend could be observed for nosocomial CNS bacteremias (R=.36, *P*=.38) nor for the combined hospital- and community-acquired CNS bacteremias (R=.44, *P*=.075).[9,22,24,25,33,35,36]

The largest increase was reported from the University of Iowa Hospitals, with 0.97 episodes per 1,000 admissions from 1981 to 1983, compared to 7.04 per 1,000 admissions from 1990 to 1992.[6] In the 1980s, the incidence of nosocomial CNS bacteremia was reported to be higher in the United States than in Europe, ranging from 0.26 to 7.04 episodes per 1,000 admissions in the United States[3,6] and from 0.15 to 1.16 in Europe.[9,33] Between 1990 and 1992, Rubio et al [23] reported an incidence of 4.23 episodes of CNS bacteremia per 1,000 admissions in a Spanish university hospital.

Community Hospitals

In the setting of community hospitals, only a few studies were conducted, obviating any pooled trend analysis. In the United States, Scheckler et al[5] reported an increase of CNS nosocomial bacteremia from 0.02 episodes per 1,000 admissions from 1970 to 1973 to 0.47 in 1987 (1.2% and 16% of all BSI, respectively). In a community hospital in Toronto,[38] the proportion of BSIs due to CNS was found to be 6.7% from 1980 to 1984.

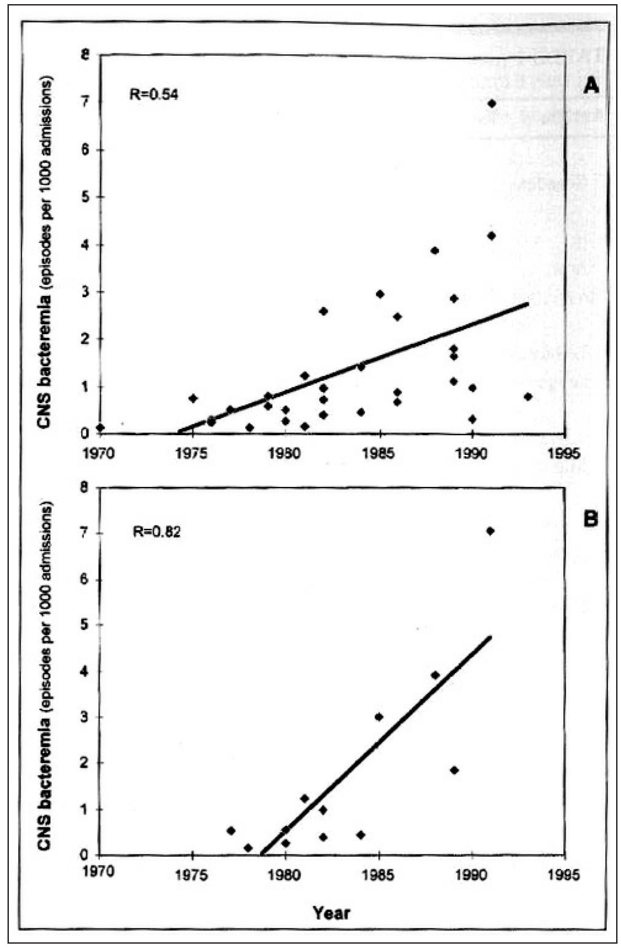

FIGURE 2. Trends in the overall incidence of coagulase-negative staphylococci (CNS) bacteremia.
FIGURE 2a. Hospitalwide studies from university hospitals.[3,4,6,7,9,10,17-25,31,33,35] Overall incidence of CNS bacteremia per 1,000 admissions (If data only for nosocomial CNS bacteremia were available, this was used).
FIGURE 2b. CNS nosocomial bacteremia per 1,000 admissions in university hospitals in the United States.[3,4,6,18,19,51]

In Europe, Iversen et al [8] reported the hospital-acquired incidence in three local hospitals in northern Norway to be 0.12 episodes per 1,000 admissions in 1985 and 1.05 in 1989 (4% and 28% of all BSIs, respectively). Similar numbers were reported from a community hospital in Israel in an 18-month prospective study from 1990 to 1991.[25] The authors found an incidence of 1.13 nosocomial episodes of CNS bacteremia per 1,000 admissions, representing 27% of all BSIs.

Intensive-Care Units

Generally, high incidence rates of CNS nosocomial bacteremia are reported from ICUs worldwide,[39,40] with a mean of 8.76 episodes per 1,000 admissions in the studies reviewed (range, 4.7-12.7; Table 2). In a National Nosocomial Infection Surveillance (NNIS) System report from 1986 to 1997,[41] CNS represented 33% of all primary BSIs in ICUs. In a multicenter study from Spain, Valles et al[42] reported CNS to represent 24% of BSIs in 1993. In another study from Spain, 19% of BSIs were caused by CNS from 1988 to 1990.[43]

TABLE 2
COAGULASE-NEGATIVE STAPHYLOCOCCAL BACTEREMIA: COMPARISON BETWEEN RATES IN HOSPITALWIDE SURVEYS AND SPECIAL-CARE UNITS

	Hospitalwide Surveys				Specific-Care Units			
	University Hospitals		Community Hospitals		Intensive-Care Units		High-Risk Nurseries	
	Proportion*	Incidence	Proportion	Incidence	Proportion	Incidence	Proportion	Incidence
Mean	11%	1.38	9%	0.74	26%	8.76	33%	2.18
Range	1.6%-30%	0.13-7.04	1 .7%-21%	0.09-1.46	19%-34%	4.7-12.7	3%-78%	0.34-6.90
Median	9%	0.80	6%	0.63	24%	8.88	24%	0.74
No. of studies	25		3		4		7	
References	4, 6, 7, 9, 10, 14, 16-27, 29-31, 33, 35, 74, 75		5, 8, 25		41-43, 64		37, 44-48, 66	

*Proportion refers to the percentage of all episodes of bloodstream infections due to coagulase-negative staphylococci. Incidence refers to episodes or isolates per 1,000 admissions.

Neonates

A high proportion of BSIs among neonates has been attributed to CNS in recent years (mean, 33%; range, 3%-78%; Table 2). They primarily are associated with late-onset bacteremia and seen among neonates with very low birth weight.[1] Beck-Sague et al,[44] from 1989 to 1991, and Gaynes et al[45] from 1989 to 1994, reported that 43% and 51%, respectively, of BSIs in high-risk nurseries are due to CNS. In a study of very-low-birth-weight infants by Gray et al,[46] conducted from 1989 to 1990, 78% of all BSIs were attributed to CNS.

In Europe, CNS bacteremia also has emerged in recent years in neonatal ICUs. A striking increase was described at St Thomas Hospital in London,[47] where, in the 1970s, only 3% of isolates were CNS; in the 1980s, 20%; and in the 1990s, 44%. Källman et al[37] in Örebro, Sweden, found an increase from 15% from 1981 to 1987 to 24% from 1988 to 1994. Finally, at the Karolinska Hospital in Sweden,[48] 22% of all neonatal septicemia was attributed to CNS in a prospective study from 1981 to 1985.

Number of Blood Cultures

In several longitudinal studies,[5,8-10] a strong increase over time has been noted in the number of blood cultures performed per 1,000 admissions. The most striking increase was reported by Scheckler et al,[5] from the University of Wisconsin, where the number of blood cultures increased sixfold from 1973 to 1987. In the few studies reporting the number of blood cultures, we could not find a significant correlation between total CNS bacteremia incidence and the number of blood cultures drawn (R=.30, *P*=.28); however, a trend can be noted between incidence of nosocomial CNS bacteremia and number of blood cultures drawn (R=.59, *P*=.092; Figure 3). These numbers should be interpreted with caution, as they are based on few studies,[5,8-10,17,21,22,31,33,35,36,49] and complete data are not given in all studies.

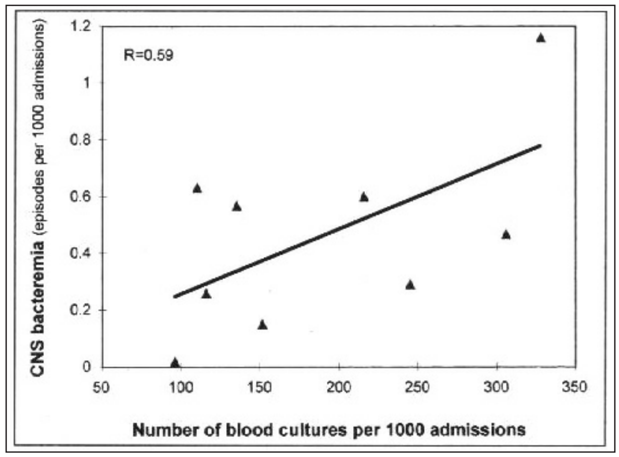

FIGURE 3. Relation between obtaining blood cultures and incidence of coagulase-negative staphylococci (CNS) bacteremia. Incidence of CNS nosocomial bacteremia per 1,000 admissions versus number of blood cultures performed per 1,000 admissions.[5,9,22,33,35,36]

Mortality

The attributable mortality of CNS bacteremia is difficult to compare, as different methods were used to estimate it. Most studies attribute death within 7 days of bacteremia to the infection if no other cause can be found; this will be referred to as associated mortality.

Martin et al[18] conducted a matched cohort study to assess the attributable mortality of CNS bacteremia. In this study, the mortality among the case-patients was 31%, compared with 17% among matched controls; thus, the attributable mortality was 14%. Apart from this study, all other studies report associated mortalities. In the United States, Weinstein et al[14] reported an associated mortality of 5.5%, and Roberts et al,[17] using cumulative mortality, reported 5.3% mortality after 5 days, 16% after 30 days, and 25% at discharge. Pittet et al[50] reported 17% mortality after 28 days and 29% at discharge. Importantly, nosocomial bacteremia due to CNS was associated with a significantly lower risk of death than other nosocomial bloodstream pathogens after adjusting for other confounders.

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In Germany, Geerdes et al,[7] using the definition of all deaths within 30 days after the onset of septicemia, found an associated mortality rate of 28% in 1979, which decreased to 22% in 1989. In Spain, Fidalgo et al[36] reported an associated mortality of 19%, and Gatell et al[24] found an associated mortality of 11% (not specifying any time limits). In Norway, the associated mortality was reported to be 4.9% from 1974 to 1979 and 5.9% from 1988 to 1989.[9] Finally, in the United Kingdom, the associated mortality was reported to be 10% from 1980 to 1983.[33]

DISCUSSION

In this review, we confirm the increasing proportion of BSIs due to CNS, compared to other pathogens, and the overall increasing incidence of CNS bacteremias over the past 2 decades. In addition, we observed increasing nosocomial CNS bacteremias in the United States, whereas, in Europe, no such trend could be found. An explanation of this is the lack of data on incidence of nosocomial CNS bacteremia in Europe, with only six large studies from teaching hospitals available, impeding meaningful comparisons. It is also important to make a distinction concerning the validity of studies between prospective hospital surveillance data and laboratory data having little or no clinical feedback. Most of the large studies in the United States were based on prospective surveillance, whereas, in Europe, the data often are based on laboratory reviews. Therefore, an increasing trend of CNS bacteremia in Europe cannot be ruled out on the basis of this review.

The greater heterogeneity in defining CNS bacteremia in Europe compared to the United States probably explains in part the wide variation of results in Europe. In the studies analyzed for an increase in incidence, 4 of 11 studies in Europe required at least two positive blood cultures, whereas, in the United States, all investigators evaluated each blood culture with reference to the clinical picture of the patient (Table 1). The differences in CNS distribution between the different regions in Europe was described by Dornbusch et al[29] in the European Study Group on Antibiotic Resistance. For unknown reasons, the proportion of staphylococci other than *Staphylococcus aureus* isolated from consecutively collected blood samples ranged from 2% in Portugal to 28% in Switzerland.

For the observed increase of CNS bacteremia to be validated,[40] several hypotheses need to be investigated to define potential biases or confounding factors. First, there has been increased recognition and awareness of CNS infections among clinicians due to the increased reporting in recent years. CNS, has, in a relatively short period of time, gone from being regarded as a harmless cutaneous microorganism to being, in many studies, the most common cause of bacteremia with a substantial related mortality.

Second, there has been a gradual change in the definition of bacteremia, from an obligatory two positive blood cultures to one positive blood culture and a clinical picture compatible with infection, as a result of several studies demonstrating no difference in the positive predictive value of one or two positive blood cultures.[18,51-53] Although Kirchhoff et al[20] described in a retrospective study (1978-1980), that the proportion of cultures positive for CNS is much larger among true bacteremic patients (71%) than among patients with contamination (34%), this may have been influenced by their definition of true bacteremia, which required at least two positive blood cultures. An increased caution when judging one positive blood culture allows for a more active approach to diagnosing CNS bacteremia; this possibly leads to increased reporting.

Third, there has been a change of blood culture practices and techniques. Sterilization of the venipuncture site, the choice of venipuncture or drawing blood from an existing intravenous (IV) line, the inoculum volume, and the medium used for culture all affect the sensitivity and specificity of blood cultures.[40,54] It is not within the scope of this review to compare each study's techniques and practices, but it should be remembered as an important potential confounder. Pittet et al[6] estimated that changing from the BACTEC 460 (Johnston Laboratories, Towson, MD) to the BACTEC 660 nonradiometric system and increasing the inoculum from 5 mL to 10 mL enhanced the recovery by 33%. That the inoculum volume is the most important factor determining the sensitivity of blood cultures has been shown by several studies, including that performed by Mermel and Maki.[55] In their study comparing normal-volume to low-volume inoculum, the difference in yield was 23%. Furthermore, they reported that 88% of 158 US clinical laboratories accepted blood cultures from adults containing less than 5 mL. The conclusion is that a substantial number of BSIs have gone undiagnosed. In the study by Weinstein et al[56] comparing 5-mL to 10-mL inoculum in the BacT/Alert (Johnston Laboratories, Towson, MD) system in 13,128 pairs of blood cultures, an overall increased yield was found, but not a significantly larger yield for gram-positive bacteria specifically.

Fourth, the importance of adjusting the incidence of infection to the number of blood cultures performed was shown by Haley et al in 1985.[57] As mentioned before, several longitudinal studies reported important increases in the number of blood cultures performed. Although we did not find a significant correlation between the incidence of CNS bacteremia and the number of blood cultures performed, there was a possible correlation between the incidence of CNS nosocomial bacteremia and the number of blood cultures. This finding suggests that both the number of blood cultures performed and the technique used should be taken into account when studying trends in BSIs. Importantly, this is advisable even for gram-negative bacteremia. In our institution, the incidence of gram-negative bacteremia increased linearly ($R=.90$, $P=.014$), from 7.07 to 8.32 episodes per 1,000 admissions between 1989 and 1994,[58] but this trend was no longer significant after adjustment for the number of blood cultures drawn per year ($R=.22$, $P=.68$).

Fifth, more severe underlying illnesses and an aging population affect the incidence.[5,40,59-62] The proportion of patients with ultimately or rapidly fatal underlying disease increased from 9% from 1974 to 1979 to 17% from 1988 to 1989 at Bergen University Hospital,[9] affecting the rates of BSI. In an NNIS System report from 1986 to 1990,[63] 54% of nosocomial infections occurred in elderly patients (65 years and older).

Finally, CNS bacteremias are highly associated with intravascular device use.[7,14,18,22,24,26,36,42,43,45,51,64-67] In a comparison between the former East and West Germany, Rüden et al[68] found a lower prevalence of nosocomial infections in the former East German states, mainly due to a lower use of devices. An estimated 5 million central venous catheters are inserted into patients in the United States each year,[69] but it is difficult to measure how much the utilization of infusion IV devices has increased in recent years. However, the increased use of intravascular devices has been implicated in the increased rates of BSI from 1979 to 1987 that were recorded by the National Hospital Discharge Survey.[70] Maki and Mermel [71] estimated that more than 50% of all BSI episodes are associated with intravascular devices. Of all catheter-associated infections, CNS represent between 30% to 60%.[72]

There are several difficulties in making comparisons between studies regarding CNS bacteremia. The first major limitation is that the different authors present their data in various ways and choose to focus on different rates (prevalence, incidence, or incidence densities), risk factors, and outcomes. Overall, this makes it difficult in many instances to make appropriate comparisons. This is underscored by an NNIS System report by Jarvis et al in 1991,[15] where the importance of the denominator is acknowledged. This study demonstrates the need not only for patient-related data but also for data related to device use and length of hospitalization when making comparisons between different units or hospitals. It has not been possible to compare these variables, as very few authors present their data in this way. Only a few studies[5,6,9,20,25]report incidence densities of BSI, which constitutes the most appropriate way to study secular trends and adjust for confounders.

Second, different definitions are used to distinguish between true BSI and the large number of contaminated blood cultures. Obviously, the stringency in the judging of positive blood cultures and the clinical state of the patient affect the observed incidence. The main differences in defining a true bacteremia stem from whether or not one positive blood culture of two prompts evaluation of the significance of this finding (Table 1). In many studies, these episodes are excluded as contaminants per se. The justification of the latter viewpoint is questionable, considering that several studies have shown little difference in the positive predictive value of one-of-two or two-of-two positive blood cultures.[18,51-53]

Finally, the heterogeneity of the patient populations and their varying susceptibility to infection influences the rates and outcomes reported. For the purpose of this review, the studies were stratified into four categories, with a focus on large tertiary-care centers. For community hospitals, ICUs, and high-risk nurseries, only a brief review was done to show the differences between different hospitals and wards (Table 2). However, it should be noted that most studies from teaching hospitals include several ICUs, high-risk nurseries, and oncology clinics. As these units have the highest incidences reported, it is clear that the hospitalwide incidence depends largely on their profile. For example, some studies report data based only on adults, hence removing the effect of neonates on the reported rates. Thus, to make a comparison and an overview of trends possible, the assumption was made that tertiary-care referral centers have an approximately similar case mix and severity of illness in their patient populations.

CONCLUSIONS

In summary, there is an overall increasing trend of true CNS bacteremia, both measured as a proportion of BSI and as an incidence. Furthermore, there is a trend of increasing nosocomial CNS bacteremias in the United States, whereas no trend could be found in Europe. Possible explanations for this are a lack of studies reporting data on CNS nosocomial bacteremia in Europe, regional differences in Europe regarding rates, and a less uniform definition of CNS bacteremia in Europe. The reasons for the regional differences in Europe could be several; speculative explanations include IV-device use, blood culture practices, and heterogeneous methods for surveillance and definitions of infections.

The influence of the number of blood cultures performed is difficult to determine, as we found partly contradicting results. It can only be recommended that, in future epidemiological studies, rates be reported as incidence densities, number of blood cultures be assessed, and rates be adjusted for this variable to exclude a potential bias. Finally, it can be concluded that CNS bacteremia is a reality and an important cause of bacteremia, with a morbidity and a mortality that cannot be ignored. A significant proportion of CNS bacteremia should be avoided by prevention of device-associated nosocomial infections, making explanatory epidemiology of the disease useful to the patient.

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Fluoroquinolone-Resistant *Neisseria gonorrhoeae*

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The fluoroquinolones ciprofloxacin and ofloxacin are among the antimicrobials recommended for treating uncomplicated gonorrhea. Fluoroquinolone-resistant strains of *Neisseria gonorrhoeae* have been identified frequently in the 1990s in the Far East. In the United States, fluoroquinolone-resistant *N gonorrhoeae* has been reported previously in only one person, who probably acquired the infection in the Philippines.

The CDC recently reported two cases of gonococcal infection in San Diego involving strains with a higher level of fluoroquinolone resistance than reported previously; there was clinical treatment failure in one case.

Because fluoroquinolone-resistant *N gonorrhoeae* is rare in the United States, the CDC recommends fluoroquinolones to treat gonococcal infections. However, ceftriaxone, cefixime, or spectinomycin should be used if the infection was acquired in Asia. In some areas of the United States, (eg, Cleveland, Ohio) where strains with decreased susceptibility to fluoroquinolones are endemic, fluoroquinolones should not be used to treat gonococcal infections, because these strains may represent a pool from which fluoroquinolone-resistant strains may emerge. Laboratories serving patients with gonococcal infections should maintain culture capabilities to evaluate patients with apparent treatment failures. Laboratories should report any isolate meeting proposed National Committee for Clinical Laboratory Standards criteria for resistance to ciprofloxacin (minimum inhibitory concentration [MIC] >1.0 μg/mL; zone inhibition diameter [5 μg disk] <27 mm) or ofloxacin (MIC >2.0 μg/mL; zone inhibition diameter [5 μg disk] <24 mm) to their state public health laboratory; CDC laboratories will confirm resistant isolates.

FROM: Fluoroquinolone-resistant *Neisseria gonorrhoeae*—San Diego, California, 1997. *MMWR* 1998;47:405-408.

Anesthetist Transmits Hepatitis C to 217 Patients

On April 28, 1997, the Valencia Health Department in Spain announced that 217 people who had surgery within the past year in two Valencian hospitals have been infected with hepatitis C virus (HCV). The source of the HCV infection was an anesthetist who had been working at the hospitals for the past 5 years.

The anesthetist, a morphine addict for many years, has the same HCV genome as the infected patients. It was reported that, in the immediate postoperative period, just before he gave intravenous opioid analgesia to patients, he gave himself part of the syringe contents and then gave the remainder to the patient via the same syringe. He had been obliged to retire from a post at another Valencian hospital when it became known that he had falsified signatures to obtain opioids from the pharmacy.

Health Department chief Joaquín Farnós said that more than 2,000 patients will be screened for HCV in the next few weeks. The results of the outbreak investigation, which may take approximately 3 months to complete, then will be sent to the appropriate court to decide legal action. The Health Department already has started disciplinary proceedings against seven of the anesthetist's colleagues for an apparent "silence pact," because none raised the alarm despite knowledge of these activities.

FROM: Bosch X. Hepatitis C outbreak astounds Spain. *Lancet* 1998; 351:1415.

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