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## SESSION I

### Changing Etiology of Nosocomial Bacteremia and Fungemia and Other Hospital-Acquired Infections

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Serial surveys on the etiology of nosocomial bacteremia have been conducted over a period of years at Boston City Hospital (Boston) and Grady Memorial Hospital (Atlanta). A comparison of the information from these surveys with that from single-period surveys at 10 other hospitals in the United States illustrates changes in the etiology of nosocomial bloodstream infection over the past five decades. Prominent trends include an increased frequency of episodes of polymicrobial bacteremia, an increased frequency of sequential episodes of bacteremia in the same patient, a resurgence of infection due to *Staphylococcus aureus*, the recognition of *Staphylococcus epidermidis* and other components of the endogenous flora as pathogens, and an increased prominence of enterococci, gram-negative aerobic bacilli, anaerobes, and fungi as agents of nosocomial bloodstream infection. Changes in the etiology of nosocomial infection that are not illustrated by the data on bacteremia include an increased appreciation of the importance of viruses, a diminished role for *Mycobacterium tuberculosis*, and the description of new and unusual pathogens, usually in patients with compromised host defenses. This last trend can be expected to continue.

Infection acquired in the hospital remains a major problem for patient and physician alike [1]. Nosocomial infection continues to be a significant cause of death among hospitalized patients [2]. The consequences of nosocomial cross-infection for the community were recently emphasized again by the community spread of strains of *Staphylococcus aureus* resistant to methicillin [3]; only a few years ago in the United States, these strains were predominantly restricted to hospitals [4]. New schemes for hospital reimbursement further emphasize the costs associated with nosocomial infection [5, 6].

For all of these reasons, hospitals have taken renewed interest in the problem of nosocomial cross-infection and what can be done to control it. However, control schemes are made more difficult by changes in the etiology of nosocomial infection

during recent years. In this review I examine selected aspects of these changes over the past five decades, using data on nosocomial bacteremia and fungemia to illustrate a number of trends. I then consider other changes in etiology that are not reflected by the data on bacteremic infection.

#### **Nosocomial Bacteremia and Fungemia: Observations over Five Decades**

Nosocomial bacteremia and fungemia are useful indicators of overall changes in nosocomial infection. The study of bloodstream infections is not subject to some of the difficulties involved in defining infection at other sites [6, 7]. Changes over a period of years in the organisms recovered from blood have been studied at a number of hospitals in the United States [8-16]. Studies on the incidence and etiology of nosocomial bacteremia and fungemia in total hospital populations over periods of three months or more are included in the present analysis. Surveys involving the prevalence of bacteremia and fungemia are not addressed, as prevalence information must be adjusted if it is to be comparable to inci-

I am indebted to Carl A. Perlino, Patricia L. Parrott, Elizabeth N. Whitworth, and Loretta W. Frawley of the Epidemiology Department, Grady Memorial Hospital, who kindly identified the cases in table 2 as nosocomial.

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**Table 1.** Occurrence of and deaths associated with nosocomial bacteremia and fungemia due to selected organisms, by group, at Boston City Hospital during seven selected years, 1935–1972.

Group, organism*	No. of cases (no. of deaths) in survey year†						
	1935	1941	1947	1953	1961	1969	1972
<b>Gram-positive aerobic cocci</b>							
<i>Streptococcus pneumoniae</i>	34 (28)	11 (5)	3 (1)	3 (0)	10 (2)	8 (3)	9 (1)
$\beta$ -hemolytic, non-group D <i>Streptococcus</i>	38 (27)	8 (2)	1 (0)	2 (2)	8 (3)	14 (5)	20 (5)
Viridans <i>Streptococcus</i>	20 (8)	14 (4)	9 (4)	5 (0)	10 (2)	14 (3)	29 (9)
Enterococci	0	2 (1)	13 (4)	10 (3)	16 (6)	22 (13)	27 (12)
<i>Staphylococcus aureus</i>	29 (11)	39 (15)	32 (7)	61 (20)	102 (55)	60 (32)	56 (21)
Total	121 (74)	74 (27)	58 (16)	81 (25)	146 (68)	118 (56)	141 (48)
<b>Gram-negative aerobic bacilli</b>							
<i>Escherichia coli</i>	17 (7)	23 (6)	24 (10)	25 (15)	25 (11)	33 (12)	49 (26)
<i>Klebsiella-Enterobacter</i>	0	0	24 (15)	23 (12)	36 (16)	65 (35)	69 (31)
<i>Proteus</i> species	6 (5)	1 (1)	16 (7)	23 (15)	18 (9)	30 (21)	19 (12)
<i>Providencia, Citrobacter, "Paracolon"</i>	0	0	0	0	4 (2)	1 (0)	1 (1)
<i>Serratia</i> species	0	0	0	0	0	2 (1)	16 (4)
<i>Pseudomonas aeruginosa</i>	1 (0)	5 (3)	4 (3)	9 (6)	16 (6)	26 (21)	15 (11)
<i>Herellea</i> species	0	0	0	0	13 (6)	5 (1)	8 (3)
<i>Flavobacterium, Alcaligenes</i>	2 (2)	1 (0)	2 (0)	4 (2)	1 (0)	1 (0)	2 (1)
<i>Salmonella</i> species	2 (1)	5 (1)	2 (2)	0	0	4 (0)	0
Total	28 (15)	35 (11)	72 (37)	84 (50)	113 (50)	167 (91)	179 (89)
<b>Anaerobes</b>							
<i>Bacteroides</i> species	0	0	0	0	0	1 (0)	2 (2)
<b>Fungi</b>							
<i>Candida</i> species	0	0	0	6 (3)	9 (4)	23 (12)	28 (17)
<i>Torulopsis</i> species	0	0	0	0	1 (1)	1 (0)	4 (2)
Total	0	0	0	6 (3)	10 (5)	24 (12)	32 (19)
All organisms‡	149 (89)	109 (38)	130 (53)	171 (78)	269 (123)	310 (159)	354 (158)
All patients	147 (86)	107 (38)	120 (48)	167 (75)	258 (116)	271 (130)	280 (110)

NOTE. Data are adapted from [8], with additional details supplied by the author. See original paper for description of methods and the selection procedure.

\* *Staphylococcus epidermidis*, *Bacillus* species, diphtheroids, and anaerobes other than *Bacteroides* species were arbitrarily excluded from the study.

† Figures in parentheses indicate numbers of bacteremic/fungemic patients who died during the relevant period of hospitalization.

‡ Multiple organisms from one patient were counted separately. Thus, more cases than patients are shown. (The data for patients agree with table 4 of [8], and the number of organisms agrees with tables 9 and 10 of [8]).

dence data [17]. Also excluded are reports of bloodstream invasion in specialized centers, such as pediatric [18] or army [19] hospitals; surveys of subsets of patients, such as those on oncology wards [20]; and studies of selected organisms, such as *Pseudomonas aeruginosa* [21].

Comparison of data from one hospital to another or from one period to the next in the same hospital inevitably is confounded by differences in the manner in which data are collected, in the laboratory facilities available, in the populations of patients being served, and in the procedures and techniques available for patient care [17]. Thus, the comparisons made here are intended only to provide a broad overview of general trends and changes.

#### Boston City Hospital: 1935–1972

The longest study of bacteremic infection was done at Boston City Hospital during 12 selected years in the period 1935–1972 [8]. This study had the singular advantage of the guidance provided by Maxwell Finland and Mildred Barnes as principal investigator and data collector, respectively, throughout the entire period. As a result, there was excellent continuity in methods of data collection, recording of data, and definitions used. In 1973 the size, administration, and population of patients at Boston City Hospital changed markedly [22], and these changes profoundly affected the comparability of information collected subsequently with prior data. Some

factors were not necessarily constant or controlled during the study period. These variables included methods and techniques available in the microbiology laboratory and changes in the population of the hospital. These and other factors are discussed in the original report on this study [8].

Cases included in the survey were selected on the basis of laboratory reports of positive blood cultures and the suggestion in patients' records of clinical findings consistent with infection due to the organism recovered from the blood. No case-finding was performed outside the laboratory. This study used an arbitrary definition of nosocomial cases of bacteremia as those occurring on or after the third day of hospitalization; the advantages and disadvantages of such a definition and its applicability to data from the 1972 survey are discussed in the original paper [8].

The 12 years reviewed were selected because new, effective antimicrobial agents had been introduced into general use in the periods between the study years. Certain organisms that are usually considered separately today because of their different epidemiologic implications were lumped together because they could not be distinguished microbiologically in the early years of the study. For example, *Klebsiella* and *Enterobacter* species were reported together because they were grouped as "*Klebsiella-Aerobacter*" or "*Klebsiella-Enterobacter*" in some study years. In addition, some isolates were arbitrarily excluded from the study; these included *Staphylococcus epidermidis*, diphtheroids, *Bacillus* species, and "others considered by the bacteriologist to be contaminants" [8].

Observations on the microbial etiology of nosocomial bacteremia in six of the 12 years of the original study [8] are shown in table 1. I have supplied some additional details from the original data sheets to help illustrate some of the trends that were observed. Of note were the markedly different case-fatality ratios associated with the different organisms causing bacteremia.

**Grady Memorial Hospital: 1975 and 1983**

Grady Memorial Hospital is a county-municipal hospital serving the indigent of metropolitan Atlanta [9]. There are a number of similarities between this hospital and Boston City Hospital [23]. Data on nosocomial bacteremia and fungemia are collected at Grady by infection control nurses, who use laboratory reports of the isolation of an organism from

**Table 2.** Organisms associated with nosocomial bacteremia and fungemia during six-month surveillance periods in 1975 and 1983 at Grady Memorial Hospital, Atlanta.

Group, organism	No. of cases in survey year*	
	1975†	1983‡
Gram-positive aerobic cocci		
<i>Streptococcus pneumoniae</i>	1	2
Group A <i>Streptococcus</i>	0	0
Group D <i>Streptococcus</i>	4	14
Other <i>Streptococcus</i>	6	2
<i>Staphylococcus aureus</i>		
Methicillin-sensitive	14	25
Methicillin-resistant	0	4
<i>Staphylococcus epidermidis</i>	1	9
Total	26 (25)	56 (37)
Gram-negative aerobic bacilli		
<i>Escherichia coli</i>	19	19
<i>Klebsiella</i> species	13	20
<i>Enterobacter</i> species	10	15
<i>Serratia</i> species	5	2
<i>Proteus</i> species	6	1
<i>Pseudomonas</i> species	5	10
<i>Acinetobacter</i> species	1	9
Other	1	2
Total	60 (57)	81 (53)
Anaerobes		
<i>Bacteroides</i> species	10	4
Other	8	4
Total	18 (17)	8 (5)
Fungi		
<i>Candida</i>	0	8
<i>Torulopsis</i>	1	2
Total	1 (1)	10 (7)
All organisms	105 (100)	152 (100)
All cases	91§	134

\* Numbers in parentheses are percentages of the total number of cases. There were a total of 4.8 cases per 1,000 admissions in 1975 and 5.8 cases per 1,000 in 1983.

† Data are adapted from [9]. The surveillance periods were January 1 through March 31 and October 1 through December 31.

‡ The surveillance period was July 31 through December 31. Cases were identified as nosocomial by C. Perlino, P. Parrott, E. Whitworth, and L. Frawley, Epidemiology Department, Grady Memorial Hospital.

§ In eight of the 91 cases, two organisms were isolated; in three cases, three organisms were isolated.

|| In 12 of the 134 cases, two organisms were isolated; in three cases, three organisms were isolated.

blood culture supplemented by review of the patient's chart and/or examination of the patient, as necessary [9]. Whether the infection is nosocomial or community acquired is determined from clinical and lab-

**Table 3.** Isolates from the blood of patients with nosocomial bacteremia and fungemia: selected incidence studies, 1935–1983.

Year(s)*	Hospital† [reference]	Hospital type	No. of admissions or discharges	Total no. of bacteremia/fungemia isolates (attack rate‡)
1935	Boston City [8]	City/county	39,724	149 (3.8)
1941	Boston City [8]	City/county	43,178	109 (2.5)
1947	Boston City [8]	City/county	38,463	130 (3.4)
1953	Boston City [8]	City/county	37,557	171 (4.6)
1961	Boston City [8]	City/county	32,750	269 (8.2)
1969	Boston City [8]	City/county	25,643	310 (12.1)
1968–1974	Johns Hopkins [10]	Teaching	227,917	935§ (4.1)
1969–1970	Hartford [11]	Teaching	26,223	97 (3.7)
1970–1973	St. Mary's [12]	Community	61,481	85 (1.4)
1972	Boston City [8]	City/county	21,133	354 (16.8)
1974	Bellevue [13]	City/county	15,160	247 (16.3)
1975	Grady Memorial [9]	City/county	18,852	105 (5.6)
1975	University of Virginia [14]	Teaching	NA	131 (. . .)
1975–1977	University of Colorado/Denver VA# [15]	Teaching/federal	40,000**	402 (10.1)
1977–1979	Columbia A [16]	City/county	69,619	444†† (6.4)
1977–1979	Columbia B [16]	Community	22,257	64†† (2.9)
1977–1979	Columbia C [16]	Community	64,843	57†† (0.9)
1977–1979	Columbia D [16]	Federal	19,695	193†† (9.8)
1983	Grady Memorial [present report]	City/county	22,908	152 (6.6)

\* Each study was not necessarily conducted for the entire period indicated.

† Locations of hospitals are as follows: Boston City Hospital, Boston; Johns Hopkins Hospital, Baltimore; Hartford Hospital, Hartford, Conn.; St. Mary's Hospital, Madison, Wis.; Bellevue Hospital, New York; Grady Memorial Hospital, Atlanta; University of Virginia Hospital, Charlottesville, Va.; University of Colorado Medical Center, Denver; and Columbia Hospitals A, B, C, and D, Columbia, S.C.

‡ The attack rate is the number of bacteremia/fungemia isolates per 1,000 admissions or discharges (definition is different from that used in table 2).

§ Only first episodes of bacteremia and fungemia were included.

|| NA = information not available.

# Data are combined for the University of Colorado Medical Center and Denver Veterans Administration hospitals.

\*\* Figure is extrapolated from data in [15].

†† Fungi were excluded from the study.

oratory information; in contrast, in the study at Boston City Hospital, laboratory information was the primary consideration in defining nosocomial cases. For example, cases of bacteremia related to prior hospitalization would be included as nosocomial in the data from Grady Memorial Hospital but excluded from the data for Boston City Hospital.

Data on cases of nosocomial bacteremia and fungemia in a six-month period of 1975 at Grady Memorial Hospital already have been published [9]. The microorganisms identified in the 1975 study, as well as comparable data for a six-month period in 1983, are shown in table 2.

#### Other Hospitals in the United States

Other hospitals in the United States have summarized their experience with nosocomial bacteremia

and fungemia for various periods since 1968 [10–16]. These hospitals have markedly different characteristics and overall attack rates of nosocomial bacteremia and fungemia (table 3). Data on the microbial agents recovered at the various institutions are summarized in tables 4–6.

#### National Nosocomial Infections Study Surveillance Data: 1976–1982

The Centers for Disease Control (CDC) in Atlanta conduct a surveillance program designated the National Nosocomial Infections Surveillance System (NNIS). In this program hospitals voluntarily report their surveillance information on hospital infection to the CDC [21, 24–26]. A varying number of hospitals have reported their data during the past 10 years. The hospitals employ a variety of surveillance sys-

**Table 4.** Proportion of gram-positive aerobic cocci (GPAC) among isolates from the blood of patients with nosocomial bacteremia: selected incidence studies, 1935–1983.

Year(s)*	Hospital [reference]	Total no. of isolates	Percentage of all isolates made up by indicated group				
			<i>Staphylococcus aureus</i>	<i>Staphylococcus epidermidis</i>	Enterococci†	<i>Streptococcus pneumoniae</i>	Other GPAC
1935	Boston City [8]	149	19	... ‡	0	23	39
1941	Boston City [8]	109	36	...	2	10	20
1947	Boston City [8]	130	25	...	10	2	8
1953	Boston City [8]	171	36	...	6	2	4
1961	Boston City [8]	269	38	...	6	4	7
1969	Boston City [8]	310	19	...	7	3	9
1968–1974	Johns Hopkins [10]	935§	9	3	3	2	NA
1969–1970	Hartford [11]	97	8	8	4	0	7
1970–1973	St. Mary's [12]	85	14	1	7	1	5
1972	Boston City [8]	354	16	...	8	3	14
1974	Bellevue [13]	247	16	5	5	1	NA
1975	Grady Memorial [9]	105	13	1	4	1	6
1975	University of Virginia [14]	131	8	<1	1	0	5
1975–1977	University of Colorado/Denver VA# [15]	402	10	NA	5	2	7
1977–1979	Columbia A [16]	444**	19	10	4	1	NA
1977–1979	Columbia B [16]	64**	8	6	11	2	NA
1977–1979	Columbia C [16]	57**	7	0	5	2	NA
1977–1979	Columbia D [16]	193**	12	5	4	3	NA
1983	Grady Memorial [present report]	152	19	6	9	1	1

NOTE. For locations of hospitals, see table 3.

\* Each study was not necessarily conducted for the entire period indicated.

† These organisms were described in some instances as *Streptococcus faecalis* or group D streptococci—terms assumed to be equivalent for this analysis.

‡ Ellipsis points indicate the arbitrary exclusion of *S. epidermidis* from the study.

§ Only first episodes of bacteremia were included.

|| NA = information not available. (Some studies included an “Other Pathogens” category.)

# Data are combined for the University of Colorado Medical Center and Denver Veterans Administration hospitals.

\*\* Fungi were excluded from the study.

tems, and the methods used in their microbiology laboratories probably differ as widely as did those used at the hospitals listed in table 3.

Surveillance of bacteremic infection in the NNIS is directed at the entity of primary bacteremia, which is defined as a case of bloodstream invasion for which no preceding or simultaneous site of infection with the same pathogen can be identified [21]. Cases involving such a preceding or simultaneous site are defined as secondary. Only in the most recent NNIS report (that for 1980–1982) is secondary bacteremia addressed [26], and the information given is incomplete. Thus, NNIS data on primary bacteremia are shown for selected years in table 7, but these data are not comparable to those in tables 1–6.

**Trends and Changes in the Etiology of Nosocomial Bacteremia and Fungemia**

Major changes have occurred in the etiology of

hospital-associated bacteremia and fungemia in the five decades since 1935 (table 8).

**Increased Frequency of Polymicrobial Bacteremia**

The increase in the average number of organisms isolated from culture per infection is illustrated by the data from Boston City Hospital (table 1). In the early study years, virtually every case involved a single isolate; for example, there were 149 isolates from 147 patients in 1935. In succeeding years the average number of isolates per case gradually increased; by 1972 there were 354 isolates from 280 patients, for an average of 1.3 organisms per patient. This trend has continued to the present; the NNIS data for 1980–1982 [26] indicate the isolation of multiple pathogens in 20% of cases, a single pathogen in 65%, and no pathogen in the remaining 15%.

The likelihood of isolation of multiple pathogens is particularly high for patients in intensive care, for

**Table 5.** Proportion of Enterobacteriaceae among isolates from the blood of patients with nosocomial bacteremia: selected incidence studies, 1935–1983.

Year(s)*	Hospital [reference]	Total no. of isolates	Percentage of all isolates made up by indicated group				
			<i>Escherichia coli</i>	<i>Klebsiella</i>	<i>Enterobacter</i>	<i>Serratia</i>	Other Enterobacteriaceae
1935	Boston City [8]	149	11	0	0	0	7
1941	Boston City [8]	109	21	0	0	0	6
1947	Boston City [8]	130	18		18 <sup>†</sup>	0	14
1953	Boston City [8]	171	15		13	0	13
1961	Boston City [8]	269	9		13	0	8
1969	Boston City [8]	310	11		21	1	11
1968–1974	Johns Hopkins [10]	935 <sup>‡</sup>	14	25	7	4	4
1969–1970	Hartford [11]	97	16	7	6	3	9
1970–1973	St. Mary's [12]	85	19	5	8	2	6
1972	Boston City [8]	354	14		20	5	6
1974	Bellevue [13]	247	11	29	3	NA <sup>§</sup>	NA
1975	Grady Memorial [9]	105	18	12	9	5	7
1975	University of Virginia [14]	131	18	18	7	5	8
1975–1977	University of Colorado/Denver VA <sup>  </sup> [15]	402	16	8	NA	NA	NA
1977–1979	Columbia A [16]	444 <sup>#</sup>	13	7	3	1	NA
1977–1979	Columbia B [16]	64 <sup>#</sup>	16	3	11	2	NA
1977–1979	Columbia C [16]	57 <sup>#</sup>	35	5	5	0	NA
1977–1979	Columbia D [16]	193 <sup>#</sup>	19	10	4	8	NA
1983	Grady Memorial [present report]	152	13	13	10	1	2

NOTE. For locations of hospitals, see table 3.

\* Each study was not necessarily conducted for the entire period indicated.

<sup>†</sup> Numbers set between columns are combined totals for *Klebsiella* and *Enterobacter*.

<sup>‡</sup> Only first episodes of bacteremia were included.

<sup>§</sup> NA = information not available. (Some studies included an "Other Pathogens" category.)

<sup>||</sup> Data are combined for the University of Colorado Medical Center and Denver Veterans Administration hospitals.

<sup>#</sup> Fungi were excluded from the study.

diabetics, and for individuals with altered host defenses [27]. For example, one-third of the nosocomial bloodstream infections encountered in a study of patients at a cancer treatment hospital were polymicrobial [20].

#### Increase in Sequential Episodes of Infection in the Same Patient and at Multiple Sites

Not only are more organisms being found in each episode, but many patients now have more than one episode of nosocomial infection. Peterson et al. recently described infection after bone marrow transplantation [28] and noted both polymicrobial infections and multiple separate episodes of infection. In addition, patients in various studies have been noted to have infections (whether bloodstream or otherwise) at more than one site. For example, the "multiplicity" (mean number of infections per infected patient) was 1.25 for a series of patients examined

during a prevalence survey at Boston City Hospital in 1973 [29]. Perhaps the most prominent example of this phenomenon was provided by Leviten and Shulman, who described the case history of a patient with multiple episodes of infection and 16 different organisms both colonizing and infecting different sites during a long period of hospitalization [30].

#### Resurgence of *S. aureus*

The coagulase-positive *Staphylococcus* was the major nosocomial pathogen encountered in bacteremic infections during the 1940s and became the scourge of hospitals during the 1950s and early 1960s (tables 1 and 4). With the introduction of penicillinase-resistant penicillins and cephalosporins in the mid-1960s, the role of this organism began to diminish; in the 1960s and 1970s, some hospitals found *S. aureus* to be implicated in fewer than 10% of bac-

**Table 6.** Proportion of gram-negative aerobic bacilli, anaerobes, and fungi among isolates from the blood of patients with nosocomial bacteremia or fungemia: selected incidence studies, 1935–1983.

Year(s)*	Hospital [reference]	No. of total isolates	Percentage of all isolates made up by indicated group				
			<i>Pseudo-</i> <i>monas</i>	<i>Acineto-</i> <i>bacter</i> †	Other non-fermenters	Anaerobes	Fungi
1935	Boston City [8]	149	1	0	1	0	0
1941	Boston City [8]	109	5	0	1	0	0
1947	Boston City [8]	130	3	0	2	0	0
1953	Boston City [8]	171	5	0	2	0	4
1961	Boston City [8]	269	6	5	1	0	4
1969	Boston City [8]	310	8	2	1	1‡	8
1968–1974	Johns Hopkins [10]	935§	8	NA	NA	6#	6**
1969–1970	Hartford [11]	97	14	2	3	4	4
1970–1973	St. Mary's [12]	85	6	0	0	20	5
1972	Boston City [8]	354	4	2	1	1‡	9
1974	Bellevue [13]	247	5	NA	NA	NA	NA
1975	Grady Memorial [9]	105	5	1	0	17	1
1975	University of Virginia [14]	131	11	2	1	8	7
1975–1977	University of Colorado/Denver VA†† [15]	402	9	1	0	11	12
1977–1979	Columbia A [16]	444‡‡	5	NA	NA	6§§	‡‡
1977–1979	Columbia B [16]	64‡‡	6	NA	NA	10§§	‡‡
1977–1979	Columbia C [16]	57	2	NA	NA	16§§	‡‡
1977–1979	Columbia D [16]	193‡‡	4	NA	NA	5§§	‡‡
1983	Grady Memorial [present report]	152	7	6	1	5	7

NOTE. For locations of hospitals, see table 3.

\* Each study was not necessarily conducted for the entire period indicated.

† This organism was reported in some instances as *Herellea*—a designation assumed to be equivalent for this analysis.

‡ Figure includes *Bacteroides* only (with *Clostridium* arbitrarily excluded).

§ Only first episodes of bacteremia and fungemia were included.

|| NA = information not available. (Some studies included an “Other Pathogens” category.)

# Figure includes *Bacteroides* and *Clostridium* only (with the presence or absence of other anaerobes not specified).

\*\* Figure includes *Candida* only (with the presence or absence of other fungi not specified).

†† Data are combined for the University of Colorado Medical Center and Denver Veterans Administration hospitals.

‡‡ Fungi were excluded from the study.

§§ Figure includes *Bacteroides* species only (with presence or absence of other anaerobes not specified).

teremic cross-infections (table 4). However, the organism once again was a frequent pathogen at Grady Memorial Hospital in 1983 (table 2) and has remained important in the NNIS study (table 7).

The increase in the frequency of staphylococcal infections at Grady Memorial Hospital in 1983 paralleled the appearance of methicillin resistance in many hospitals [31]. However, both methicillin-susceptible and methicillin-resistant strains appear to have been involved in nosocomial infections at many hospitals in recent years [32].

**Recognition of *S. epidermidis* and Other Endogenous Flora Components as Pathogens**

Earlier studies either ignored or discounted *S. epidermidis* (which will be used in this review to represent all pathogenic coagulase-negative staphylococci) as

a likely cause of nosocomial bacteremia. For example, the Boston City Hospital study [8] arbitrarily excluded this organism from consideration. However, studies since 1968 have described *S. epidermidis* as a true pathogen in 1%–10% of cases (table 4). Certainly not all isolates of this species from blood represent true pathogens [15]. Nevertheless, in the right host setting, the organism must be considered virulent [33]. Outbreaks of nosocomial infection due to this species have been reported and environmental reservoirs identified [34, 35]. Resistance to antimicrobial agents in nosocomial strains of *S. epidermidis* is thought to have become more frequent; one recent study details an increase in strains resistant to penicillin, erythromycin, tetracycline, gentamicin, and clindamycin [36].

Other components of the endogenous flora are now known to have a similar potential to infect the

**Table 7.** Relative frequency of selected organisms as a cause of primary bacteremia: National Nosocomial Infections Surveillance System, 1976, 1978, and 1980–1982.

Organism	Percentage of cases due to indicated organism in indicated year(s) [reference]		
	1976 [24]*	1978 [25]†	1980–1982 [26]‡
<i>Staphylococcus aureus</i>	13	14	13
<i>Staphylococcus epidermidis</i>	8	9	10
Group D <i>Streptococcus</i>	7	6	7
<i>Streptococcus pneumoniae</i>	1	1	NA
<i>Escherichia coli</i>	14	16	13
<i>Klebsiella</i> species	11	11	9
<i>Enterobacter</i> species	5	5	7
<i>Serratia</i> species	3	3	4
<i>Pseudomonas</i> species	7	7	6
Fungi	5	5	NA

NOTE. *Primary bacteremia* is defined as a blood infection for which no preceding or simultaneous site of infection involving the same pathogen can be identified [21].

\* Data are from 82 hospitals, with a total of 2,185 blood isolates.

† Data are from 82 hospitals, with a total of 2,317 blood isolates.

‡ Data are from 60 hospitals, with a total of 6,843 blood isolates. NA = information not available because organism was included in “All Others” category.

patient whose host defenses are sufficiently impaired. For example, the JK diphtheroid organism can cause outbreaks of nosocomial infection related to environmental reservoirs [37].

#### Increased Prominence of the Enterococcus

Some of the studies listed in table 4 included reports on enterococci, some included information on group D streptococci without differentiating enterococci from nonenterococci, and some included a description of infections due to specific enterococcal species. All, however, revealed much the same trends: a gradual increase in prominence of the organism after introduction of the penicillins (illustrated by the 1947 survey at Boston City Hospital) and a relatively stable frequency of occurrence in subsequent years through the mid-1970s. Since then, the organism has again become more prominent. In 1977–1979 more than 10% of all isolates from the blood of patients with nosocomial bacteremia at one hospital in Columbia, South Carolina, were enterococci (table 4), and the relative frequency of cases associated

with this organism at Grady Memorial Hospital in 1983 tripled in comparison with that in 1975 (table 2). However, there has been no great increase in the frequency with which the organism appears in primary bacteremia (table 7). This lack of increase may be a matter of definition; i.e., the organism seems prone to reach the bloodstream after initial infection at another site [38], and such instances would be defined by the NNIS study as secondary bacteremia [21, 26].

Enterococcal colonization appears to be enhanced by use of the newer broad-spectrum  $\beta$ -lactam antimicrobial agents for prolonged periods [39]. Such colonization may explain the increasing numbers of reports of superinfection with this organism since these antimicrobial agents were introduced [40].

#### Decline in Importance of Pneumococci and Group A Streptococci

*Streptococcus pneumoniae* has been a frequent cause of community-acquired pneumonia and bacteremia. Since the introduction of antimicrobial drugs, however, the organism has only infrequently been a source of bacteremic nosocomial infection (tables 1, 2, 4, and 7). Cases still occur. Mylotte and Beam [41] reviewed 37 episodes over a 42-month period in a Veterans Administration hospital. They found patients with nosocomial pneumococemia to have more severe underlying diseases and to have undergone respiratory tract procedures (bronchoscopy, intubation, etc.) more frequently than other patients [41].

Many cases of nosocomial bacteremia at Boston City Hospital in 1935 and 1941 were due to group A streptococci (shown under “other GPAC” in table 4). After that time the relative frequency of isolation of group A streptococci from patients with endemic nosocomial bacteremia declined. Since 1972 group A streptococci, together with streptococci other than *S. pneumoniae* and group D streptococci, have accounted for 5%–7% of nosocomial cases of bacteremia (table 4). Group A streptococci are implicated occasionally as a cause of outbreaks of nosocomial infection [42, 43]. Group B streptococci continue to be recovered on occasion, especially in cases of neonatal bacteremia and meningitis [44].

#### Continued Importance of the Enterobacteriaceae

*Escherichia coli* has been found to be a cause of nosocomial cases of bacteremia in all surveys at Bos-

**Table 8.** Changes in selected organisms as causes of nosocomial bacteremia and fungemia in U.S. hospitals during two surveillance periods, 1935 to present.

Organism	Trend during indicated period	
	1935-1972	1973 to present
<i>Staphylococcus aureus</i>		
Methicillin-susceptible	Important	Resurgent
Methicillin-resistant	Absent	Increasing
<i>Staphylococcus epidermidis</i> ,* other "endogenous flora"	Ignored	Recognized
Group D <i>Streptococcus</i> , "enterococci"	Moderate	Increasing
<i>Streptococcus pneumoniae</i>	Decreasing	Minor
Group A <i>Streptococcus</i>	Decreasing	Minor
Other streptococci	Decreasing	Minor
<i>Escherichia coli</i>	Increasing	Stable
<i>Klebsiella</i> species	Increasing	Major
<i>Enterobacter</i> species	Increasing	Major
<i>Serratia</i> species	Began	Major
Other Enterobacteriaceae	Increasing	Stable
<i>Pseudomonas</i> species	Increasing	Major
Other nonfermenting gram-negative aerobes	Minor	Increasing
Anaerobes	Unrecognized	Increasing
Fungi	Increasing	Increasing
Viruses	Undocumented	Recognized
<i>Legionella</i> species	Unknown	Recognized
<i>Mycobacterium tuberculosis</i>	Prominent	Decreasing
Nontuberculous mycobacteria	Unrecognized	Increasing
Other new organisms	To be determined	To be determined

\* And other coagulase-negative staphylococci.

ton City Hospital (tables 1 and 5). In the survey at that institution in 1941, the relative proportion of *E. coli* isolates had approximately doubled. The organism then diminished in relative prominence at Boston City Hospital until the 1961 survey, with a small increase noted in the two later surveys. At other hospitals *E. coli* has accounted for 11%–19% of isolates throughout the survey periods (table 5).

One of the important trends noted in the Boston City Hospital surveys was the rise in importance of *Klebsiella* and *Enterobacter* species (formerly called *Aerobacter* in many hospitals) as nosocomial pathogens during the years after the introduction of antimicrobial agents (table 1). By 1969 these two organisms together were the pathogens most frequently isolated from the blood of patients with nosocomial bacteremia at Boston City Hospital. In addition, the organisms were important agents at a number of other hospitals during the 1970s (table 5) and in 1983 at Grady Memorial Hospital (table 2).

In some hospitals *Klebsiella* is the most frequently encountered organism in nosocomial bacteremia (table 5). *Klebsiella* organisms now are divided into a

variety of species by many clinical laboratories. *Klebsiella pneumoniae* continues to be the most important species in both nosocomial and community-acquired infection, whether bacteremic or at other sites [45]. Antibiotic-resistant strains of *Klebsiella* have produced serious difficulties for some hospitals [46]. The study of problems due to these strains often requires sophisticated laboratory investigative techniques [47].

*Enterobacter* (formerly *Aerobacter*) accounted for a sizable proportion (3%–11%) of nosocomial bacteremic infections during the 1970s (tables 5 and 7). The percentage has been even a bit higher in surveys during the 1980s. The role of this organism has been enhanced by its frequent development of resistance to multiple antimicrobial agents and by its propensity to be found in contaminated products and solutions [48]. Particularly notable are those outbreaks associated with *Enterobacter*-contaminated intravenous fluids [33]. John et al. [48] described strains of *Enterobacter* as "endemic pathogens in some but not all hospitals" and noted that "they occasionally cause community-acquired infection." These authors

thought that any outbreak of infections with *Enterobacter* in hospitals should lead to a search for contaminated products or solutions.

Until the 1960s *Serratia* species were virtually unknown as a source of nosocomial infection (or perhaps were identified by another name). Subsequently, *Serratia* has accounted for up to 5% of nosocomial bacteremia isolates (table 5). Because strains of *Serratia* are notorious for persistence in hospital reservoirs, it has been suggested that the frequency of nosocomial infection due to *Serratia* be used as an indicator of the efficiency of a hospital's infection control program [49].

*Klebsiella*, *Enterobacter*, and *Serratia* are closely related organisms [50]. Other members of the Enterobacteriaceae involved in nosocomial bacteremia and other hospital-acquired infections are *Proteus*, *Providencia*, *Morganella*, *Citrobacter*, and occasionally *Salmonella*. These organisms played an increasing role in hospital-acquired infections during the 1940s and early 1950s; their incidence has been relatively stable since then (table 5). The major contexts in which these organisms have been noted are (1) outbreaks associated with intestinal colonization [51] and (2) the presence of resistance to many different antibiotics [52]. *Morganella morganii* (formerly classified as *Proteus morganii* or lumped with the other "indole-positive *Proteus*" organisms) recently has received increased attention [53]; its epidemiologic characteristics are still being elucidated.

#### Continuing Importance of *Pseudomonas* Species

*Pseudomonas aeruginosa* has been an appreciable source of nosocomial bacteremia since the earliest study at Boston City Hospital in 1935 (table 6), yet pseudomonas bacteremia was infrequently reported before the beginning of the antimicrobial era [54]. The relative contribution of *P. aeruginosa* to the total number of isolates from blood has varied markedly from hospital to hospital and from time to time (tables 6 and 7). At some hospitals (e.g., Hartford Hospital in 1969–1970 and the University of Virginia Hospital in 1975), *P. aeruginosa* has accounted for more than 10% of all blood isolates associated with hospital-acquired infections (table 6). High case-fatality ratios have characterized infections associated with this organism; the likelihood of death changed little over the decades of the Boston City Hospital study (table 1). *P. aeruginosa* has been studied extensively, and excellent reviews on its epidemi-

ologic characteristics and modes of transmission have recently been compiled [21, 55].

*Pseudomonas* species other than *P. aeruginosa* were infrequently reported in the series presented in tables 1–7. When found in patients with nosocomial infections, these species tended to appear in association with contamination of a commercial product, such as respiratory therapy equipment [56], disinfectants [57], or blood products [58].

#### Increased Recognition of Nonpseudomonas, Gram-Negative, Nonfermenting Pathogens

The so-called nonfermenters (gram-negative aerobic bacilli that do not ferment the sugars commonly tested in clinical laboratories) include both *Pseudomonas* and nonpseudomonas organisms. Among the nonpseudomonas isolates reported in studies of nosocomial bacteremia, *Acinetobacter* (formerly called *Herellea*) is probably the most prominent. In the Boston City Hospital series, *Acinetobacter* isolates first were seen in 1961 and continued to play a small role in subsequent years, as at other hospitals (table 6). *Acinetobacter* was particularly prominent at Grady Memorial Hospital in the 1983 survey (table 2), and its importance is indicated by its mention as a nosocomial pathogen over the past few years in a number of reports [59, 60].

*Flavobacterium meningosepticum* has caused a variety of nosocomial infections, including bacteremia [61]. This organism appeared sporadically at Boston City Hospital in the years studied but had to be identified in retrospect, since its name was proposed only in the late 1950s. Most hospital outbreaks of infection associated with *Flavobacterium* have involved environmental contamination of fluids, whether solutions, medications for respiratory therapy, or antiseptics [61].

#### Documentation of the Role of Anaerobes

For many years it was beyond the ability of many laboratories to isolate anaerobic bacilli from the blood [62]. This deficiency perhaps explains to some extent the lack of prominence of these organisms in bacteremia series described before the mid-1960s. In the Boston City Hospital series (table 1), such cases were not noted until 1969, but difficulties with anaerobe detection were specifically noted. Anaerobes played an important role in virtually all of the other series shown in table 6. These organisms accounted

for more than 10% of isolates from the blood of patients with bacteremia in some reports and for 20% of isolates at one community hospital.

*Bacteroides fragilis* and *Clostridium* species have been the most frequently reported anaerobic organisms. In part, this predominance may be due to a selection bias, as many laboratories identify only certain anaerobes and provide a morphologic description of the remainder [63]. Among the anaerobes infrequently related to bacteremia, *Clostridium difficile* appears to be a potential source of hospital-acquired cross-infection [64].

#### Markedly Increasing Role of Fungi

A major trend during the period under review is the rise in importance of fungemia as a nosocomial infection. Of the study years at Boston City Hospital that are listed in table 1, 1953 was the first in which *Candida* was noted. Other fungi (predominantly *Torulopsis*) appeared beginning with the 1961 survey. Fungal organisms have been found at levels of 1%–12% in more recent surveys at other hospitals (table 6). Nationally, fungi accounted for 5% of cases (“primary fungemia”?) in two of the NNIS surveys summarized in table 7. Cases due to fungi were not specifically reported in the most recent survey [26].

Hospital-acquired fungemia has been associated with prior antimicrobial therapy, indwelling intravascular catheters, parenteral alimentation, and urinary catheterization [65]. In addition, dialysis appears to be a risk factor for infection at sites other than the bloodstream [66]. Some of the increase in the frequency of isolation of these organisms may be due to the better methods of identification now available for use in clinical and research laboratories [67]. Increasing susceptibility of the average hospitalized patient may also play a part. However, much of the increase seems to be related to the increasing use of a variety of catheters at vascular and nonvascular sites [68]. In particular, the use of subcutaneous catheters for parenteral nutrition, cancer chemotherapy, long-term therapy with antibiotics or other medications, dialysis, phlebotomy, or repeated transfusion seems to have enhanced the likelihood of fungal invasion of the bloodstream [69].

#### Nosocomial Infection Trends Not Indicated by Bacteremia or Fungemia

Some changes in the etiology of nosocomial infec-

tion, including the following, are not apparent from the data on bloodstream invasion presented herein.

#### New Understanding of the Importance of Viruses

Among infections reported in the NNIS summary for 1980–1982, “91% were caused by aerobic bacteria, 2% by anaerobic bacteria, and 6% by fungi. Viruses, protozoa, and parasites each accounted for less than 1% of infections of known etiology” [26]. In 1978 viruses caused 0.2% of the total number of infections reported to the NNIS [70]. No cases of viremia were reported in the series reviewed in tables 1–6, yet viral infections can be a significant cause of cross-infection in the hospital. The importance of such infections was emphasized by Welliver and McLaughlin, whose surveillance in a children’s hospital documented viral infections to be more common than those caused by gram-negative aerobic bacilli [18]. Valenti et al., working at a hospital with excellent viral diagnostic facilities, estimated that nosocomial viral infections accounted for ~5% of the cases detected in a 17-month period beginning in 1977 [70]. The absence of viral agents from most nosocomial infection surveys results largely from the lack of adequate viral diagnostic facilities in most hospitals.

Viruses of special note as causes of nosocomial infection include cytomegalovirus [71], herpes simplex virus [72], varicella-zoster virus [73], rubella [74], hepatitis virus [75], adenovirus [76], respiratory syncytial virus [77], and influenza virus [78]. Of great importance is the recent documentation of rotavirus as an important nosocomial pathogen on both pediatric and adult wards. In addition, the precautions taken to prevent the spread of acquired immune deficiency syndrome illustrate a response to another virus with unclear but apparently small potential for hospital transmission [79].

#### Discovery of *Legionella*

*Legionella* first gained attention as the result of an outbreak of infections in a hotel. Hospitals are another type of institution where infections with *Legionella* can be prominent. In 16 reports on nosocomial infection with *Legionella pneumophila* as reviewed by Meyer [80], cases occurred in clustered, epidemic, and endemic fashion. Environmental sources have been prominent in transmission for some episodes, but the mode of spread has been less

clear for others. *Legionella micdadei* has been implicated along with *L. pneumophila* as a cause of infections among transplant recipients [81]. The recognition of *Legionella* as a nosocomial pathogen will probably increase as efficient diagnostic techniques become available to hospital laboratories [82].

#### Diminishing Role of *Mycobacterium tuberculosis* and Increasing Role of Nontuberculous Mycobacteria

The development of effective chemotherapy and of efficient ways to isolate patients with tuberculosis has decreased the spread of *M. tuberculosis* in the hospital [83]. Many of the episodes of cross-infection with this organism that do occur today are related to improper cleaning of diagnostic equipment [84]. However, even as the transmission of "typical" tuberculosis decreases in frequency, nontuberculous mycobacteria are seen with increased frequency as a cause of postoperative wound infection and in other hospital settings [85].

#### Variable Role of Unusual Organisms

Unusual causes of nosocomial infection are continually being described in the medical literature [86, 87]. Many of the cases involved a patient or employee who is unable to respond in the usual fashion to a microorganism that ordinarily presents no threat.

#### Conclusion

Marked changes in the etiology of nosocomial infection have occurred during the past five decades. The current rapid pace of such changes is illustrated by the large number of recent references cited in this review. New diagnostic techniques and therapies that increase the compromise of host defenses will continue to be developed, and their use should provide us with an array of new microbial opponents.

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