

Bayer-Symposium III

Bacterial Infections

Changes in
their Causative Agents —
Trends and
Possible Basis

Edited by
M. Finland, W. Marget and K. Bartmann



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With 53 Figures



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Welcome

K. BARTMANN

My dear lady colleague and gentlemen!

It is really a great pleasure for me to welcome you to our symposium which is the third one. I thank you for accepting the invitation, especially those of you who have had a long journey.

The basic idea of these symposia is to give a small group of scientists the opportunity to deal with, and to discuss an important and current item of medicine in a quiet atmosphere with plenty of time. The first symposium was devoted to problems of immunology, the second to catechol amines.

Our subject, changes of causative agents in bacterial infections, is of interest from biological, epidemiological and therapeutic points of view. It implies problems of general biology, pathogenicity, host resistance and iatrogenic influences. We have tried to cover the subject as completely as possible. I thank very much Dr. FINLAND and Dr. MARGET for their great and continuous help in reaching this target. But it is quite clear from the programme as it looks now that we will miss some important aspects. This is in part due to the fact that some colleagues were unable to attend and had to cancel their participation in the last minute. Omissions are further due to lack of knowledge. For instance, this holds true for the present status of virulence. Except for a few bacterial species we don't know their current virulence for experimental animals and moreover we don't know the meaning of virulence tests for human beings. But I hope that the discussion will fill the gaps to some extent.

The original meaning of the word symposium in Greek has nothing to do with science but much with enjoying life. I think, at least in the evening we should try to realize the original meaning to some extent, transformed into our present-day way of life, but still in the spirit of PLATON and of EPIKUR as well.

I. Bacterial Infections:
Changes in their Causative Agents. Trends

Changing Prevalence of Pathogenic Bacteria in Relation to Time and the Introduction and Use of New Antimicrobial Agents*

M. FINLAND

It should be pointed out, at the very start, that the material to be presented under the title assigned to me is a sort of replay of an old record (FINLAND, 1970; FINLAND, JONES and BARNES, 1959), but in a new edition, with some different material to bring it more nearly up to date in line with some new developments. The bulk of the data consists primarily of surveys of material from the Boston City Hospital where we have been monitoring serious infections over the course of several decades. The first portion will deal with the bacteria which have been isolated from blood cultures of patients with compatible infections, and the changes in the frequency with which different bacterial pathogens have been encountered.

Background Data: Hospital Admissions

A few bits of background information will serve as sort of denominators for some of the data to be presented. First is the number of admissions to all services of the main general hospital each year over the period of the study; this has declined steadily from a peak of about 43,000 in 1941 to about 33,000 in 1961, and then the annual number of admissions stabilized at that figure through 1965. This represents about a 25% drop in the number of admissions to this hospital over the 25 years. Second, the number of deaths over the three decades between 1935 and 1965 declined more or less steadily from nearly 3,000 to just under 2,000 annually, a drop of about one-third for the entire period. Third, the mortality rate for all hospital admissions showed some fluctuations up to 1947, after which it dropped progressively from about 7.3% in that year to about 6% in 1965, a decline of about one-sixth over less than two decades.

Incidence and Mortality of All Bacteremic Infections

Data concerning all patients with bacteremia were collected for 10 selected years to reflect the impact of the introduction and widespread use of the successive antibacterial agents that became available over this interval. Only organisms considered to be true pathogens related to compatible infections in the patients were included. For the present purpose, organisms commonly found as contaminants (*Staphylococcus albus* and diphtheroids are examples) were totally excluded, even when repeatedly cultured, and when they clearly did cause disease.

* Most of the studies on which this paper is based were supported in part by grants 5R01-AI-00023 and 2T01-AI-00068 from the National Institute of Allergy and Infectious Disease.

The year 1935 was selected to represent the situation just before the sulfonamides were introduced; 1941 was chosen to reflect the effects of those agents just prior to the introduction of penicillin; 1947 to reflect the full impact of the use of penicillin and streptomycin before the first broadspectrum antibiotics, Aureomycin (chlortetracycline) and Chloromycetin (chloramphenicol), became available. The year 1951 was chosen as the year when penicillin-resistant staphylococci had become very common and before the first "anti-staphylococcal" antibiotic (erythromycin) was introduced, and 1961 was the year before the new semisynthetic penicillins and cephalosporins became available. Intervening years between 1951 and 1961 and additional years after that were also included to verify any trends.

In marked contrast to the steadily declining numbers of admissions to the hospital for all causes with the declining numbers of deaths and drop in mortality rate among those patients, there was a steady and marked increase in the annual number of bacteremic patients in the hospital and in the number of deaths among the bacteremic patients. Over the entire period of this study, the number of bacteremic patients increased steadily, from under 300 in 1935 to over 1,000 in 1965. The number of deaths in patients with verified bacteremic infections dropped slightly over the early years, just after the first introduction of effective antibacterial agents, from 168 in 1935 to 143 in 1947. The number of deaths in bacteremic patients then rose gradually but steadily to 400 in 1965. The case-fatality ratio, which was nearly 60% for all bacteremic patients in 1935, dropped sharply after the sulfonamides became widely used and dropped further to 30% in 1947 following the availability of penicillin and streptomycin. After the introduction of the broad-spectrum antibiotics the mortality rate among the bacteremic patients showed a steady increase to more than 40% in 1961, after which there was a slight tendency of the mortality to decline following the general availability of the semisynthetic penicillins and cephalosporins. However, the changes in case-fatality ratios varied with the different bacterial invaders, as will be detailed later.

Age has always been recognized as a major determining factor in the case-fatality ratio from various specific infections and this was equally true for the patients with bacteremia due to each of the various specific categories and for all the bacteremic patients combined. Beginning with a varying case-fatality ratio in those under 10 years old (most of those deaths being in newborns and in infants under 2 years old), the mortality dropped to its lowest rate in the second and third decades of life and then rose steeply for each advancing decade. The case-fatality ratio for patients in each decade of life during the 10 selected years reflected the overall decline for all ages through 1947, rising after that until 1961 and then declining again through 1965.

Factors Related to Changing Mortality: Age of the Patients

I shall not undertake to analyze all the factors entering into the changes in the overall mortality rates in bacteremic patients except as they relate to the changes in the age distribution of all the bacteremic patients over the period of this study. Table 1 shows the distribution of the bacteremic patients by decades of age for each of the selected years of the study and Table 2 shows the corresponding data for the bacteremic patients who died. In Table 1 it is seen that in the years 1935

and 1941 the bacteremic patients were distributed more or less evenly over the various decades of age, especially between the ages of 10 and 69 years; there was a sharp drop in the numbers of patients of 70 years or older and there were none more than 90 years old. Beginning in 1947, the age distribution of the patients changed markedly, the proportion of those between 10 and 40 years old dropping steadily, while the proportion of those 70 years of age or older were increasing even more strikingly, and there were also appreciable, and increasing numbers of patients in the tenth decade of life.

Table 1. *Age distribution of patients with bacteremia, Boston City Hospital (ten selected years, 1935—1965)*

Year	Number of patients, age (years)										Total
	<10	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—89	90 +	
1935	23	34	53	38	40	43	39	18	3	0	291
1941	53	42	54	60	60	64	44	34	11	0	422
1947	30	37	52	58	57	74	75	67	18	1	469
1951	24	27	30	37	65	63	99	86	45	2	478
1953	39	21	41	59	51	74	110	113	61	2	571
1955	79	23	26	33	64	72	96	102	75	4	574
1957	124	15	25	23	49	65	100	112	79	6	598
1961	113	21	72	50	66	97	122	164	81	9	795
1963	110	21	48	68	97	137	132	177	100	20	910
1965	137	17	47	64	112	125	165	238	143	28	1076

Year	Distribution, percent of total, age (years)									
	<10	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—89	90 +
1935	7.9	11.7	18.2	13.1	13.7	14.8	13.4	6.2	1.0	0
1941	12.6	10.0	12.8	14.2	14.2	15.2	10.4	8.1	2.6	0
1947	6.4	7.9	11.1	12.4	12.2	15.8	16.0	14.3	3.8	0.2
1951	5.0	5.6	6.3	7.7	13.6	13.2	20.7	18.0	9.4	0.4
1953	6.8	3.7	7.2	10.3	8.9	13.0	19.3	19.8	10.7	0.4
1955	13.8	4.0	4.5	5.7	11.1	12.5	16.7	17.8	13.1	0.7
1957	20.7	2.5	4.2	3.8	8.2	10.9	16.7	18.7	13.2	1.0
1961	14.2	2.6	9.1	6.3	8.3	12.2	15.4	20.6	10.2	1.1
1963	12.1	2.3	5.3	7.5	10.6	15.1	14.5	19.5	11.5	2.2
1965	12.7	1.6	4.4	6.0	10.4	11.6	16.3	22.1	13.3	2.6

These changes in age distribution are even more striking among the bacteremic patients who died. Most noteworthy were first, the fact that for some of the years of the study, beginning in 1953, there were either no deaths at all, or only 1 or 2 deaths among bacteremic patients in the second and third decades of life; second, the numbers and proportions of those over 70 years of age rose steadily; and third, there were increasing numbers of patients and deaths among bacteremic patients 90 years of age or older. It is of particular interest to point out that there were 40% more bacteremic patients and 27% more deaths among those bacteremic patients over 70 years in the year 1965, as compared to the corresponding totals for all ages in the year 1935.

Other Contributing Factors

Many factors other than age (though some were related to the advanced age of the patients) influenced the increased occurrence of bacteremic infections. The changes in the character of the bacterial invaders and in mortality was similar in many respects to those which are also generally related to nosocomial (hospital-acquired) infections, a large number of which are included among these cases. They also involve organisms formerly considered to be nonpathogenic, or at most mildly pathogenic—the so-called opportunistic pathogens. These contributing

Table 2. *Age distribution of deaths among patients with bacteremia, Boston City Hospital (ten selected years, 1935—1965)*

Year	Number of deaths, age (years)										Total
	<10	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—89	90 +	
1935	7	7	18	27	25	32	32	17	3	0	168
1941	11	13	12	12	19	34	24	22	9	0	156
1947	9	2	2	9	14	33	31	35	7	1	143
1951	4	2	2	4	11	24	52	40	27	1	167
1953	6	0	1	12	7	25	49	60	40	1	201
1955	7	1	0	4	13	20	44	63	54	3	209
1957	10	1	2	5	13	26	58	61	53	5	234
1961	12	2	5	10	25	39	65	94	53	8	313
1963	22	1	3	10	34	49	73	90	65	14	361
1965	20	0	4	20	36	41	66	121	72	20	400

Year	Distribution, percent of total, age (years)									
	<10	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—89	90 +
1935	4.2	4.2	10.7	16.1	14.9	19.0	19.0	10.1	1.9	0
1941	7.1	8.3	7.7	7.7	12.2	21.8	15.4	14.1	5.8	0
1947	6.3	1.4	1.4	6.3	9.8	23.1	21.7	24.5	4.9	0.7
1951	2.4	1.2	1.2	2.4	6.6	14.4	31.1	24.0	16.2	0.6
1953	3.0	0	0.5	6.0	3.5	12.4	24.4	29.9	19.9	0.5
1955	3.3	0.5	0	1.9	6.2	9.6	21.1	30.1	25.8	1.4
1957	4.3	0.4	0.9	2.1	5.6	11.1	24.8	26.1	22.6	2.1
1961	3.8	0.6	1.6	3.2	8.0	12.5	20.8	30.0	16.9	2.6
1963	6.1	0.3	0.8	2.8	9.4	13.6	20.2	24.9	18.0	3.9
1965	5.0	0	1.0	5.0	9.0	10.3	16.5	30.3	18.0	5.0

factors included multiple chronic, disabling and degenerative diseases; malignant diseases and the so-called autoimmune or collagen diseases; prolonged therapy of these and other conditions with immunosuppressive and corticosteroid drugs; the use of large doses of antimicrobial agents—often multiple agents, given simultaneously—particularly over long periods; the increasing use of endoscopies, intubations, tracheostomy tubes, indwelling venous and urethral catheters; resort to long operations of increasing complexity involving much manipulation and instrumentation, and insertion of foreign substances, particularly in cardiac surgery and organ transplantations. All of these, and others, appear to predispose to infections, sometimes recurrent, with organisms which are increasingly resistant to

more and more of the antimicrobial agents that are commonly used. Data on the role of these factors will not be presented here. I have recently reviewed the changing antibiotic resistance patterns among the bacteria encountered over the period of this study (FINLAND, 1971), so I shall not consider that aspect here.

Bacteremia Due to Specific Organisms

In addition to changes in age distribution of the patients with bacteremia the major changes that followed the introduction and widespread use of the succession of antibacterial agents was the altered incidence of the different etiologic bacteria causing the invasive infections. Notable has been the relative stability of the frequency with which certain bacteria have been found in bacteremic patients each year; outstanding in this respect have been the pneumococci and the viridans group (alpha hemolytic, and gamma or nonhemolytic) of streptococci. Over the same period, the occurrence of other organisms, notably group A beta hemolytic streptococci declined sharply; still others fluctuated in incidence (*Staphylococcus aureus* being the most striking example), whereas the group of "enterobacteria", which includes the enterococci and the gram-negative bacilli—other than the usual enteric pathogens, namely *Salmonella* and *Shigella*—increased steadily in numbers and in relative incidence, and new species appeared and assumed importance as causes of serious bacteremic infections over the 35 year period of the study. It is therefore of some interest to summarize the changes in the numbers and relative incidence of cases and deaths among patients with bacteremia due to the more important of the specific bacterial species.

Diplococcus pneumoniae

Pneumococcal pneumonia was the most frequent of the serious conditions encountered on the medical wards of the Boston City Hospital during about half of each year when I first went there as an intern in 1927, and it remained so until well into the antibiotic era. Next to the advanced age of the patient, the demonstration of pneumococcal bacteremia was the most serious prognostic feature in the cases of pneumonia. In a study of the clinical significance of bacteremia in the cases of pneumococcal pneumonia observed at that hospital between November 1929 and May 1935 (TILGHMAN and FINLAND, 1937) the mortality rates in all cases were shown to rise steadily with increasing age—from 10% in the 10 to 19 years old to about 90% in those 70 years of age or older. The corresponding case-fatality ratios for the nonbacteremic patients ranged from about 7% to nearly 80%, whereas in those with positive blood cultures they ranged from 27% to 100%. Within each decade of age, except in the "70 and over" category, the case-fatality ratio was $2\frac{1}{2}$ - to 6-fold greater in bacteremic than in nonbacteremic patients. The proportion of patients with pneumonia in which bacteremia was demonstrated also rose steadily with advancing age, from 15% in those 10 to 19 years old to nearly 60% in the seventh decade of life, but it was slightly lower in those over 70 years old.

The present study includes patients with pneumococcal bacteremia from all causes (pneumonia, meningitis, peritonitis, and "cryptogenic" cases or those without demonstrable foci) and, although pneumonia accounted for the great majority of the cases, the deaths included a large proportion of others, notably

those with meningitis. Over the 30 years of the study there were moderate fluctuations in the numbers of patients with pneumococcal bacteremia seen during each of the 10 selected years, but the average and median numbers were about 100 cases annually.

In 1935, pneumococcal bacteremia accounted for slightly more than one-third of all bacteremic patients observed in the hospital and nearly one-half of all the deaths in patients with bacteremic infections, and the case-fatality ratio among these bacteremic pneumococcal infections was 78%. Following the successive introduction of effective sulfonamide drugs and penicillin, the proportion of all bacteremic infections that were due to pneumococci dropped to 21%; that of the deaths in these bacteremic cases dropped to 18% and the case-fatality ratio dropped first to 36% under the impact of the sulfonamides, and then to 21% after penicillin came into use. After 1947, the proportion of the bacteremic patients due to *Pneumococcus* stabilized at about 14% of all bacteremic patients and at about 10% of the deaths among those patients, with the case-fatality ratio in the patients with pneumococcal bacteremia hovering around 25%.

Beta-Hemolytic Streptococci (Group A)

The organism which ranked second in importance, from the point of view of mortality, among bacteremic patients, was the beta-hemolytic streptococcus. In the earlier years some of the strains were presumed and others proved to be group A, whereas during most of the study nearly all were definitely identified as group A. KEEFER, INGELFINGER and SPINK (1937) analyzed 246 cases of beta hemolytic streptococcal bacteremia that occurred at Boston City Hospital, all but a few of them before the introduction of sulfonamides. The mortality in all these cases was more than 70%. The incidence of bacteremia, and the case-fatality ratio in those cases rose steadily with increasing age of the patients.

In 1935, the first year of the present study, beta hemolytic streptococcus was the causative organism in 18% of all bacteremic infections and nearly one-fourth of all deaths from such infections at this hospital. These proportions dropped sharply after the introduction and use of the sulfonamide drugs to 4% of all bacteremic cases and 7% of the deaths in 1941. After that, the decline continued until 1955 when group A beta hemolytic streptococcus accounted for less than 1% of all bacteremic infections and there were no deaths due to this organism in that year. Subsequently the number of patients and deaths has been rising steadily until 1965, when 4.4% of all bacteremic patients and 5% of deaths from all invasive infections were due to this organism. The case-fatality ratio since 1961 has ranged from 31% to 45%, the large majority of the fatal cases being recognized late in the disease or as a terminal event in serious chronic diseases.

Staphylococcus aureus

Ranking third among the causative organism of serious bacteremic infections at the start of this study was *Staphylococcus aureus*. An analysis of 122 cases of bacteremia due to *Staphylococcus aureus* which occurred at this hospital between 1934 and 1941 was published by SKINNER and KEEFER (1941). The mortality in

those cases was 82% and nearly all of the survivors were under 40 years old. The largest number of patients were in the second decade of age; the incidence declined, but the case-fatality increased with advancing age.

In 1935, the first year of the present study, *Staphylococcus aureus* accounted for 22% of all bacteremic patients and 18% of all deaths among such patients. There was an epidemic of staphylococcal pneumonia complicating influenza A in 1941, when there were 145 patients and 43 deaths due to bacteremic staphylococcal infections. Excluding that year, there was a steady increase in the number of patients with staphylococcal bacteremia from 66 in 1935 to 225 in 1957; after that the number dropped appreciably, but there were still 192 cases in 1965. The proportion of all patients with bacteremic infections that were caused by *Staph. aureus* rose to nearly 40% in 1955 and 1957, and the same was true of the proportion of deaths among all bacteremic infections; these proportions dropped back to 18% and 19% respectively by 1965. The case-fatality ratio among the patients with bacteremia due to *Staph. aureus* dropped from 47% in 1935 to 30% in 1941 and to 19% in 1947, but after that year it rose steadily to 48% in 1961 and then dropped again to 35% in 1956.

Viridans Streptococci

The number of patients with bacteremia due to *Streptococcus viridans*, in which are included both the alpha hemolytic and the gamma streptococci, varied only moderately and irregularly in the different years of the study, around a mean and median of 49 patients for the 10 selected years. The pathogenic significance of these organisms is often in question, except in well-defined clinical cases of subacute bacterial endocarditis, because these are common as transient invaders of the blood stream, generally from the mouth, in patients with poor dental hygiene and periodontal infections. Although patients with proved endocarditis were included, they constituted a minority each year, but all of the patients who were included had positive blood cultures for these organisms on repeated occasions, were febrile, or had some other focal lesion such as meningitis, pneumonia or empyema from which the same organism and no other significant pathogen was recovered. Some of those patient may have been in an early stage of *endocarditis lenta* which was lacking the classical peripheral signs and which, in those who recovered, may have responded favorably to therapy with effective antibiotics—usually penicillin, alone or with streptomycin, and thus that diagnosis could not be fully confirmed.

In 1935, the patients with bacteremia due to *Streptococcus viridans* constituted about 15% of all the bacteremia patients and 12% of the cases that were fatal. This proportion declined steadily until 1953 to 6% of all bacteremic patients and about 3% of the cases that were fatal, and remained at that level with some aberrations in 1 or 2 of the subsequent years of the study. The case-fatality ratio in these cases was 48%, in 1935, dropped in successive stages to 11% by 1951, but varied irregularly between 13% and 27% after that year.

Enterococcus (Group D Streptococcus)

Enterococcus, generally identified also as group D streptococci, and which included mostly *Streptococcus zymogenes*, *Str. liquefaciens*, *Str. faecalis* and its