A CLINICAL EVALUATION OF POSITIVE BLOOD CULTURES AND BACTEREMIA

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SYNOPSIS

Over a 6 month period 218 blood cultures were reported as "positive" in 215 patients. There were 67 episodes of clinically confirmed bacteremia in 66 patients. We estimated the overall frequency of bacteremia to be 9% of all blood cultures taken. In the 66 patients with bacteremia the mean age was 53.5 years with a female predominance. Seventeen (26%) patients died and 17 (26%) patients developed septic shock. Most patients were above 50 years of age and had either ultimately fatal or non fatal underlying disease states. There were few patients with rapidly fatal underlying disease (7%), unknown source of sepsis (16%) or nosocomial bacteremia (28%). Patients with nosocomial bacteremia had a high Case Fatality Rate (CFR) (53%). Sixty-four percent of the patients had gram negative bacteremia, 30% had gram positive bacteremia and 6% polymicrobial bacteremia. Escherichia coli was the most common infectious agent and Acinetobacter calcoaceticus the most important nosocomially acquired agent. Early use of appropriate antibiotics reduced the CFR by half.

INTRODUCTION

Bacterial blood stream infection is a major example of serious bacterial infections in general. This is particularly true of aerobic gram negative bacteremia acquired from the hospital environment (1, 2). Despite the use of more potent antimicrobial agents in the last forty years bacteremia had increased in frequency and continues to be plaqued by a high case fatality rate of 20 — 50% (2, 3, 4, 5, 6).

Prognosis is heavily biased by the patient's underlying illness, but the overwhelming concern for the physician faced with a seriously ill patient with possible bloodstream infection is the identification of the source and species of infective agent and prompt institution of the appropriate antimicrobial agent (1, 5, 6).

A positive blood culture remains the sine qua non for the diagnosis of bacteremia. Blood cultures are often taken from patients with suspected severe bacterial sepsis but true bacteremia is not always confirmed bacteriologically. Other investigations have shown that the frequency of confirmed bacteremia is about 10% of all blood cultures obtained (7).

In Singapore, the Bacteriology Laboratory performs 15,000 to 20,000 blood cultures yearly and reports about 30% as "positive" (8). Only a proportion of these reported "positive" represent true bacteremia after all possible contaminants have been excluded.

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We have prospectively studied over a six month period all patients who had "positive" aerobic blood cultures to correlate the growth of potential pathogens from the blood with epidemiological and clinical characteristics of patients with systemic sepsis. We have also evaluated the clinical outcome of these patients and the use of antibiotics.

MATERIALS AND METHODS

Over a six month period from June to December 1982 all patients with reported positive blood cultures were studied.

Multiple positive cultures taken from the same patient in the same day were considered a single "positive" episode whether they grew single or multiple organisms.

Cultures were considered "contaminated" if:—

1. Well known skin contaminants were grown e.g. bacillus and diptheroids,
2. Another cause was found for the "septic" illness e.g. malaria, collagen vascular disease or tuberculosis and
3. The clinical cause was not consistent with bacteremia.

The "confirmed" group was classified into 3 categories based upon severity of underlying disease (5):—

1. Rapidly fatal underlying disease: patients with acute myeloid leukemia or chronic myeloid leukemia in blastic crisis.
2. Ultimately fatal underlying disease: patients with underlying diseases which were of sufficient severity to appear likely to prove fatal within the next 5 years and
3. Non fatal underlying disease.

Nosocomial infections were identified as those occurring after 5 days in hospital unless they originate from a source of infection noted previously (9).

Shock was defined as sudden circulatory decompensation with mental obtundation, tachycardia, hypotension and oliguria.

Death was considered the result of bacteremia if it occurred in the presence of clinical sepsis unless another potentially lethal event was present.

Antibiotic use was evaluated with regard to empiric use before definitive bacteriological data within 24 hours of suspected sepsis. "Inappropriate" therapy was defined according to invitro susceptibility testing. If no antibiotics were given in "confirmed" bacteremia therapy would also be considered "inappropriate".

RESULTS

During the six month period of the study 218 cultures were reported "positive" in 215 patients. There were 151 "contaminants" and 67 (30%) "confirmed bacteremia". These 67 episodes occurred in 66 patients. Figure 1 illustrates our estimate of the frequency of true bacteremia in the population who had blood cultures taken. Since our Bacteriological Laboratory reports on the average 30% of all blood cultures taken annually as "positive", and we found 30% of these "positive" cultures to be true bacteremias, overall, the frequency of bacteremias must be about 9%.

There were 66 patients with true bacteremia. Their age ranged from 17 years to 85 with a mean of 53.5 years. There was a predominance of women of 1.4:1.

Overall 17 patients (26%) died as a direct result of bacteremia. There were 17 patients who experienced the Shock Syndrome out of which 13 (76%) died. Ten out of 12 patients with gram negative bacteremia who developed shock died.

Figure 2 indicates the incidence of bacteremia and death, comparing age and death, distribution by decades. Majority of patients were above 50 years of age.

Table 1 lists the number of patients in each category of underlying disease against the case fatality rates (CFR). The majority of patients were in the last two categories and the highest CFR occurred among those with ultimately fatal underlying disease. They were mainly patients with advan-

Table 1: Distribution of Categories of Underlying Disease in Relation to Case Fatality Rates in Bacteremia

Categories of Underlying Disease	Patients	Deaths (%)
Rapidly Fatal	4	1 (25)
Ultimately Fatal	31	14 (45)
Non Fatal	31	2 (7)
Total	**66**	**17 (26)**

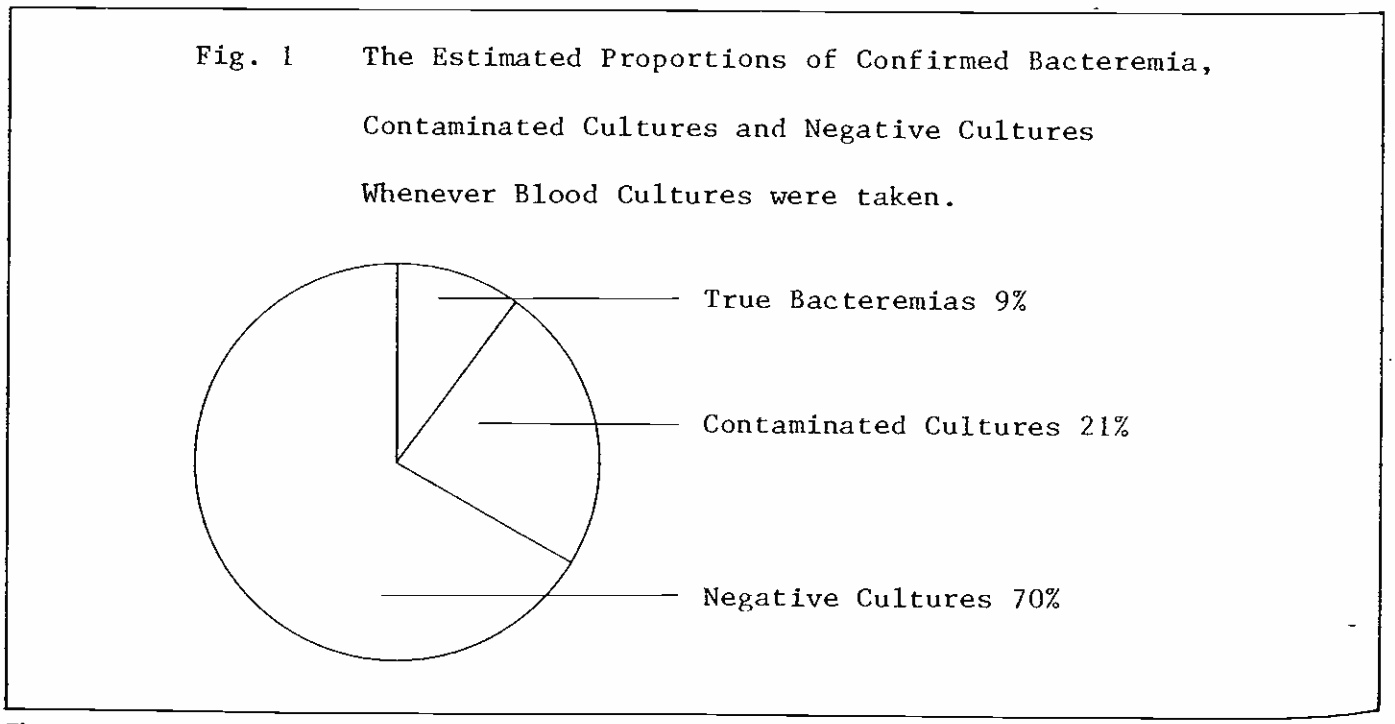

Figure 1

Fig. 2 Incidence of Bacteremia and Deaths Comparing Age Distribution in Decades*.

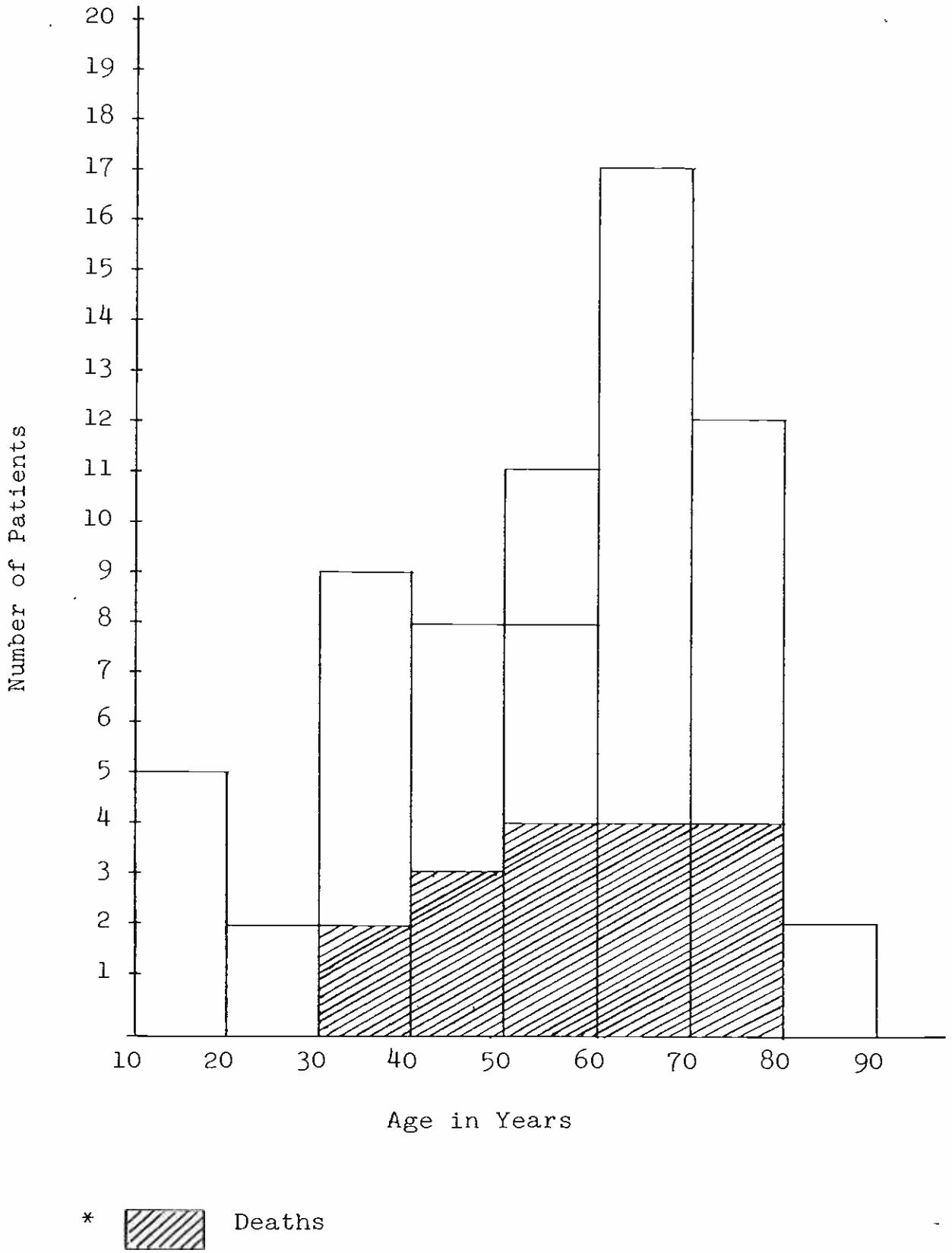

Figure 2

ced malignancies. Very few patients in the non fatal underlying disease category died. There were only 4 patients with rapidly fatal underlying disease with a single death.

Table 2 lists the episodes of bacteremia in relation to sources of infection and CFR. Episodes of infective endocarditis and enteric fever were considered separately. In only 11 (16%) of the episodes, the site of infection could not be identified. The urinary tract was the most common source of bacteremic sepsis followed by the respiratory tract, the gastrointestinal tract and skin in that order. There was one patient with septicemia from a dental abscess. There were five patients with infective endocarditis and salmonella septicemia each. The CFR was lowest in association with a urinary source of bacteremia but CFR in patients with associated respiratory, skin and gastrointestinal tract sepsis appeared relative high (30 — 45%) in comparison. On the other hand one has to consider that the numbers involved were small and severity of underlying disease had not being accounted for.

The patient with infective endocarditis died from a massive intracranial hemorrhage following a ruptured mycotic aneurysm. The single death in salmonella bacteremia occurred in a patient with blastic crisis before appropriate antibiotics were exhibited.

Table 3 compares the CFR and relative frequencies in nosocomial and community acquired infections. There were 19 episodes of nosocomial bacteremia with a CFR of 53%. There were 48 episodes of community acquired bacteremia with a CFR of 15%. Eight out of ten deaths in nosocomial bacteremia were caused by gram negative organisms, the most important organism being Acinebacter calcoaceticus which occurred four times.

Table 4 illustrates the relative frequencies of etiologic agents identified. There were 71 organisms identified in 67 episodes of bacteremia. Four episodes of bacteremia were polymicrobial with two organisms each. This constitutes 6% (4/67) of polymicrobial bacteremias in this report. Twice as many times gram negative organisms were reported in comparison to gram positive organisms. Staph. epidermidis bacteremia occurred in two patients with severe neutropenia and a skin source of sepsis. A young man with pyogenic abscess of his liver developed flavobacterium bacteremia, his liver abscess was not aspirated. A middle aged man with liver cirrhosis and ascites developed peritonitis and enterococcocal (group D streptococcus) bacteremia.

Table 5 relates the episodes of bacteremia to etiologic agents and CFR. The CFR from gram positive, gram negative and polymicrobial bacteremias were 15%, 28% and 50% respectively. For specific etiologic agents, CFR were highest in pseudomonas bacteremia (67%) followed by Acinebacter calcoaceticus and the klebsiella-enterobacter group. Escherichia coli bacteremia, although the most common had the lowest CFR (16%). They were mainly community acquired and associated with urinary infections in healthy women. On the other hand, all the patients with pseudomonas and Acinetobacter bacteremia had either a nosocomial infection or severe underlying illness.

Table 6 relates the appropriateness of antibiotic use to the outcome of bacteremia. It will be noted that in almost half of the episodes of bacteremia, empiric use of antibiotics were judged "inappropriate" according to in vitro sensitivity data. Appropriate and early use of antibiotics reduced the CFR by half. Seven out of the 11 patients who died in the "inappropriate" group had infections with organisms which were resistant to either ampicillin or gentamicin or both, the two antibiotics most commonly used in empiric therapy. The four other patients in the "inappropriate" group who died did not receive antibiotics within 24 hours of onset of sepsis. There were six patients who died despite receiving early and appropriate antibiotics. They were all critically ill with severe underlying diseases although we felt that sepsis was the terminal event.

DISCUSSION

In general we found that only in one out of ten instance (9%) could we expect to bacteriologically confirm bacteremia whenever blood cultures were taken from a patient. Our estimate of 9% overall bacteremic rate in all blood cultures taken is partly inferential since the Bacteriology Laboratory reports positive results in about 30% of all aerobic blood cultures taken and we found that only 30% of these "positive" cultures represented true bacteremias clinically (8). This concurs with the frequency of documented bacteremias in other studies (7).

Table 2: Sources of Bacteremia in Relation to Case Fatality Rates

Sources of Infection	Episodes (%)	Deaths (%)
Unknown	11 (16)	2 (18)
Urinary	16	2 (13)
Chest	11	5 (45)
Gastrointestinal	10	3 (30)
Skin	8	3 (38)
Dental	1	0
Infective Endocarditis	5	1
Salmonella	5	1
Total	**67**	**17**

Table 3: Distribution of Nosocomial and Community Acquired Infection in Relation to Fatality in Bacteremia

	Episodes (%)	Deaths (%)
Nosocomial	19 (28)	10 (53)
Community	48 (72)	7 (15)
Total	**67**	**17**

Table 4: Etiologic Agents in Bacteremia

Etiologic Agents	Frequency
Esch. coli	19
Klebsiella-enterobacter	12
Acinetobacter	7
Pseudomonas	4
Proteus	1
Salmonella	5
Subtotal	**58**
Staph. aureus	6
Alpha-strept.	8
Beta-strept.	3
Pneumococcus	2
Staph. epididermidis	2
Strep. group D	1
Flavobacterium	1
Subtotal	**23**
Total	**71**

Table 5: Relation of Bacteremia episodes to Etiologic Agents and Case Fatality Rates

Etiologic Agents	Episodes	Deaths (%)
Esch. coli	19	3 (16)
Klebsiella-enterobacter	9	3 (33)
Acinetobacter	6	3 (50)
Pseudomonas	3	2 (67)
Proteus	1	0
Salmonella	5	1
Total gram negative	43 (64)	12 (28)
Total gram positive	20 (30)	3 (15)
Polymicrobial	4 (6)	2 (50)
Total	**67**	**17**

Table 6: Relation of Appropriate Antibiotic Therapy to Case Fatality Rates

	Episodes	Deaths (%)
Inappropriate	32	11 (34)
Appropriate	35	6 (17)
Total	**67**	**17**

We studied bacteremia in a very selected group of patients i.e. adult in-patients from general medical wards. We examined only episodes of aerobic bacteremia but included both gram positive and negative isolates. Since this is a prospective study we feel that it reflects an accurate picture of the spectrum of aerobic bacteremia encountered in general medical practice.

Our observed CFR of 26% in all bacteremic patients compares favourably with the 30% CFR rate reported in the classic bacteremia at Boston City Hospital Study by Maxwell Finland who analysed data up to 1972 (1). We have included only deaths directly related to bacteremia but the other major determinants of outcome have to be considered i.e. age, severity of underlying disease, site and circumstance of sepsis, organisms involved and antibiotic treatment (5, 6).

Underlying illness had been well established as a major prognostic factor in gram negative bacteremia since the observations of McCabe and Jackson in 1962 (5). Most of our patients were equally distributed into the ultimately fatal and non fatal disease groups. We observed major difference in CFR between these two categories of patients with most of the deaths occurring in the ultimately fatal group (Table 1). We saw only a small number of patients in the rapidly fatal disease category with a relatively low case fatality rate which is against the general experience (5, 6, 10).

Comparatively few of our patients had bacteremia from unknown sites or in the nosocomial setting (Tables 2 and 3). This is probably because only a small number of patients are severely immune compromised when they are at risk of developing bacteremia without an obvious source of infection. We did not study patients in the intensive care areas or surgical wards where we would expect nosocomial infections to be more prevalent (11). Nevertheless, we found nosocomial bacteremia to be particularly virulent with a CFR of 53% (10/19). They were mainly from gram-negative-rod infections. Acinetobacter calcoaceticus accounted for half (4/8) of the deaths associated with nosocomial gram negative bacteremia. Acinetobacter calcoaceticus is our major single nosocomial bacterial species and we feel that it may rapidly become the major causative agent of nosocomial infection in the Singapore General Hospital (12).

In the antibiotic era gram negative organisms have emerged as major pathogens of bacteremia particularly in hospitalised patients with immune deficiency given broad spectrum antibiotic "cover". This increasing frequency of occurrence and fatality of gram negative bacteremia, first observed in the 1950's, have continued unabated into the 1970's, despite the increasing use of potent antibiotics and supportive techniques (1, 2, 6). We found gram negative organisms to be the predominant group of organisms causing bacteremia. Our observation of greater frequency of acinetobacter than pseudomonas bacteremia is against the general experience (1, 5, 6, 10). This may reflect a high "endemicity" of nosocomial acinetobacter infection in our wards rather than an "epidemic" common-source outbreak since the patients with acinetobacter bacteremia were from different wards and developed sepsis at different times (2).

Septic shock is the most feared complication of gram negative bacteremia. Shock developed in 12 patients (28%) out of which 10 died (83%). This is an extremely high mortality when compared to other reports (6, 10). Despite improved understanding of the multiple deleterious effects of gram negative endotoxin on the patient's immune, hemostatic, hemodynamic and metabolic systems no treatment modality has been found to unequivocally reduce mortality once established septic shock occurs (13, 14, 15). There is great controversy about the efficacy of corticosteroids in septic shock and despite encouraging results from a large controlled study the issue appears unresolved (16, 17). The success of an antiserum against the lipid A moeity of endotoxin have been proven in a large clinical trial and it is an important breakthrough (18).

Early use of appropriate antibiotics had been shown to halve the CFR in some reports (6, 10). We found very similar results in our study (Table 6). Nevertheless, longitudinal data from the Boston City Hospital reveal that the mortality rate in 1965 was nearly the same as that observed in 1941 before penicillin first became available (3).

In Figure 3 we have charted mortality rates from bacteremia per 100,000 mid year population from 1940 to 1980 according to the Registry of Births and Deaths for the Republic of Singapore. There was a marked decline in mortality rates in the 1950's and early 1960's from widespread use of sulphonamides, penicillin, streptomycin and the tetracyclines (20, 21, 22). This was followed by a steady rise in mortality rates in the late 1960's to a peak in 1974. This trend seemed to have reversed slightly in the last 6 years with the intensive use of ampicillin and gentamicin (23). Yet in 1980 the mortality rate remains higher than in the years immediately after 1945. Most of the patients who die from bacteremia in our study have acquired infectious agents resistant to gentamicin or ampicillin.

Despite the many pitfalls in the use of Death Certificate data to evaluate infectious disease we feel that the trends observed in Figure 3 reflect in general the complex interplay of multiple host and bacterial factors in a milieu of more intense and often indiscriminate antibiotic use. It remains to be seen how the newer aminoglycosides, cephalosporins and semi-synthetic broad spectrum penicillins will affect the changing ecology of bacterial blood stream infection.

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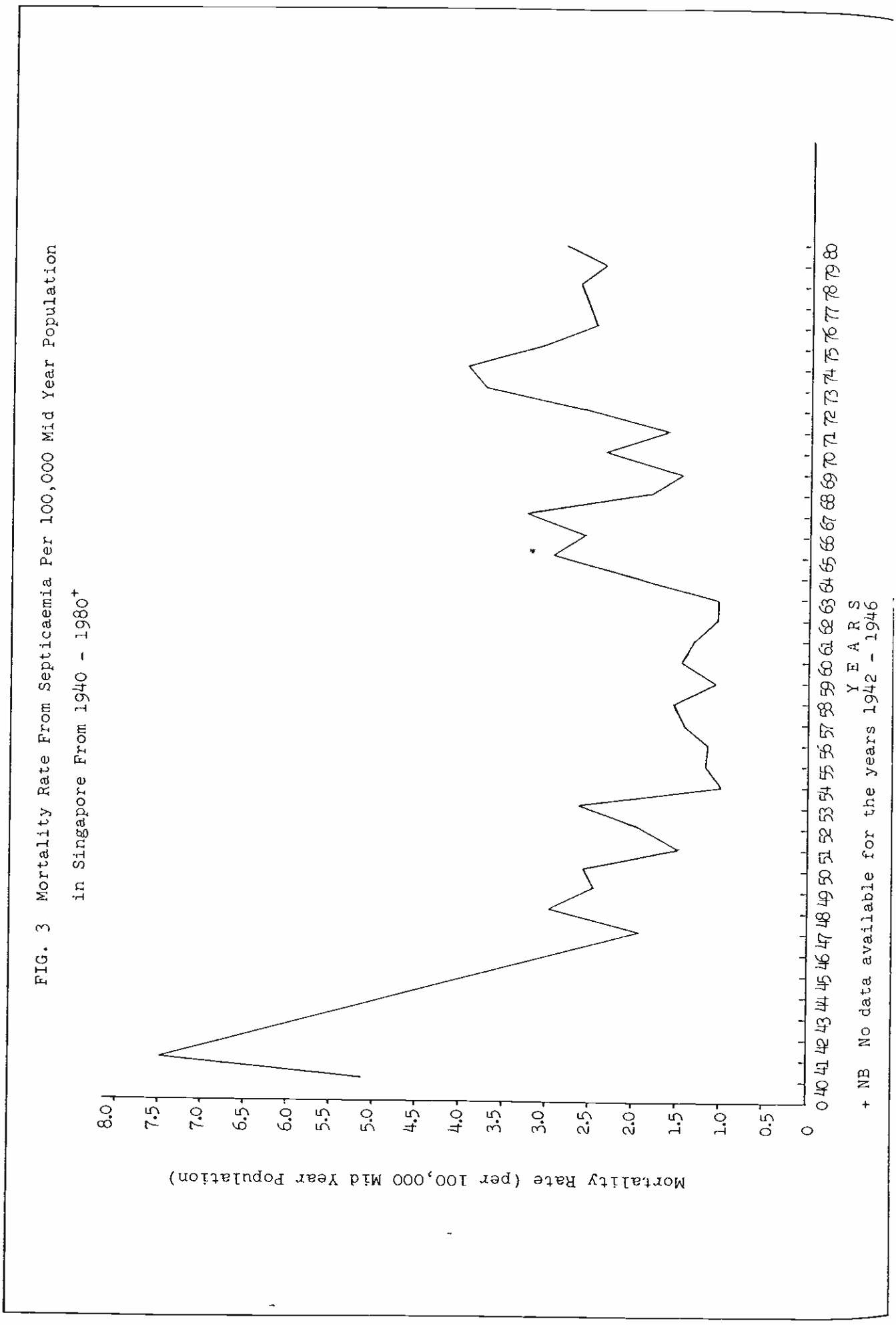
FIG. 3 Mortality Rate From Septicaemia Per 100,000 Mid Year Population
in Singapore From 1940 - 1980+
Mortality Rate (per 100,000 Mid Year Population)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
0 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
Y E A R S
+ NB No data available for the years 1942 - 1946

Figure 3

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