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Some bacteraemias encountered in hospital practice

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SYNOPSIS This is a retrospective study of the results of 4,642 blood cultures taken from 2,190 patients from 1960 to 1967 in one London hospital. The results suggested that an increased incidence of bacteraemias at this particular hospital was mainly due to the increase in the number of patients having blood cultures. Some of the bacteraemias were terminal or transient and probably of doubtful clinical significance.

During the last eight years the Royal Free Hospital laboratories received four times as many requests for blood culture as in the previous decade, in spite of the loss in 1962 of 60 beds admitting cases of infectious disease and of septic abortion. The total admissions for this period were 104,239 rising from 12,083 yearly in 1960 to 14,990 in 1967. The number of bacteraemias per 1,000 admissions was 2·4 in 1960 rising to 5·9 in 1965. This pointed to a real increase in the incidence of bacteraemias comparable with the experience at Hammersmith Hospital between 1958 and 1965 described by Watt and Okubadejo (1967).

This is a general hospital but also admits large numbers of patients with diseases of the liver and biliary tract (nearly 700 cases of cirrhosis admitted during the period). From 1962 increasing numbers of patients with acute and chronic renal failure were admitted and readmitted for dialysis (15,000 dialyses).

The possible causes of the increased incidence of bacteraemias are reported in this paper, which also examines the significance of the findings in this particular hospital.

Method of Blood Culture

Each blood sample (approximately 10 ml) was distributed into three bottles containing 50 ml broth. Two bottles contained brain-heart infusion with agar (Difco) and one contained tryptose broth (Difco), the latter being incubated with CO_2. Liquoid was not normally used. The agar in the broth prevented coagulation of the blood. The dilution afforded by the broth was considered sufficient to overcome the effect of the usual therapeutic doses of antibiotics if these had already been given. Penicillinase was used in cultures from patients being treated for bacterial endocarditis with penicillin. After overnight incubation subcultures were made from one brain-heart infusion bottle in triplicate aerobically, anaerobically, and with CO_2. The tryptose bottle was subcultured after 36 hours. Thereafter one or other of these two bottles was subcultured every other day, but the spare brain-heart infusion bottle was not opened until an organism had been isolated, or until the final subculture of the other two. The cultures were usually kept for two weeks, except those from patients suspected of having bacterial endocarditis, which were kept for three weeks. At a branch laboratory the volume of broth used was reduced to 25 ml per bottle in 1963, which did not appear to have any effect on the number of bacteraemias detected.

A pure growth at first subculture from two or three bottles was accepted as positive for most organisms other than the common skin commensals and aerobic spore-bearing bacilli. Growth from one of three bottles was also obviously acceptable as positive for organisms such as

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Neisseria meningitidis, *Streptococcus pyogenes*, *Salmonellae*, and *Bacteroides spp.* Isolates of *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus faecalis* from only one bottle were reported with circumspection as possible transient bacteraemias or contaminants and were excluded from the positive blood cultures described here.

The samples were usually taken by house officers or medical students, which explains the absence of pour plates. Although they were advised to take three samples within a few hours of clinically diagnosed bacteraemia, with the exception of cases of bacterial endocarditis when multiple samples were encouraged, there was no general consistency in numbers or timing.

Patients

Four thousand six hundred and forty-two cultures were taken from 2,190 patients. Although the requests increased from approximately two in 1960 to more than three per patient in 1967, 1,241 patients had only one blood culture. The other 949 had two or more, of which 357 patients had samples taken within 36 hours after admission or onset of symptoms in hospital. The remainder had two or more taken during one to four days, or irregularly.

Ninety-one patients were admitted more than once. Patients with hepatic cirrhosis admitted in precoma had routine blood cultures, which were also usually taken from patients with fever after surgical operations on the biliary and portal systems. Routine blood cultures were also taken from patients being treated by exchange blood transfusion, and until recently from all patients treated by haemodialysis.

Results

THE INCIDENCE OF BACTERAEMIA

Two hundred and forty-eight bacteraemias (403 positive samples) were detected in 225 patients (124 males and 101 females). Seventeen patients had two or several bacteraemias with different bacterial species (42 bacteraemias). Forty-four other patients may have had transient bacteraemias, but because the organisms may have been contaminants these have been excluded. One hundred and fifty-four cultures were contaminated with skin commensals or aerobic spore-bearing bacilli and were discarded early.

	Patients Having Blood Cultures	*Number of Blood Cultures*	*Number of Bacteraemias*	*Percentage of Patients with Positive Cultures*	*Number of Bacteraemias per 1,000 Admissions*
1960 to 1963	657	1,416	93	14·1	3·3
1964 to 1967	1,533	3,226	155	9·8	3·6
Total	2,190	4,642	248	11·3	3·5

Table I *Comparison of results of blood cultures taken at the Royal Free Hospital between 1960 and 1963 and 1964 and 1967*

Table I shows the results for two successive four-year periods. Although the difference in the total admissions between the two periods was only 2,247, more than twice as many patients had blood cultures in the last four years. The number of bacteraemias was increased if related to the number of admissions but decreased if related to the number of patients having blood cultures. The higher percentage of patients with positive cultures between 1960 and 1963 was due to the increased number of admissions of patients with renal disease in 1963, when the number of bacteraemias per 1,000 admissions was 10·6. Eighteen per cent of these patients had positive blood cultures, pointing to a real increase in incidence clearly related to the disease and treatment.

Table II shows the results at one branch hospital, which suggest that the conventional method of relating bacteraemias to admissions to obtain a figure for incidence may be misleading. Nearly twice as many patients had blood cultures between 1964 and 1967 than between 1960 and 1963, and there were twice as many bacteraemias. At this branch the clinical material was not changed by any influx of special patients.

In Table III the patients are divided into four groups. Those in group I usually had a blood culture taken soon after admission or onset of symptoms in hospital. From the results for group II it appears superficially that the more samples taken during the 36 hours after onset of symptoms the more positive cultures will be obtained. Table IV, however, shows that this was not so. In group II the average number of cultures per patient was three, but in groups III and IV it was four.

Bacteraemias were found in nearly 30% of group II patients, however, compared with nearly 6% in group III. The group II patients were not selected by one or two clinicians who were skilled in the clinical diagnosis of bacteraemia, but represented a cross section of hospital patients in the care of many different people. It is clear that timing was the important factor, as shown in Table IV.

The first two blood cultures always yielded the greatest number of positive results, the first yielding the higher of the two. Nearly 8% of second samples were positive when the first were negative. Four new positive cultures (nearly 3%) were nevertheless obtained from third samples. Only one new positive culture was obtained from third samples taken 36 hours after the first.

Fourth and all later samples yielded eight new positives. Five were terminal isolates of *E. coli*. Of the remaining three, one patient with low-grade pyrexia had had nine negative cultures. He was given corticosteroids for an obscure allergy, and

Year	Admissions Served	No. of Patients with Blood Cultures	Number of Cultures	Number of Bacteraemias	Number of Bacteraemias per 1,000 Admissions	Percentage of Patients with Positive Blood Cultures
1960	4,546	91	161	11	2·4	12·0
1961	4,863	101	218	10	2·0	9·9
1962	4,873	109	207	14	2·9	12·8
1963	5,642	162	343	17	3·2	10·5
Total	19,925	463	929	52	2·6	11·25
1964	5,728	216	418	28	4·9	12·8
1965	5,397	282	511	32	5·9	11·3
1966	5,522	204	465	18	3·5	8·8
1967	5,625	239	595	22	3·9	9·2
Total	22,272	941	1,989	100	4·5	10·6
Grand totals	42,197	1,404	2,918	152	3·6	10·5

Table II *Change in the incidence of bacteraemias at a branch hospital during eight years*

Group	Number of Blood Cultures per Patient	Number of Patients	Number of Bacteraemias	Total Number of Blood Cultures	Percentage of Bacteraemias per Number of Cultures	Percentage of Patients with Positive Cultures
I	One	1,241	114	1,241	9·2	9·2
II	Two or more taken within 36 hours	357	110	1,015	10·0	29·8
III	Two or more during 1 to 4 days	274	16	1,144	1·4	5·8
IV	Two or more irregularly	318	8	1,242	0·65	2·5
Total		2,190	248	4,642	4·6	11·3

Table III *The number of blood cultures taken per patient and the numbers of positive cultures*

Number of Blood Cultures Compared	Time from Onset of Symptoms	Number of Patients	Percentage of Positive Cultures	Total of Positive Cultures	Percentage of Positive Cultures			
					First Sample	Second Sample	Third Sample	Fourth Sample
Two[1]	< 36 hrs	210	33	69	25·2 (53)	17·9 (45)	—	—
	> 36 hrs	270	17	46	12·6 (34)	8·9 (24)	—	—
Three[2]	< 36 hrs	147	28	41	21·2 (31)	19·8 (29)	14·3 (21)	—
	> 36 hrs	225	16·4	37	15·0 (14)	12·8 (13)	4·9 (7)	—
Four[3]	< 36 hrs	56	21·4	12	17·8 (10)	10·7 (6)	5·35 (3)	3·6 (2)
	> 36 hrs	149[4]	23·5	35	17·5 (26)	14·8 (22)	12·1 (18)	8·8 (13)

Table IV *Comparison of positive results from first blood cultures with those of second or later samplings related to the time of onset of symptoms*

[1] 3·8% were positive at the first sample but negative at the second and 7·6% were positive at the second but not at the first.
[2] 2·7% were detected by the third sample which were previously negative.
[3] 3·9% were detected by the fourth sample or later sample which were previously negative (see above).
[4] This group of patients included five cases of bacteraemia who were positive on each occasion and five terminal bacteraemias.

a *Bacteroides sp.* was isolated from the tenth culture. Lancefield group F haemolytic streptococci were isolated from the seventh of 10 blood cultures of a patient with low-grade pyrexia and deep vein thrombosis. In neither case was the bacteraemia considered relevant to the clinical condition: no antibiotic treatment was given. The eighth patient was a child with sickle cell disease, known to have a bone abscess, from whom a *Salmonella sp.* was isolated from the fourth of four samples.

These findings suggested that the great increase recently in the number of blood cultures taken from some patients was only justified if an effort

was made to take the samples at short intervals within a few hours of onset of symptoms. With the exception of patients suffering from bacterial endocarditis, few of the bacteraemias were sustained. The chance of getting a positive culture decreased sharply after 12 hours.

THE PATIENTS WITH BACTERAEMIAS

Sixty-eight patients (74 admissions) were admitted with bacteraemia. One hundred and fifty-seven patients (174 bacteraemias) had bacteraemic episodes during admission. Only 30 were normally healthy people before admission. These included the cases of puerperal and postabortion sepsis, osteomyelitis, enteric fever, meningococcal septicaemia, five cases of pneumococcal pneumonia, and one of severe burns. Table V shows that a third of the patients had diseases of the liver or biliary tract, including the nearly 11% who had earlier or recent operations on the portal and biliary systems. Together with cases of diseases of the kidney and urinary tract, these provided more than half the bacteraemias. The high incidence of bacteraemia in patients with hepatocellular and hepatobiliary disease has been reported by Tisdale and Klatskin (1960), McCabe and Jackson (1962), Maiztegui, Biegeleisen, Cherry, and Kass (1965), and by Jones, Crowley, and Sherlock (1967).

Septic foci

Seventy-five patients had a focus of infection (some having more than one) from which the same strain or species was isolated as that found in the blood. The foci yielded 82 isolates, 48 Gram-positive, 30 Gram-negative, and four mixed cultures. The septic foci were deep abscesses (10 cases), operation wounds and skin lesions (11), nasopharynx and sputum (19), pleural fluid (8), peritoneal fluid (5), bile (1), renal tissue (2), urine or infections of the genital tract (5).

Diagnostic and therapeutic procedures

Thirty-two bacteraemias followed procedures: radiological 2/>5,000, needle biopsies 4/450, haemodialyses 23/15,000, peritoneal dialyses 1/600, exchange blood transfusions 2/14. Jones *et al* (1967) reported that eight cirrhotic patients had bacteraemias following needle biopsies and intravenous catheterization with long tubes left *in situ*. Fourteen bacteraemias were in patients with intravenous catheters *in situ* and in eight the same organism was isolated at the site of insertion. Infections at arteriovenous shunt sites were the cause of seven bacteraemias which followed haemodialysis.

Immunosuppression

Fifty-four bacteraemias occurred in 43 patients receiving corticosteroids (28) or both corticosteroids and immunosuppressive drugs (15). Seventeen bacterial species were isolated from these patients, including common pathogenic organisms but also species infrequently isolated from the blood in other circumstances, namely, *Acinetobacter* (=Herellea, Mima) *Achromobacter*, and *Micrococcus spp* (Table VI).

Cross infection

S. aureus strains, of the same phage type in two or more blood cultures, were isolated from 16 patients in whom there was no obvious portal of entry. In seven instances strains of the same phage type had been isolated from other patients in the same ward. Five of the patients with staphylococcal bacteraemia were having treatment with corticosteroids or antimetabolites. Six patients with group A streptococcal bacteraemias were receiving either corticosteroids, antimetabolites, or both. In four instances cross infection was established by serotyping of strains.

Diseases	*Number of Patients*	*Percentage of Total*	*Number of Bacteraemias (248)*		
			Gram-positive	*Gram-negative*	*Mixed*
Pneumonia	17	7·8	13	4	
Bacterial endocarditis	12	5·3	12	0	
Puerperal or post abortion sepsis	10	4·4	5	5	
Osteomyelitis	5	2·2	5	0	
Diseases of the liver [1,2]	55	24·4	37	29	
Surgical operations, of biliary and portal systems	24	10·8	11	11	2
Diseases of the kidney: [2]	35	15·5	12	17	1
Surgical operations of the urinary tract	7	3·1	2	5	
Other surgical operations[1]	22	9·8	14	5	3
Diseases of the blood and lymphoreticular systems[2]	11	4·9	7	7	
Sickle cell disease[2]	2	0·89	3	2	
Miscellaneous	25		13	10	
Total	225		134	95	6

Table V *Diseases of patients with bacteraemias*

[1]In these disease categories eight patients had cancer and eight had had portocaval shunts.
[2]Seventeen patients in these categories had multiple bacteraemias (42).

BACTERIAL SPECIES ISOLATED FROM BLOOD CULTURES AND THEIR RELEVANCE TO CLINICAL CONDITION

The bacterial species isolated are shown in Table VI. In 50% of the bacteraemias the species isolated were clearly relevant to the clinical condition of the patient. In this group 92 patients improved on antibiotic and supportive therapy, but 32 failed to improve, of whom thirteen died of septicaemia, nine being moribund on admission. In the remaining 50% the relevance of some of the species isolated was conjectural because of their low order of pathogenicity, as in cases where viridans group streptococci and *Streptococcus faecalis* were isolated from patients with no evidence of bac-

Gram-positive Species	*Totals*	*Gram-negative Species*[1]	*Totals*	*Mixed*	*Totals*
Staphylococcus aureus	58	*Escherichia coli*	37	*E. coli and Streptococcus faecalis*	5
Streptococcus spp.		*Klebsiella spp.*	15	*Bacteroides sp.* and microaerophilic streptococcus	1
group A	7	*Pseudomonas spp.*	14		
group C	2	*Proteus spp.*	12		
group G	1	*Salmonella typhi*	2		
group F	3	Salmonella serotypes	3		
group H		*Achromobacter spp.*	3		
Streptococcus faecalis group D	18	Unidentified Gram-negative rods[2]	3		
Streptococcus spp. group M	1	*Hafnia alvei*	1		
Streptococcus viridans group	13	*Enterobacter cloacae*	2		
Microaerophilic streptococcus	1	*Haemophilus influenzae*	1		
Diplococcus pneumoniae	23	*Bacteroides spp.*	3		
Clostridium welchii	3	*Vibrio fetus*[3]	1		
Listeria monocytogenes	1	*Neisseria meningitidis*	1		
Candida albicans	1				
Yeasts	2				
Staphylococci, coagulase negative	3				
Micrococcus spp.	2				
Total	144	Total	98	Total	6

Table VI *Bacterial species isolated from blood cultures*

[1]In three instances of Gram-negative bacteraemia, an additional Gram-negative species was isolated at a second or later blood culture.
[2]*Acinetobacter spp.* according to definition of Steele and Cowan (1964).
[3]Darrell, Farrell, and Mulligan (1967).

terial endocarditis. In this group 82 patients improved on antibiotic and supportive therapy but 31 failed to improve. Eleven patients, including the two mentioned on p. 167, received no antibiotic treatment but improved. In both groups there were patients who improved although the antibiotic administered was not the most appropriate. Response to treatment with an appropriate antibiotic is not by itself a satisfactory criterion for asessment of the significance of the bacteraemia. Other criteria were also used in this instance, namely the presence of a septic focus, treatment with immunosuppressants, or recent diagnostic procedure.

Mortality

Sixty-three patients died soon after the bacteraemic episode but 40 more had died by February 1968. Seventeen died in hospital at a later admission, death being unrelated to the previous bacteraemia. Thirty-four were terminal bacteraemias, the severity of the preexistent disease being a sufficient cause for death. The bacteraemia in 28 patients was regarded clinically as a precipitating factor for the terminal illness. These patients were treated with an appropriate antibiotic and had had one or more negative blood cultures after treatment. Only two of the patients who died were previously healthy people; one patient had postabortion sepsis, and the other wound sepsis following Caesarean section.

Discussion

An increase in the number of bacteraemias found in hospital patients in recent years has been reported by Munroe and Cockroft (1955), Finland, Jones, and Barnes (1959), Faber, Jessen, Rosendal, and Eriksen (1960), McCabe and Jackson (1962), McHenry, Martin, and Wellman (1962), Maiztegui *et al.* (1965), and Watt and Okubadejo (1967). Most laboratories have been receiving more blood cultures every year. This, no doubt, is partly a reflection of the general increase in all laboratory tests. Apart from an awareness that certain groups of patients are particularly liable to have frequent bacteraemias, the indications for blood culture cannot be said to change very much. Assuming that requests to the laboratory are made on a rational basis, it might be supposed that more blood cultures are now being taken because more patients have clinically recognizable bacteraemia. Were this true, the number of bacteraemias sampled in every 100 patients might be expected to show an increase comparable with the figure obtained by relating bacteraemias to the number of admissions per annum. At this hospital, although more blood cultures per patient were taken every year, the number of bacteraemias increased in rough proportion to the number of patients sampled, and not to the total number of cultures. This certainly suggested not only a less selective clinical approach, but also a need for reappraisal of the method of blood culture.

The reliability of a blood culture method is difficult to assess in clinical practice because of the variability of the clinical material. The brain-heart infusion broth with agar used here supports the growth of fastidious organisms from small inocula. *B. pneumoniae* and streptococci, excluding *S. faecalis*, formed 21% of the isolates. It was disconcerting to find that nearly 30% of positive cultures were obtained from one group of patients (Table III) but only about 6% from a smaller group which had more cultures taken per patient. This can be accounted for only by the difference in the timing of the samples in relation to onset of the episode, unless indeed it was due to chance. In theory the more blood cultures taken within a few hours of onset of symptoms, the greater the chance of a positive result. In practice, there must be some limit to the number of venepunctures for the sake of the patient. It is unnecessary to demonstrate bacteraemia 10 times if two or three times will serve. Single cultures are unjustified except in certain moribund patients and single positive results may be difficult to interpret. Three samples taken within eight hours cause little discomfort to the patient and no disproportionate labour for the bacteriologist. Even in patients with bacterial endocarditis it is exceptional to obtain a positive culture late when early ones have been negative. In this disease, since bacteraemia is prolonged and appropriate treatment

vital, it may sometimes be reasonable to relax the rule and take more than three samples.

In 1968, not included in the figures shown previously, 10% more patients had blood cultures than in 1965, the year with the previous highest total. The number of patients with bacteraemia was not significantly different (11%) from the previous years.

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