Occasional Review

Staphylococcus aureus bacteraemia: 400 episodes in St Thomas's Hospital

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Abstract

Four hundred episodes of *Staphylococcus aureus* bacteraemia occurred in St Thomas's Hospital from 1969 to 1983, accounting for 17.5% of all episodes of bacteraemia. The mortality was 24%, half attributable to underlying disease, and was highest in patients over 50. Almost 60% of the bacteraemias were acquired in hospital, and the source of the organism was generally obvious, with vascular access sites the most common (37%). Bone and joint infections accounted for 11.5% of episodes and endocarditis for 7%. Most staphylococci were resistant to penicillin only; three isolates were resistant to methicillin and five to fusidic acid. Microbiologists seldom influenced directly the choice of initial antibiotic treatment (though this usually conformed to the hospital's antibiotic prescribing policy) but had considerable influence over definitive treatment, usually cloxacillin or flucloxacillin alone or in combination with fusidic acid.

S. aureus bacteraemia is easy to identify and treat, though underlying disease may influence the outcome. Efforts should be made to prevent the largely iatrogenic disease.

Introduction

There have been few studies of serious staphylococcal infections in the past 20 years, during which the decline of the "hospital staphylococcus" has continued and the use of effective anti-staphylococcal agents become commonplace. We have reviewed all episodes of *Staphylococcus aureus* bacteraemia in St Thomas's Hospital in the past 14 years.

Methods

All episodes of *S. aureus* bacteraemia diagnosed at St Thomas's Hospital from 1969 to 1983 were reviewed.

Medical microbiologists kept a record of all patients with bacteraemia, including brief clinical details, treatment received, and relevant microbiological details. Microbiology staff collected blood

for culture at the request of a clinician. Culture methods have been previously described.¹ Organisms were identified by conventional means and antibiotic sensitivities determined by the disc method. Phage typing was performed by the Staphylococcus Reference Unit, Division of Hospital Infection, Central Public Health Laboratory, Colindale.

Antibiotic treatment was classified as initial (started before culture results were available) and definitive and was assessed as appropriate or inappropriate according to the sensitivity of the isolate.

Host factors noticeably affect the outcome of bacteraemia.² Thus at the outset an attempt was made to classify the prognosis of each patient. Some patients were clearly well before the bacteraemic episode and had a good prognosis; others already had surgical or medical disorders of such severity that recovery from their primary disease was unlikely, and they were classified as having a poor prognosis. The remainder were classified as having an intermediate prognosis.

Results

During the period studied there were 2290 episodes of bacteraemia, in 400 (17.5%) of which *S. aureus* was the organism responsible. The annual total of all bacteraemias rose from 120 in 1970 to 231 in 1982, but the proportion of *S. aureus* infections remained constant.

PATIENTS

Staphylococcal bacteraemia affected both sexes equally, but occurred more often in the elderly, in whom there were more deaths. Twenty two patients were diabetic (5.5%), and there were 13 drug addicts (3.2%). One hundred and thirty five patients (34%) were in general medical beds, 100 (25%) were in surgical beds, and 88 (22%) were patients of the renal unit (including 16 recipients of renal transplants). Of the remaining patients, 30 were in orthopaedic beds (8%), 17 in obstetric and gynaecological (4%), 15 in haematological (4%), and 15 in paediatric beds (4%).

Most patients had an appreciable fever, but a few, usually the elderly, had minimal signs or symptoms. Though staphylococcal bacteraemia occasionally led to death within 24 hours of admission, it generally ran a more prolonged course with fever and rigors. Forty seven patients (12%) were shocked, but in only 22 (5.5%) could this be clearly attributed to bacteraemia.

Clinical evidence of meningeal infection was seen in three patients during their septicaemia. In one, with staphylococcal arthritis, the organism was grown from the cerebrospinal fluid. In the other two the cerebrospinal fluid was sterile though it contained lymphocytes. One of these two patients had undergone a transurethral resection of the prostate and the other had staphylococcal endocarditis on a previously normal mitral valve, presenting with meningism, but initially no cardiac murmur.

Most patients had conspicuous leucocytosis and only 14 (3.5%) had neutrophil counts of less than $1.0 \times 10^9/l$, resulting from either a haematological disorder or treatment with immunosuppressive drugs.

Eighteen patients, 12 undergoing regular haemodialysis, had more than one episode of staphylococcal bacteraemia, usually with an organism with the same phage type.

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MAIN SITE OF INFECTION

Table I shows the main sources of infection. Intravenous lines were mainly catheters in the neck or subclavian veins, but included peripheral lines and cardiac pacing wires. Skin and soft tissue sources were predominantly infected skin lesions, pressure sores, and various abscesses. The meninges were the main site of infection in two patients, one unexplained and the other related to a Spitz-Holter shunt. Eight of the 13 drug addicts had tricuspid endocarditis. The patient's skin flora was the probable source of infection in the addicts and in eight of 14 neutropenic patients who usually had minor lesions.

About 60% of staphylococcal bacteraemias were acquired in hospital and about 30% were acquired outside. The remainder occurred in patients attending hospital for haemodialysis and were difficult to classify.

TABLE I—Main site of clinical infection at onset of bacteraemia

Site of clinical infection	No of episodes	%
Intravenous lines*	93	23
Haemodialysis fistula or shunt	56	14
Wound	14	19.5
Skin and soft tissue	56	14
Bone†	25	11.5
Joint	21	
Heart Valve†	28	7
Urinary tract	14	3.5
Respiratory tract	11	3
Peritoneal dialysate	5	1
Meninges	2	0.5
None apparent	13	3
Total	402	

*Neck/subclavian 71, arm 15, cardiac pacing wire four, groin one, umbilicus one, right atrium tunnelled subcutaneously one.

†Two patients had osteomyelitis and endocarditis.

BACTERIOLOGY

The results of phage typing were unremarkable. Group 1 was the most common (30%) followed by group 3 (20%), and isolates which could not be typed accounted for 12%. Most isolates were resistant to penicillin only (75%) and 13% were fully sensitive. Resistance to gentamicin, fusidic acid, or methicillin was rare (1.8%, 1.2%, and 0.8%, respectively). Multiple resistance was also unusual, with 2%

only of isolates resistant to four or more antibiotics. Two of the five patients from whom staphylococci resistant to fusidic acid were isolated came from other hospitals, and in two others resistance developed during treatment with fusidic acid despite the use of an additional antibiotic.

TREATMENT AND OUTCOME

Table II shows antibiotic regimens used in 350 patients before a bacteriological diagnosis had been made. They commonly included penicillins sensitive (174) and resistant (171) to penicillinase. Initial treatment was judged appropriate for *S aureus* in 314 of 350 cases (90%).

Table III lists the common regimens for definitive antibiotic treatment: cloxacillin or flucloxacillin were preferred, with the addition of fusidic acid for severe infection. Vancomycin was usually given for bacteraemias associated with fistulas or shunts in patients on haemodialysis.

Sixteen patients either had no definitive treatment or it was withdrawn because recovery from their primary disease was not expected. A further three responded to removal of a focus of infection without antibiotics, and nine recovered on inappropriate treatment.

Most patients survived, including nine who had a recurrence of their infection during the same admission. Table IV shows the outcome of infection in the three prognostic groups.

It was difficult to correlate any particular regimen with outcome because many deaths were the result of underlying disease.

TABLE IV—Outcome and prognosis for patients with bacteraemia

Prognosis in absence of bacteraemia	Total	Survived		Died	
		No	%	<i>S aureus</i> infection No	Other disease No
Good	84	83	(99)	1*	(1)
Intermediate	274	219	(80)	31	(11)
Poor	42	1†	(2)	20	(48)
Total	400	303	(76)	52	(13)

*A 15 year old boy with suppurative arthritis.

†A 74 year old woman with metastatic breast tumour.

TABLE II—Initial treatment regimens (350)

	No (%) treated with each regimen shown below											Occasions used in other combinations	Total use
	61 (17)	42 (12)	35 (10)	34 (10)	20 (6)	16 (5)	10 (3)	9 (3)	8 (2)	7 (2)	7 (2)	7 (2)	
Flucloxacillin or cloxacillin	•		•	•					•			•	34
Fusidic acid				•					•			•	19
Penicillins*	•	•			•			•				•	35
Vancomycin						•							11
Lincomycin or clindamycin											•		9
Erythromycin									•				8
Gentamicin					•		•	•					44
Cephalosporins†													10
Metronidazole								•					15
Co-trimoxazole										•			3
Other agents‡													13

*Including benzyl penicillin, ampicillin and amoxycillin.

†These include: cephalothin (four), cephaloridine (three), cephalazolin (one), cephalixin (one) and cefuroxime (one).

‡These include: tetracycline (one), sulphonamide (two), trimethoprim (one), chloramphenicol (one), colistin (one), carbenicillin (five), azlocillin (one) and mezlocillin (one).

TABLE III—Definitive treatment regimens (372)

	No (%) treated with each regimen shown below														Occasions used in other combinations	Total use
	105 (28)	45 (12)	26 (7)	19 (5)	14 (4)	13 (3)	13 (3)	12 (3)	10 (3)	10 (3)	9 (2)	8 (2)	7 (2)	6 (2)	4 (1)	
Flucloxacillin or cloxacillin	•	•	•		•		•	•	•	•	•	•				28
Fusidic acid	•				•		•	•	•	•						31
Penicillins*			•				•	•				•	•	•		17
Vancomycin				•					•	•						16
Lincomycin or clindamycin						•										19
Erythromycin					•											6
Gentamicin											•					22
Cephalosporins†														•		8
Other agents‡																12

*Including benzyl penicillin, ampicillin, and amoxycillin.

†These include: cephalothin (six), cephaloridine (three), cephalazolin (one), cefuroxime (one), and cefotaxime (one).

‡These include: co-trimoxazole (eight), chloramphenicol (three), and streptomycin (one).

Discussion

This prospective study is the largest comprehensive survey of bacteraemic staphylococcal infection in Britain for the past 20 years. Reports submitted to the Public Health Laboratory Service and recently published by the Communicable Disease Surveillance Centre³ provide a basis for comparison, given the probability of inadequate or incomplete notification.

Our finding of an increase in *all* bacteraemias agrees with the report from the Communicable Disease Surveillance Centre. Staphylococcal bacteraemias also increased but the incidence as a proportion of all bacteraemias remained constant at 17.5%, similar to that reported by the centre for 1975-80. Staphylococcal bacteraemia was seen at all ages and in both sexes equally; we did not find the slight preponderance of male patients reported in three early large studies.⁴⁻⁶ The report of the Communicable Disease Surveillance Centre of 31% of patients aged 65 and over compares with our figure of 21.5%. The proportion of diabetics in our series, 5.5%, is no greater than that of our hospital population (4-6%).

S aureus bacteraemia emerges as a predominantly iatrogenic disease. In over half of the episodes the main site of infection was a vascular access site or an infected surgical wound. To these could be added endocarditis originating in infected sternal wounds and bacteraemia from instrumentation of the urinary tract. In the series of *S aureus* bacteraemia from the Communicable Disease Surveillance Centre, 14% were associated with intravenous lines, and our figure of 37% probably reflects greater accuracy of recording. Watt and Okubadejo ascribed 17.8% of all cases to infected infusion sites,⁷ while Faber *et al* noted that a quarter of their 201 episodes of bacteraemia resulted from infected vascular access sites and wounds.⁵ A more recent survey in adults quoted 10 out of 68 episodes of *S aureus* bacteraemia with an intravenous catheter site as the portal of entry.⁸

Fourteen per cent of episodes of staphylococcal bacteraemia occurred in patients undergoing haemodialysis for chronic renal failure. Infection at the access site may not always be apparent, or may appear unimportant,⁹ but the resultant septicaemia is usually severe.

Seventeen per cent of cases updated by the Communicable Disease Surveillance Centre resulted from bone and joint infections, slightly more than our figure of 11.5%. Endocarditis accounted for 5% of that series and 7% of ours. Elsewhere the proportion has been variously reported as 3.4% of 1969 cases,⁶ and 24.8% of 105 cases.¹⁰ In the Mayo Clinic staphylococcal bacteraemia is said to occur at least five times as frequently as endocarditis.¹¹

Bacteraemic staphylococcal pneumonia was rare, whereas isolation of *S aureus* from the sputum without evidence of pneumonia was common. Only 3% of our bacteraemias derived from the lower respiratory tract, and none occurred after influenza. This is less than the 5.5%⁵ and 5%⁶ in two other series and substantially less than the 15 out of 68 cases reported by Weinstein *et al*.⁸ Our prospective study allowed a critical assessment of the clinical relevance of such isolates at the time of the illness. The organism was also often isolated from urine without symptoms referable to the urinary tract, a well known association¹² though unexplained.

No particular phage type or group was associated with bacteraemia, and analysis of the phage types showed no appreciable variation from those of all our isolates when last surveyed.¹³ Sensitivity patterns confirm the well documented decline of multiply resistant *S aureus*.¹³⁻¹⁸ Staphylococci resistant to four or more antibiotics accounted for only seven episodes. We have not shared the experience of some centres in Britain and elsewhere, with staphylococci resistant to gentamicin and methicillin.¹⁹⁻²¹

The choice of an antibiotic for treating *S aureus* bacteraemia presents few problems. Our usual regimen was cloxacillin or flucloxacillin and fusidic acid, with flucloxacillin correctly included as initial treatment in almost half of the episodes in accordance with our antibiotic policy.¹⁴ The choice of peni-

cillinase-sensitive penicillins, metronidazole, and gentamicin indicates empirical broad spectrum treatment with staphylococci unsuspected but covered. Occasionally the initial choice was inappropriate, as in those instances where antipseudomonal agents were used. It is difficult to determine the benefit or otherwise of the addition of fusidic acid, and its use in 131 (33%) of our patients has been described.²² Because of the confusion that jaundice (usually reversible) contributes to clinical management, we now use it for severely ill patients, given by mouth rather than intravenously whenever possible. Vancomycin is useful for patients undergoing haemodialysis since therapeutic serum concentrations can be maintained for a week after a single dose.²³ Erythromycin was used mainly in patients allergic to penicillin, usually in combination. We have not recommended cephalosporins for staphylococcal infections and they were used on 12 occasions only as definitive treatment, and then usually to treat mixed infections.

The duration of antibiotic treatment was largely determined by the clinical response and site of infection. In general, patients with bacteraemia acquired in hospital and an obvious primary source responded to a short course of antibiotics and removal of sources of infection. Infections acquired outside hospital, more often severe, as noted before,¹⁰ were treated for several weeks.

The overall mortality at 24% is less than that reported by Faber *et al* (41%)⁵ or by Jessen *et al* (43%)⁶ though similar to that reported from Seattle in 1976 (21%).¹⁰ In 46% of our cases death was attributed to underlying disease rather than to staphylococcal infection. If these patients are omitted the mortality was 13%. Similarly, Jensen and Lassen quote a "reduced mortality" of 23% for their 43 cases of septicaemia and endocarditis.²⁴ Delay in starting effective treatment in a patient who has a good prognosis initially can prove fatal, and it might thus be argued that initial antibiotic treatment, especially for a severe bacteraemia contracted outside hospital with no obvious source, should always include an anti-staphylococcal agent.

Infection at a vascular access site, especially the subclavian or neck veins, was the commonest source of staphylococcal bacteraemia. Though these catheters had been in situ for an average of six days, it was sometimes for only two days.

Patients with *S aureus* endocarditis are a particularly interesting group. In St Thomas's Hospital *S aureus* has accounted for 21% of 134 cases of endocarditis in the past 14 years, a slightly higher proportion than the 15% in the Mayo Clinic,¹¹ though our series covers only the latter period of their study. Staphylococcal endocarditis is more often acquired outside than in hospital^{9,11} and may affect a native valve (either normal or abnormal) or a prosthetic valve. Our incidence of early prosthetic valve endocarditis (predominantly a staphylococcal disease) has decreased.²⁵ The association between drug addiction and staphylococcal endocarditis is well known. Endocarditis in such patients carries a good prognosis particularly when only the right side of the heart is affected. The remaining cases of native valve endocarditis may pose a diagnostic problem in that the distinction between acute endocarditis and bacteraemia without valvular infection may be initially difficult. The characteristic signs of microembolisation may be absent.¹¹ Factors suggestive of staphylococcal endocarditis include a new pathological or changing murmur, a major embolic event, and bacteraemia acquired outside hospital. Presentation with neurological symptoms is a recognised though uncommon feature of endocarditis with any organism, and staphylococcal meningitis without an obvious source is strongly suggestive of the disease.¹¹

S aureus is second only to *Escherichia coli* as a common cause of bacteraemia acquired in the community or in hospital. It is readily diagnosed in the laboratory and is not difficult to treat, though the outcome of the infection will be adversely influenced by coincidental underlying disease and delay in starting appropriate treatment. Its increasing incidence probably reflects the enlarging population of susceptible patients.

As a largely iatrogenic disease it should be preventable and efforts to this end should be directed particularly towards improved care of vascular access sites.

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Contemporary Themes

Smoking, tobacco promotion, and the voluntary agreements

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The control of advertising and promotion of tobacco goods has been a controversial political issue for many years. While a growing number of countries have enacted legislation in an attempt to control these activities,¹⁻³ Britain, despite repeated calls for legislative action by numerous distinguished medical bodies,⁴ has made depressingly little progress. The sole piece of British legislation aimed at curbing tobacco advertising remains the Television Act 1964 (since replaced by the Independent Broadcasting Act 1973), which made it possible for the

Home Secretary to prohibit cigarette commercials in 1965. Indeed, this Act, along with another prohibiting the sale of tobacco goods to children, constitutes one of only two pieces of legislation in the control of smoking. Its present inadequacy is illustrated by the proliferation of cigarette brand names on television through the medium of sport sponsorship.

Control of tobacco promotion

Spurning the use of legislation, successive British governments have attempted to deal with the issue of tobacco promotion by means of a series of so called voluntary agreements between the Department of Health and Social Security (and other government departments) and the advisory council of the tobacco industry.⁴⁻⁶ I would suggest that these agreements, as well as pre-empting legislative measures, provide the tobacco industry with several benefits. At the same time, they have effectively

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