Staphylococcal septicaemia, endocarditis, and osteomyelitis in dialysis and renal transplant patients

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Summary

Septicaemia is a common and potentially lethal hazard of haemodialysis and renal transplantation; it is usually caused by *Staphylococcus pyogenes*. In 6 patients with *S. pyogenes* septicaemia, fatal endocarditis and spinal osteomyelitis have each occurred once, and 3 patients have had recurrent episodes of septicaemia. The management of septicaemia in these patients must include a search for metastatic infection, and prolonged therapy with 2 antistaphylococcal agents is necessary to ensure eradication of infection. Access site infection in dialysis patients must be treated vigorously, and recognized as potentially hazardous by patients. The risk of sepsis in dialysis and transplant patients cannot be excluded, but devastating consequences may be avoided by simple measures.

Introduction

Immune competence is characteristically depressed in uraemia (Wilson, Kirkpatrick and Talmage, 1965; Lawrence, 1965; Dobbstein, 1976), with a correspondingly enhanced susceptibility to infection (Montgomerie, Kalmanson and Guze, 1968). Regular dialysis might be expected to correct this depression of the immune response (Newberry and Sanford, 1971) but this has not been demonstrated (Gombos, Jefferson and Bhat, 1975) and frequent infections are common in dialysis patients. Following renal transplantation, the use of immunosuppressive drugs is accompanied by a constant threat of serious infection which is the leading cause of death in transplant patients, and the second most common cause of death in patients on dialysis (Wing *et al.*, 1978).

In addition to conventional infections of the skin, chest and urinary tract, dialysis patients face the special hazard of access site infection. Apparently trivial sepsis at a shunt site or overlying a subcutaneous fistula may herald more serious complications including septicaemia (Ralston *et al.*, 1971;

Dobkin, Miller and Steigbigel, 1978), septic pulmonary emboli (Levi, Robson and Rosenfeld, 1970), infective endocarditis (Cross and Steigbigel, 1976; Lavelle and Dentino, 1978) and osteomyelitis (Leonard *et al.*, 1973a). *Staphylococcus pyogenes* is the usual causal organism in such cases, although Gram-negative bacilli are also encountered (Dobkin *et al.*, 1978). Total eradication of micro-organisms may prove difficult if an infective nidus exists in bone or on a heart valve; when associated with endarteritis of the fistula itself, the fistula may need to be removed if disseminated disease is to be managed successfully (Cross and Steigbigel, 1976). Recurrent episodes of septicaemia can occur in dialysis patients (Levi *et al.*, 1970); they may harbour quiescent foci of infection which can be reactivated by immunosuppressive therapy following renal transplantation.

This paper deals with *S. pyogenes* septicaemia in a dialysis and transplant unit. Over a 3-year period the authors have seen 11 septicaemic episodes in 6 patients, 8 of these episodes having occurred during 1978.

Patients and methods

At the end of the 3-year period 1976-1978, 20 patients were on home dialysis, 16 on hospital dialysis and 21 had functioning renal transplants. Twenty-five patients dialysed using a standard radial or ulnar Cimino-Brescia type fistula; 7 patients used implanted woven polytetrafluoroethylene (Gore-tex) grafts for access; one had a bovine xenograft; and 2 used Scribner shunts in the leg. Blood cultures were only considered positive if both of a simultaneous pair of culture bottles grew a typical pathogen in an appropriate clinical setting. There were 11 cases of *S. pyogenes* septicaemia (2 episodes of septicaemia due to *Escherichia coli* which occurred in renal transplant recipients are not reported here).

Case reports

Case 1

A 34-year-old man with Alport's syndrome developed a febrile illness in October 1976, one month after being transferred to home dialysis; his most prominent uraemic symptom had been intractable pruritus. Several blood cultures grew *S. pyogenes*: gentamicin was given for 4 days and oral flucloxacillin for 2 weeks. Two months later an identical bacteraemic illness was treated with 2 weeks of cloxacillin at first parenterally and later orally. Three months later he complained of thoracic backache; initially the X-rays were considered as showing only features of renal osteodystrophy (Fig. 1), but his back was explored as osteomyelitis could not be excluded. Pus aspirated from a thoracic vertebra grew *S. pyogenes* on culture. Cloxacillin 2 g daily for 8 weeks settled his backache. In April 1978 his right knee became painful and swollen; no fluid could be aspirated, and blood cultures were sterile, but flucloxacillin was given for 2 weeks. One month later he had a further febrile illness with backache, right knee pain and right shoulder pain. *S. pyogenes* was again isolated from his blood, and

he was treated with gentamicin and cloxacillin for 4 weeks. Renal transplantation was performed a few weeks later, and after 18 months he remains well. *S. pyogenes* has not been isolated from his skin or nose.

Comment. This patient had severe pruritus during regular dialysis therapy, and developed septicaemia from skin sepsis. Inadequate early therapy of his septicaemias allowed metastatic spread to bone. His uneventful course following transplantation probably reflects relief of pruritus, and there is now no skin carriage of *S. pyogenes*.

Case 2

A 56-year-old man with chronic pyelonephritis developed an itchy infection lesion on his left leg. He then developed a florid septicaemic illness, with acute-on-chronic renal failure, and *S. pyogenes* in blood cultures. He was treated with cloxacillin and erythromycin for 5 weeks. He was also dialysed, first through a Scribner shunt in the right leg, and then via a standard radiocephalic fistula as there was no return of renal function. Nine months later, in April 1978, he felt unwell and had a low grade

FIG. 1. Case 1: Lateral tomogram of thoracic spine showing destruction of the lower border of T8 and the upper border of T9 with loss of the disc space.

fever. His right shoulder was painful, and he had a right olecranon bursitis. *S. pyogenes* was grown on repeated blood cultures, and he received cloxacillin for 3 weeks. In August 1978 he developed fever, malaise and pericarditis. Echocardiography showed a small pericardial effusion, but normal heart valves. *S. pyogenes* was grown in his blood, and he was treated with cloxacillin and erythromycin for 3 months. He has remained well for >one year, and is not a nasal or skin carrier of *S. pyogenes*.

Comment. His original septicaemia was probably under-treated; subsequent episodes might have been averted with more prolonged initial therapy. Since receiving antibiotics for 3 months there have been no further problems.

Case 3

In May, 1978, a 40-year-old male with obstructive uropathy damaged his fistula with a needle, but dialysed successfully. Three days later he had a high fever, breathlessness, confusion, extensive purpura on his trunk, splinter haemorrhages and a left pleural effusion; the heart was clinically normal. He was given i.v. cloxacillin and gentamicin on admission to hospital. Swabs from a septic lesion overlying his fistula, pleural aspirate, and blood cultures all grew *S. pyogenes*. One week later he remained confused; an EMI scan showed 2 areas of cerebral infarction, but no abscess. There was

still no clinical cardiac abnormality. A further specimen of pleural fluid grew an unidentified *Staphylococcus* sensitive to cloxacillin and gentamicin. Three weeks after admission he had signs of aortic incompetence, confirmed by echocardiogram, which also showed valvular vegetations (Fig. 2). Blood cultures were now negative, but his condition deteriorated steadily and cardiac surgery was considered too hazardous. In mid-June, a new, louder systolic murmur appeared, and he rapidly developed progressive and terminal cardiac failure. Post-mortem revealed acute bacterial endocarditis affecting aortic, mitral and tricuspid valves, the foci of infection being linked by a myocardial abscess (Fig. 3). The clotted fistula was sterile, but a scanty growth of *S. pyogenes* was isolated from the heart.

Comment. The source of infection was the fistula, which had become infected after faulty needle insertion. Emergency heart surgery might have saved this patient, as he died despite appropriate antibiotic therapy.

Case 4

A 37-year-old male with obstructive uropathy had been dialysed for one year when, in March 1977, his fistula became infected around a clot-lined pseudoaneurysm. The fistula was excised, and oral

FIG. 2. Case 3: Echocardiogram. Aorto-mitral sweep showing aortic valve vegetations (VEG, single arrow), acute left ventricular dilation (LV) due to aortic regurgitation, and premature closure (PC, double arrow) of the mitral valve (MV).

FIG. 3. Case 3: Post-mortem. The aortic root and left ventricle have been opened to show a large friable haemorrhagic vegetation on the ventricular aspect of the non-coronary cusp of the aortic valve. The probe lies through one of 2 one-cm perforations in the cusp.

flucloxacillin was given for 10 days. Renal transplantation was successfully performed in May 1978, but 5 months later, whilst on prednisolone 15 mg/day and azathioprine 100 mg/day, the patient developed malaise, fever and chills. *S. pyogenes* was isolated from blood, urine and a throat swab, and gentamicin and cloxacillin were given for 2 weeks. Two months later, *S. pyogenes* bacteraemia recurred, and a 2-month course of cloxacillin was given. He remains well, and nose, throat and skin swabs have not grown *S. pyogenes* on culture since the second illness.

Comment. The second septicaemia probably resulted from inadequate treatment of the previous episode. In the presence of immunosuppressive therapy, antibiotic treatment should be administered for longer than in other patients. His previously infected fistula was probably unrelated to the infections following transplantation.

Case 5

A 53-year-old man with a history of proteinuria and hypertension commenced haemodialysis in January 1978 via a shunt in the left leg. In September 1978 the shunt was removed because of local infection and he received flucloxacillin for 2 weeks. In November 1978 he presented with chest pain, malaise, fever, pericarditis and splenomegaly. A small pustule overlying his fistula had been present

for 3 days, unreported by the patient. Pus from this lesion and blood cultures grew *S. pyogenes* sensitive to cloxacillin, which was given for 8 weeks following initial i.v. therapy. Echocardiography showed a small pericardial effusion but no valvular dysfunction. The fistula clotted a few days after admission, and dialysis is now effected via a right leg shunt.

Comment. The importance of sepsis overlying a fistula must be understood by patients: prompt therapy is essential if septicaemia is to be avoided. The authors have adopted a policy of prolonged antibiotic therapy for septicaemia in the light of their experience with the preceding patients.

Case 6

A 48-year-old man with renal failure of undetermined cause received a renal transplant in December 1977 following 10 years' haemodialysis. Postoperative complications included gastrointestinal haemorrhage and cytomegalovirus infection, but the patient recovered and remained well on azathioprine 50 mg/day and prednisolone 17.5 mg/day during 1978. In October and November he developed several boils on his trunk and neck which were treated by drainage and antibiotics. In December 1978 he became unwell for 3 days with malaise, lethargy, rigors and fever. Throat swabs

and blood cultures showed profuse *S. pyogenes* sensitive to cloxacillin and cefuroxime which were given i.v. Eventually he recovered and was given oral cloxacillin and erythromycin for 2 months. He remains well with no evidence of skin or nasal carriage of *S. pyogenes*.

Comment. This case resembles case 4; a prolonged course of antibiotics was given in an attempt to avoid a recrudescence of infection. In contrast to case 4, a source of *S. pyogenes* was evident before the development of septicaemia, yet seemingly adequate therapy failed to avert major complications.

Discussion

The occurrence of these 11 episodes of *S. pyogenes* septicaemia in dialysis and transplant patients is not exceptional; the incidence of septicaemia per patient per year of only 7% for the authors' dialysis patients compares favourably with that of 15% reported in a much larger series in New York (Dobkin *et al.*, 1978). However, the much higher incidence during 1978, the problem of recurrent septicaemia in both dialysis and transplant patients, and the occurrence of endocarditis and osteomyelitis has provoked a further examination of these issues.

Endocarditis

In the early days of chronic haemodialysis when Scribner shunts were the sole means of access to the circulation, infective endocarditis was not described despite recurrent local sepsis. However, in the original account of the surgically-created subcutaneous arteriovenous fistula (Brescia *et al.*, 1966), one of the 13 patients described died of infective endocarditis, and in 1969 Goodman *et al.* described 2 further cases of bacterial endocarditis in patients using fistulae for dialysis. Also in 1969, Kurtz described the first case of endocarditis associated with a shunt: the patient died.

Since these early reports there have been several other accounts of endocarditis in dialysis patients and, in a review article (Cross and Steigbigel, 1976), 35 episodes were collected in 34 patients. The outcome was stated in 29 patients, of whom 16 died. Twelve episodes of endocarditis were associated with subcutaneous fistulae, 20 with external shunts, and 3 occurred in patients with both types of access device. There is thus little support for the opinion that disseminated infection is a greater hazard from fistulae than from shunts (Ralston *et al.*, 1971).

The recognition of endocarditis in dialysis patients can be difficult. However, one is likely to be dealing with acute rather than sub-acute or chronic disease: consequently the highly destructive vascular lesions will cause striking changes in the intensity and

quality of cardiac murmurs far more commonly than in classical sub-acute infective endocarditis (Weinstein and Schlessinger, 1974). In the setting of acute sepsis the development of a new organic regurgitant murmur is virtually diagnostic of infective endocarditis (Dorney, 1972). Echocardiography is valuable in demonstrating valvular incompetence; it is now the authors' practice to perform echocardiograms on septic patients when there is any suspicion of endocarditis. This may improve diagnosis of a condition that remains a challenge even in non-uraemic patients (Weinstein and Rubin, 1973; Wann *et al.*, 1976).

The management of infective endocarditis in dialysis patients is no different in principle from that in non-uraemic subjects. The major criterion for valve replacement is the development of severe cardiac failure (Hancock, Shumway and Remington, 1971); cardiac failure is associated with 100% mortality in non-operated haemodialysis patients with endocarditis (Cross and Steigbigel, 1976; Lavelle and Dentino, 1978). Experience with valve replacement is limited but the survival at 1-3 years of 13 dialysis patients who have had infected valves replaced is 61% (Lavelle and Dentino, 1978). Whether a more aggressive approach with early surgical intervention is justified is not clear; but in a non-dialysis population mortality in high risk patients with uncontrolled infection was reduced from 90% to 17% when a policy of early surgery was adopted (Boyd *et al.*, 1977).

Osteomyelitis

The second major issue concerns osteomyelitis. From the literature this is apparently an extremely unusual problem, having been reported from only one centre (Leonard *et al.*, 1973a). The same authors record separately 4 other patients with osteomyelitis who had co-existing bacterial endocarditis (Leonard, Raj and Shapiro, 1973b; Leonard *et al.*, 1973c). In these cases, eradication of the infecting organisms was a problem, and 2 patients died. The present authors agree with Leonard *et al.* that differentiation of osteomyelitis from renal osteodystrophy may be difficult, but in the present case the dilemma was resolved by exploration of the spine and the finding of pus. It is therefore advocated that any suspicious bony lesion which in the clinical setting might be due to osteomyelitis should be explored early. In retrospect, in their case, the duration of antibiotic for previous episodes of septicaemia was too brief, and allowed haematogenous spread of infection to bone. Whether treatment of the osteomyelitis for longer than 8 weeks would have prevented a subsequent septicaemia seems doubtful, but more prolonged therapy might be given in future cases.

Management of infection

The proper management of access site infections and septicaemia in dialysis and transplant patients is not yet clear. In particular, the optimum duration of therapy and choice of antibiotic have not been discussed in detail.

Provided that *in vitro* sensitivities are used as a guide, there is no firm evidence that the choice of antibiotic is crucial. For *S. pyogenes* infections in dialysis patients a wide variety of agents have been used, including penicillin, oxacillin, cloxacillin, gentamicin, vancomycin, chloramphenicol, cephalothin and fusidic acid (Leonard *et al.*, 1973b; Rao *et al.*, 1972; Barcnas *et al.*, 1976) and no single agent has proved outstandingly successful. Similar conclusions have been drawn from studies of *S. pyogenes* septicaemia in a non-dialysis and transplant population (Wise, 1973; Nolan and Beaty, 1976). Thus, despite the apparent efficacy of potent antistaphylococcal antibiotics, treatment failures still occur. On an empirical basis, therefore, the present authors now favour the concurrent use of 2 antistaphylococcal agents: they use gentamicin or a cephalosporin with cloxacillin or penicillin. The limited evidence available suggests that such combination therapy may be effective (Andriole, 1979).

The optimum duration of antibiotic therapy for staphylococcal septicaemia in dialysis and transplant patients is not known. Many reports in the literature detail the antibiotic used, but not the duration of therapy (Dobkin *et al.*, 1978; Levi *et al.*, 1970; Sherrard, 1970). *S. pyogenes* septicaemia is notorious for the frequency with which endocarditis occurs; in 50% of cases normal heart valves are involved (Weinstein and Rubin, 1973) and the possibility of endocarditis exists in all patients with proved *S. pyogenes* septicaemia (Gregoratos and Karlner, 1979). The dictum of Lerner and Weinstein (1966) that *S. pyogenes* septicaemia should always be regarded as involving the heart, and treated accordingly, is widely quoted; 2 reviews recommend 3 to 6 weeks of i.v. antibiotic therapy in all cases, although none of the patients in these reports was a transplant recipient or on dialysis (Nolan and Beaty, 1976; Wise, 1973). Prolonged daily i.v. therapy in dialysis and transplant patients is often difficult owing to lack of veins. An attempt (unsuccessful) has been made to overcome this problem by using vancomycin (Barcnas *et al.*, 1976).

Renal transplant recipients are most at risk from infection in the early weeks when immunosuppressive drugs are used in higher doses, but the authors' 2 cases of *S. pyogenes* septicaemia occurred some months after transplantation when the dose of immunosuppressants was modest.

It seems clear, therefore, that in all patients with *S. pyogenes* septicaemia, whether in the normal

population, on dialysis or following transplantation, total eradication of infection may prove difficult, reflecting the extreme virulence of the organism. The authors' experience indicates that in dialysis and transplant patients, 2-4 weeks' therapy is insufficient to ensure cure. In both groups of patients this is likely to be due, at least in part, to impaired immunity even though high blood and tissue levels of antibiotics are easily achieved in anuric patients. The authors therefore favour 8 weeks' antibiotic therapy for *S. pyogenes* septicaemia in their dialysis and transplant patients, although formal validation of this approach is lacking.

Prophylactic oral antibiotic therapy has been used to reduce access site infections and their complications, but uncontrolled studies suggest that it is ineffective (Dathan *et al.*, 1970; Martin *et al.*, 1967). Prophylactic parenteral antistaphylococcal therapy reduces overt staphylococcal sepsis but predisposes to Gram-negative infections (Morris and Bilinsky, 1971). The epidemiology of access site infections and their complications has demonstrated that staphylococcal carriage and endogenous infection is the most likely explanation for repeated sepsis (Dobkin *et al.*, 1978; Levi *et al.*, 1970; Martin *et al.*, 1967; McIntosh, Petrie and MacLeod, 1969; Morris and Bilinsky, 1971; Rebel *et al.*, 1975), and most episodes of septicaemia in dialysis patients follow shunt or fistula infection. Although eradication of nasal carriage of staphylococci by topical antibiotics does not reduce the incidence of access-site infection (Martin *et al.*, 1967; Morris and Bilinsky, 1971), elimination of skin carriage of staphylococci by hexachlorophane washing reduces the infection rate (Sherrard, 1970). During cannulation of a fistula, it is the occasional difficult needling associated with repeated attempts to enter the vein and consequent bruising that is most likely to predispose to local infection and subsequent septicaemia. In these circumstances, the procedure often becomes non-sterile (see case 3).

When an infected access-site gives rise to septicaemia or endocarditis, its removal may be necessary in order to control infection (Cross and Steigbigel, 1976). However, in view of the need to preserve vascular access for haemodialysis, this approach is undesirable—it has not been the authors' practice, nor that of other workers (Levi *et al.*, 1970; Ralston *et al.*, 1971; Sherrard, 1970).

The risk of infection will always be present in dialysis and transplant patients, irrespective of the precautions taken. However, simple measures including prompt and vigorous treatment of minor skin sepsis, prolonged antibiotic therapy with 2 drugs in cases of septicaemia, and a careful search for potentially lethal complications such as endo-

carditis and osteomyelitis may be expected to reduce the morbidity and mortality from infection in these patients.

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