*Epidem. Inf.* (1987), **98**, 183–190
*Printed in Great Britain*



# Human infection with *Streptococcus zooepidemicus* (Lancefield group C): three case reports

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(*Accepted 3 November 1986*)

## SUMMARY

Three unrelated severe infections with *Streptococcus zooepidemicus* occurred in England in 1985. The first patient developed septic arthritis, which has not been recorded before with this organism. The second died with septicaemia, pneumonia and post-streptococcal glomerulonephritis, the only record so far of nephritis following sporadic *S. zooepidemicus* infection and of nephritis and systemic sepsis in the same patient. The third patient experienced septicaemia during pregnancy but recovered without complications. A likely animal source of infection was found in only one case.

## INTRODUCTION

Human infection with *Streptococcus zooepidemicus* is thought to be rare (Parker, 1983) but recent outbreaks of severe infection in people consuming unpasteurized milk and dairy products have brought it to public attention (Ghoneim & Cooke, 1980; Morbidity and Mortality Weekly Report, 1983: PHLS Communicable Disease Surveillance Centre, 1984, unpublished). The infection is also of special interest as a cause of post-streptococcal glomerulonephritis (PSGN), which until recently was thought only to follow infection with *S. pyogenes* (Duca *et al.* 1969; Barnham, Thornton & Lange, 1983).

We report here on three serious, sporadic infections with *S. zooepidemicus* occurring in England in 1985, one of which was fatal and featured PSGN.

## CASE REPORTS

*Case* 1

A 70-year-old retired farmer had suffered for several years from mixed osteo- and rheumatoid type arthropathy affecting the hands, wrists, knees and feet but received no special treatment; serological tests for rheumatoid factor were nega-

tive. He also had controlled hypertension, mild congestive heart failure and angina.

In February 1985 he developed a painful swelling of the left big toe and ankle which was thought to be due to gout; he was treated with indomethacin and a course of oral ampicillin with flucloxacillin but the swelling persisted for several months without much change. Serum uric acid measured 0·51 mmol/1 in May (normal upper limit 0·47).

In mid-May he developed a painful swelling of the left knee with worsening oedema of both legs and dyspnoea. On admission to hospital 1 week after the onset of this he was apyrexial with haemoglobin 9·1 g/dl and a white blood cell count of $12{\cdot}5 \times 10^9$/l with 93 % neutrophils. Sixty-five ml of purulent fluid were aspirated from the knee; microscopy showed no uric acid crystals but culture yielded *S. zooepidemicus*, API 20 STREP profile number 4463607 (see Barnham *et al.* 1987: isolate number 4). Blood cultures yielded no growth.

He was treated with sodium fusidate and flucloxacillin which was changed to intravenous penicillin G, 600 mg three times a day, when the bacteriology became known. Soon after arrival in hospital he suffered a transient fall in blood pressure which was thought to be due to the infection; this led to acute renal failure and he was transferred to the nearest renal unit for management, where he made a rapid spontaneous recovery.

Penicillin therapy was changed from intravenous to oral administration after 1 week but swelling and fever returned; the drug was again given intravenously for 2 weeks followed by oral penicillin 750 mg four times a day for a further 3 months. He made a steady recovery from the infection but sterile effusions of the knee persisted in convalescence.

During the development of acute renal failure there was heavy proteinuria and microscopic haematuria with rising blood urea and creatinine concentrations, but serum complement levels remained close to the higher limit of the normal range. Urinalysis results soon returned to normal and PSGN did not occur. Serological studies in the acute and convalescent stages of his infection showed no elevation of anti-streptolysin O (ASO), anti-hyaluronidase (AH) or anti-deoxyribonuclease B (ADB) and there was no demonstrable antibody to the streptococcal nephritogenic protein, endostreptosin (ESS-Ab).

This man lived with his pet sheepdog in a rural area of North Yorkshire but had no direct contact with farm animals. He bought no unpasteurized milk himself but thought that he might have consumed some during recent social visits to the neighbouring farmhouses.

*Case* 2

A 38-year-old housewife living in a small village in the north-east of England was admitted to hospital in late July 1985 with a history of frank haematuria, dyspnoea and oedema of the hands and feet developing over 2 weeks. Examination showed pulmonary oedema and generalized subcutaneous oedema which was most pronounced in the pre-tibial areas. Urine testing showed proteinuria and haematuria (Labstix, Ames: + + + result for both). She suffered respiratory arrest within a few minutes of admission and was treated with artificial ventilation; her condition was at first thought to be due to intoxication rather than infection.

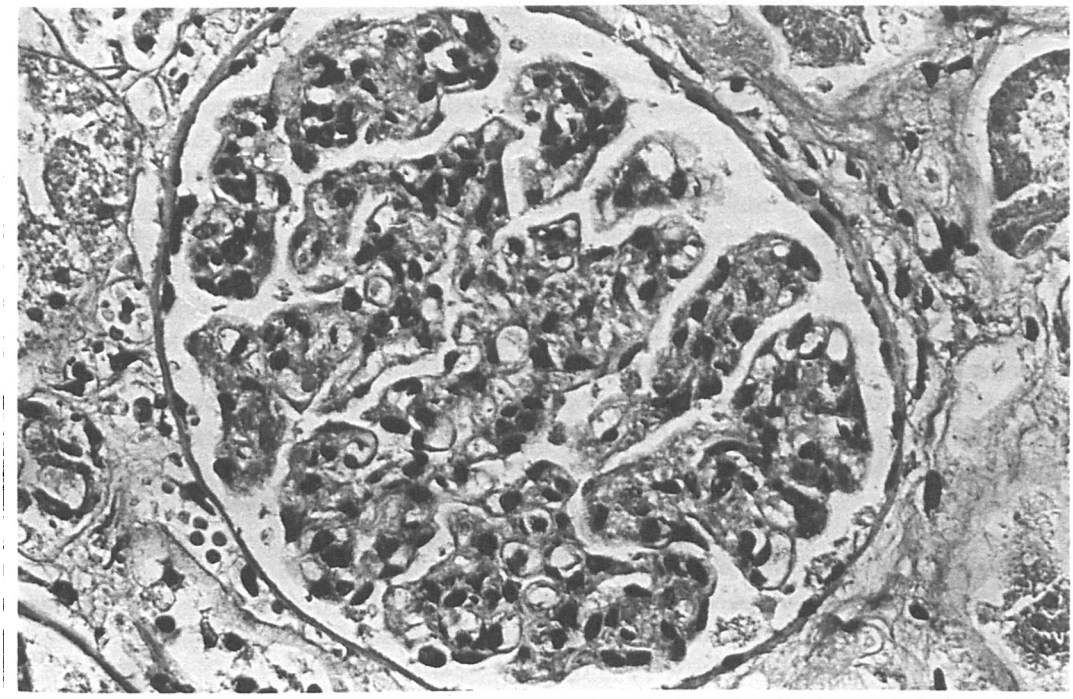

Fig. 1. *Post-mortem* kidney from patient no. 2 showing features of diffuse proliferative glomerulonephritis, including inflammatory cell infiltration, endothelial proliferation and obliteration of capillary lumina in the tufts. Trichrome stain ×460.

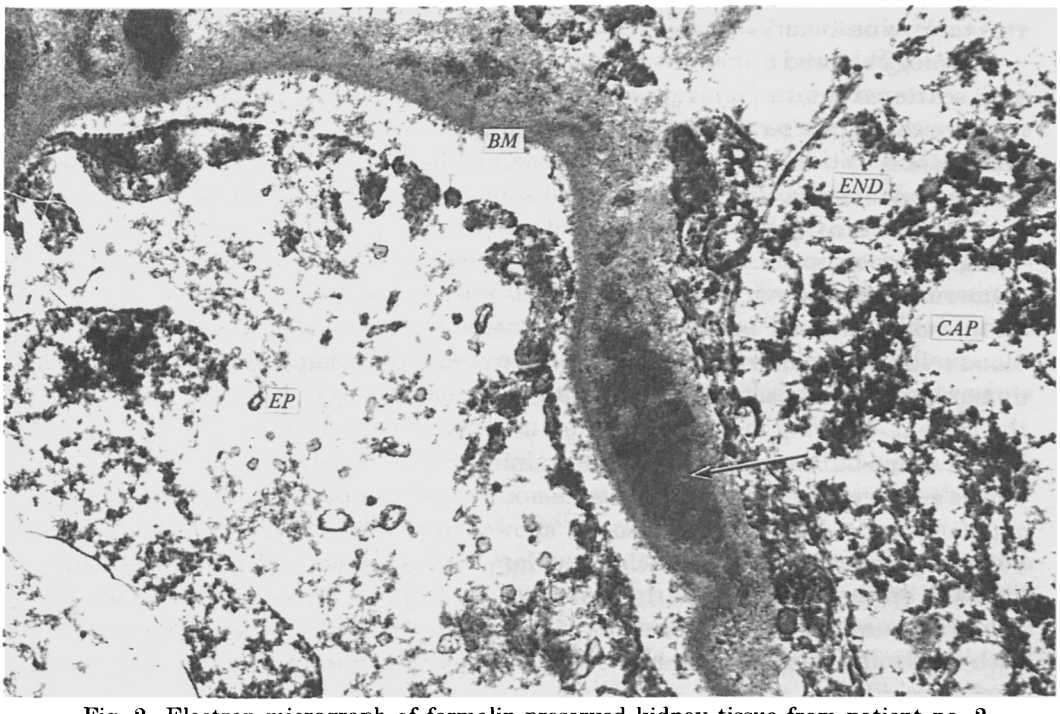


Fig. 2. Electron micrograph of formalin-preserved kidney tissue from patient no. 2 showing sub-endothelial dense deposits (arrow). *EP*, epithelium; *BM*, capillary basement membrane; *END*, endothelium; *CAP*, glomerular capillary lumen. Magnification ×16000.

https://doi.org/10.1017/S0950268800061896 Published online by Cambridge University Press

She had been afebrile on admission but her oral temperature rose from 35·2 °C on the first day to 38·6 °C on the second. Her haemoglobin fell from 12·4 to 10·9 g/dl and the white blood cell count rose to $24{\cdot}5 \times 10^9$/l. Biochemical tests showed acidosis with a blood urea rising from 5·9 to 19·0 mmol/l (normal upper limit 6·6) and creatinine 484 μmol/l (normal upper limit 130). Creatine phosphokinase was very high at 7740 IU/l (normal upper limit 175). Liver function tests showed some derangement with gamma glutamyl transferase at 130 IU/l (normal upper limit 28), aspartate transaminase at 526 IU/l (normal upper limit 35) and alkaline phosphatase 240 IU at 37 °C (normal upper limit 120); immunoglobulin levels were within normal limits. Fibrin degradation products were high at 128 mg/l (normal less than 10) suggesting that there was disseminated intravascular coagulation; serum complement was not measured. With these developments infection was suspected on the second day and she was treated with intravenous benzyl penicillin and cefuroxime; however, her condition steadily deteriorated with a series of cardiac arrests and she died 44 h after admission.

Blood cultures taken the day after admission yielded a beta-haemolytic streptococcus of Lancefield group C which proved to be *S. zooepidemicus*, API 20 STREP profile number 4463607 (see Barnham *et al.* 1987: isolate number 5). Serum collected at necropsy showed ASO and AH titres low in the normal range, an ADB titre of 2400 (normal 250 units/ml or less) and ESS-Ab complement fixation test titre of 32 (normal $< 16$).

*Post-mortem* examination showed consolidation in both lungs with some turbid fluid in the bronchi and a litre of clear fluid in each pleural sac. The liver and spleen were friable but of normal size. The kidneys were of normal size but showed congestion and oedema and some old pyelonephritic scars. There were no valvular vegetations or aneurysms and there was no evidence of meningitis.

Histology showed numerous thrombi in the blood vessels of all sections together with scattered brown pigment granules indicative of an haemolytic process. Gram positive cocci were seen in the lungs and spleen. The lungs showed congestion and oedema and sections from the right lower and middle lobes showed changes typical of lobar pneumonia. The spleen showed some reduction of the white pulp and the liver showed scattered vacuolization of parenchymal cells.

Light microscopy of the kidneys showed the changes of diffuse acute proliferative glomerulonephritis: virtually all glomeruli were swollen with endothelial proliferation, infiltration by neutrophils and occasional eosinophils and absence of red blood cells in nearly all the tufts; there were no crescents but the tubules contained numerous granular casts. Fig. 1 illustrates a glomerulus in *post-mortem* kidney from the patient, showing many of these features. Kidney tissue was preserved only in formol saline but immunoperoxidase staining in the Department of Pathology, St James's University Hospital, Leeds demonstrated complement C3c in glomerular capillary walls. Electron microscopy showed poor ultra-structural preservation but components of the glomerular capillary wall, basement membrane, endothelium and epithelium were clearly identified; there was evidence of almost complete obliteration of the capillary lumen due to swelling of endothelial cells, associated with clear cut finely granular electron dense deposits in the subendothelial region, as shown in Fig. 2.

In conclusion the cause of death was considered to be due to *S. zooepidemicus* septicaemia with pneumonia and acute proliferative glomerulonephritis.

Investigation of the background to this infection revealed that the standard of domestic hygiene was poor and that the family had an alsatian dog which was apt to roam; there was no obvious exposure to unpasteurized milk. On her way to the shops the patient was known to pass through a field where gypsy horses grazed.

*Case* 3

A 34-year-old farmer's wife from the West Midlands, 17 weeks pregnant, became ill in late August 1985 with headache, vomiting and fever. She was admitted to hospital on the eighth day of illness with an oral temperature of 37·5 °C, a pulse rate of 110 per minute but no signs of meningitis or other localized infection.

Laboratory findings included haemoglobin 11·3 g/dl, white blood cell count $10{\cdot}8 \times 10^9$/l with 92% neutrophils, ESR 58 mm/h (Westergren) and normal blood urea, creatinine, electrolytes, complement and liver function tests. After 48 h incubation one of two sets of blood cultures yielded a beta-haemolytic streptococcus of Lancefield group C, subsequently identified as *S. zooepidemicus*, API 20 STREP profile number 4463607.

While in hospital her fever reached a peak of 39·0 °C. She was treated with ampicillin 500 mg four times a day intravenously followed by the same dose orally for a further 5 days and made a rapid and uneventful recovery. Nine days after admission her haemoglobin concentration was 12·2 g/dl and white blood cell count $6{\cdot}7 \times 10^9$/l with 74% neutrophils.

At follow-up 6 weeks from the onset of illness she was well. Blood urea, creatinine, electrolytes and complement concentrations were within normal limits; the pregnancy continued with normal foetal development and a healthy baby was delivered in due course. Urinalysis throughout the illness and at follow-up showed no proteinuria, haematuria or urinary infection. Serological studies in the acute and convalescent stages showed no elevation of ASO, AH, ADB or ESS-Ab.

Further questioning showed that the patient owned a racehorse with a permanent tracheostomy due to a congenital anatomical defect. She cleared the tracheostomy tube each morning. Five days before the onset of her illness the horse had been raced and had 'blown out' (the racing term for retirement from a race through respiratory difficulties). The next morning the patient noticed copious mucopurulent secretions when she came to clean out the tracheostomy, which was at her face level. Swabs taken by her veterinary surgeon 2 weeks later from the trachea of the horse yielded two strains of *S. zooepidemicus*. These isolates and the one from the patient gave different bacteriophage typing results (see Barnham *et al.* 1987: isolates 6a, b, c) and different restriction endonuclease DNA fingerprints (see Skjold *et al.* 1987).

## DISCUSSION

These three reports emphasize the aggressive nature of *S. zooepidemicus* infection in man, a feature seen quite clearly in the recent outbreaks of sepsis in people taking unpasteurized milk and cheese. In New Mexico in 1983 at least 16 people developed systemic sepsis and 2 died in a cheese-related outbreak (Morbidity and Mortality Weekly Report, 1983) while in Halifax, Yorkshire the following year, 8 people died amongst 12 with known systemic infection in a milk-borne outbreak (PHLS Communicable Disease Surveillance Centre, 1984, unpublished). The

features of infection in these patients included septicaemia, pneumonia, meningitis, endocarditis, pericarditis and mycotic aneurysm.

In England serious infection with Lancefield group C streptococci is uncommon, with fewer reports to the PHLS Communicable Disease Surveillance Centre than with organisms of groups A, B or G (Barnham, 1983); what proportion of the group C isolates were *S. zooepidemicus* is unknown but it was probably small. A recent study of 130 group C streptococci from human specimens in a year's catchment in two districts of North Yorkshire revealed only two infections with *S. zooepidemicus* (Barnham, 1987).

As judged by published case reports and *in vitro* tests for virulence (Facklam & Rutledge, 1985), *S. zooepidemicus* is the most aggressive human pathogen in Lancefield group C. However, its occasional occurrence is likely to be obscured by the much more frequent isolation of *S. equisimilis* and group C antigen-bearing *S. milleri* from human specimens and the fact that few laboratories identify these organisms to species level (Barnham, 1987).

Case 1 describes the first record of a patient with proven *S. zooepidemicus* septic arthritis, although infection in a young veterinary surgeon who developed septic arthritis of the wrist after being kicked there by a horse was reported to the Public Health Laboratory Service 11 years ago (Communicable Disease Surveillance Centre, unpublished). Beta-haemolytic streptococci are the responsible organisms in a minority of adult patients with septic arthritis (Argen, Wilson & Wood, 1966; Goldenberg & Cohen, 1976) but very few infections have been reported with organisms of group C (Ascuitto *et al.* 1985). Our first patient had suffered arthritis for several years and this probably acted as a predisposing factor in the localization of the infection (Leading article, 1976). Infection appeared to follow an acute attack of gout and was probably blood-borne, although there was no obvious initial source or prodromal illness.

Serious infection with *S. zooepidemicus* has mostly been reported in patients over the age of 70 years or in neonates, and it seems to be rare in healthy young adults. In the milk-borne outbreak at Halifax some young people in the affected families experienced 'flu-like illnesses that were probably due to the infection, but it appeared to be limited and overcome spontaneously in these patients. Our case reports 2 and 3 describe severe infection occurring in previously healthy young women.

The patient in Case 2 is the first on record to show the combination of severe systemic sepsis with PSGN. There were difficulties in establishing a history of her infection but the development of PSGN implies a latent period of 10 days or more from first acquisition; perhaps the organism was at first localized but later able to invade as she became ill with acute PSGN.

PSGN is a well-recognized sequel to infection with *S. pyogenes* but in two recent outbreaks it has followed respiratory tract infection with *S. zooepidemicus* (Duca *et al.* 1969; Barnham, Thornton & Lange, 1983). The case described here is the first in which the complication has been seen after sporadic infection. As in patients with PSGN in the Yorkshire outbreak described by Barnham, Thornton & Lange (1983) our patient showed a raised titre of antibody to the nephritogenic streptococcal protein ESS. This substance is produced by both *S. pyogenes* and *S. zooepidemicus* and is thought to provide a common pathway in the development

of PSGN. ESS is deposited in a sub-endothelial position in the glomerulus and, after *in situ* combination with antibody and complement, migrates across the basement membrane to a sub-epithelial position (Lange, Seligson & Cronan, 1983). The finding of electron-dense sub-endothelial deposits in this patient rather than the classical sub-epithelial humps (Williams & Peters, 1983) may represent a relatively early stage in the disease process. The serological responses to ESS and streptococcal exoenzymes in our three patients are discussed in detail in a further paper (Barnham, Cooper & Lange, 1987).

*S. zooepidemicus* is commonly found in horses (Bryans & Moore, 1972) and severe infection has occasionally been reported in young adults in prolonged close contact with them. Rose, Allen & Witte (1980) described the case of a 23-year-old equestrienne who developed pneumonia after caring for horses with a respiratory illness, and Low, Young & Harding (1980) reported the isolation of *S. zooepidemicus* from the cerebrospinal fluid of a 24-year-old woman with acute meningitis and from the respiratory tract of her pet horse. The patient in Case 3 suffered infection in similar circumstances and infection probably came from the horse, although only different strains were cultured from it. Our patient was ill for 8 days before starting treatment but, nevertheless, made a good recovery. This is the only record of systemic infection with *S. zooepidemicus* in pregnancy and it is not known if it poses any special risk to the mother or foetus.

For the other two of our three patients the origin of infection was unknown but possible sources suggested by the case histories included horses, dogs and unpasteurized milk. *S. zooepidemicus* is found in infection and carriage in a wide variety of animals, including pigs, sheep, cows, goats, foxes, birds, rabbits, guinea pigs and monkeys (Stableforth, 1959). This is a large reservoir for potential human infection and it is likely that new epidemiological patterns could be found by close questioning and investigation when infection occurs.

We wish to thank Dr J. M. Iveson, Dr P. T. Pickens and Dr Popert for permission to publish details of patients under their care, the Division of Hospital Infection, Central Public Health Laboratory, Colindale for their help with serological tests for streptococcal infection, Professor K. Lange and his team at the Renal Section—Immunology, Lenox Hill Hospital, 100 East 77th Street, New York 10021, USA for testing the sera for antibody to endostreptosin and Dr S. R. Aparicio, St. James's University Hospital, Leeds for immunohistology and electron microscopy, and for kindly providing the photographs.

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