SHORT REPORTS

Interhospital spread of a multiply resistant klebsiella

One multiply resistant klebsiella strain, serotype K16, caused infection and cross-infection in at least three hospitals in the London area in 1977-80. Multiple resistance was transferred from it to other bacteria in the hospitals.

Characters of the klebsiella isolates

Year	Hospital	Serotype	No of isolates studied	Resistances*	Plasmid molecular weights (Md)	Transferred plasmid incompatibility group	Reference
1977	St Thomas's	K16	9	ApSmTcCmKmSuGmTpHg	65 90	M	1, 4
1979	Luton and Dunstable	K16	2	ApSmSuTp	40 90	X	
			6	ApSmTcCmKmSuGmTpHg	40 65 90	M	
			4	ApSmTcCmKmSuGmTpHgNal	40 65 90	M	
		K20	1	ApSmTcCmKmSuGmTpHg	65 73	M	
		K61	1	ApSmTcCmKmSuGmTpHgNal	< 10 65100	M	
1980	Hammersmith	K62	1	ApSmTcCmKmSuGmTpHg	45 65 75	M	
		K16	5	ApSmTcCmKmSuGmTpHg	65 90	M	

*Ap, ampicillin; Sm, streptomycin; Tc, tetracycline; Cm, chloramphenicol; Km, kanamycin; Su, sulphonamide; Gm, gentamicin MIC 8 mg/l; Tp, trimethoprim; Hg, mercuric chloride; Nal, nalidixic acid.

Sources of strains, methods, and results

Strains studied were from (1) an outbreak of infection at St Thomas's Hospital in 1977¹; (2) an outbreak at the Luton and Dunstable Hospital in 1979, affecting at least 48 patients; (3) patients at Hammersmith Hospital in 1980, where a cluster of infections caused by the strain was found during a larger outbreak caused by a different multiply resistant klebsiella. Most isolates were from urine, and two were from blood cultures. No unusual virulence or invasiveness was suggested by the clinical histories.

Identification of strains, sensitivity testing, and methods to characterise plasmids were as described.² All the isolates of serotype K16 (table) were identical in biochemical reactions, and all but two carried plasmids of molecular weights 90 and 65 megadaltons (Md). The plasmid of 90 Md carried no antibiotic resistance and was not transferred. The plasmid of 65 Md was transmissible to *Escherichia coli* K12, belonged to incompatibility group M (IncM), and determined resistance to ampicillin/carbenicillin/cephaloridine, tetracycline, chloramphenicol, sulphonamides, mercuric chloride, neomycin/kanamycin, gentamicin, streptomycin/spectinomycin, and trimethoprim. Its trimethoprim resistance was transposable from one genetic locus to another. The same transposon has been found in other plasmids and bacteria.³ Plasmids of the different K16 isolates were indistinguishable in molecular weights, resistance linkages, incompatibility grouping, endonuclease cleavage, and transposable DNA sequence.

The 1979 K16 isolates, from Luton, carried a third plasmid, of 40 Md. Its resistances were masked by the 65 Md, IncM plasmid but it was isolated from two gentamicin-sensitive strains that lacked that plasmid. It was IncX, determined resistance to ampicillin, sulphonamides, streptomycin/spectinomycin, and trimethoprim, and had the same transposon as the IncM plasmid, suggesting that transposition had occurred.

On the evidence of serotype, biotype, and the carriage of the 90 Md and 65 Md IncM plasmids we conclude that the same clone of bacteria was responsible for infections in different hospitals. The isolates from Luton had acquired an extra plasmid, whose absence from the 1980 Hammersmith isolates shows that the route of transmission of the strain was not from Luton to Hammersmith.

Four of the K16 strains examined were resistant to nalidixic acid, at least two of them being from patients treated with that drug. As this character can be acquired by a single-step mutation, it does not alter our conclusions on the relation of the strains.

Plasmid transfer between bacteria occurred during the 1977 outbreak.^{1,4} In the 1979 outbreak discussed here, klebsiella strains of serotypes K20, K61, and K62 were found with the same IncM plasmid as the K16 strains, evidence for resistance transfer between bacteria in the hospital.

Comment

The klebsiella strain described here remained stable in its biotype, serotype, and basic plasmid content over four years and was evidently well adapted to its habitat and a successful coloniser. The factors that make some strains successful in this way are not understood. Multiple

resistance confers an advantage, but cross-infection occurred not only in patients taking antibiotics.¹ The multiple-resistance plasmid of the K16 strain was transferred to other bacteria during the hospital outbreaks, but the new host-bacterium-plasmid combinations did not spread. This plasmid was therefore not the determining factor, nor was the serotype, since K16 is not one of the commonest in British hospitals.⁵ Better understanding of the bacterial factors that permit spread would help in planning preventive measures.

Capsular serotypes were determined by M W Casewell, St Thomas's Hospital, London, and P R Mortimer, Public Health Laboratory, Coventry.

¹ Casewell MW, Dalton MT, Webster M, Phillips I. Gentamicin-resistant *Klebsiella aerogenes* in a urological ward. *Lancet* 1977;ii:444-6.

² Datta N, Dacey S, Hughes V, et al. Distribution of genes for trimethoprim and gentamicin resistance in bacteria and their plasmids in a general hospital. *J Gen Microbiol* 1980;118:495-508.

³ Richards H, Datta N, Wray C, Sojka WJ. Trimethoprim resistance plasmids and transposons in salmonella. *Lancet* 1978;ii:1194-5.

⁴ Datta N, Hughes VM, Nugent ME, Richards H. Plasmids and transposons and their stability and mutability in bacteria isolated during an outbreak of hospital infection. *Plasmid* 1979;2:182-96.

⁵ Casewell MW, Talsania HG. Predominance of certain klebsiella capsular types in hospitals in the United Kingdom. *J Infect* 1979;1:77-9.

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Polygeline compared with plasma protein fraction as the sole replacement fluid in plasma exchange

During plasma exchange the removal of 2-5 litres of plasma from a patient necessitates the use of replacement fluid, usually a human blood protein product. Fresh frozen plasma, although freely available, may cause severe allergic reactions if used repeatedly in the same recipient. Plasma protein fraction is an ideal replacement fluid but is expensive (currently £75 per litre).¹ Dextran, polygeline (Haemacel), and various crystalloid solutions have been used, but only with plasma protein fraction, or fresh frozen plasma, in a variety of volumetric ratios.^{2,3} No previous data on the use of polygeline as sole replacement fluid in plasma exchange have been reported.

Patients, methods, and results

Six patients, aged from 16 to 56 with various types of glomerulonephritis and deteriorating renal function underwent a total of four to six 2½-litre plasma exchanges using the Haemonelects-30 intermittent flow separator at 4-7 day intervals. The replacement fluid consisted of 2 litres of either plasma protein fraction or polygeline with 500 ml of normal saline containing 5000 units of heparin as anticoagulant. A loading dose of 2000-5000 units of heparin was given before exchange.

Samples were taken for full blood count, and to measure blood concentrations of urea, electrolytes, proteins, immunoglobulins, complement, and coagulation factors before and at one and 15 hours after completion of exchange. Creatinine clearances were measured between exchanges. Blood pressure was monitored throughout the exchange and for 24 hours after its completion.

In each case plasma protein fraction was used for one exchange and polygeline for all subsequent exchanges. Concurrent immunosuppression using a combination of prednisolone, azathioprine, and cyclophosphamide was given to all patients. In all patients blood pressure and pulse remained stable throughout the procedure and for 24 hours afterwards. Renal function between plasma exchanges, as measured by serum urea and creatinine concentrations together with serial 24-hour urine creatinine clearance measurements, did not deteriorate. Plasma treatment combined with immunosuppression either stabilised or improved renal function in our patients.

The effect on serum protein concentrations is shown in the table. After

Mean serum protein concentrations using plasma protein fraction or polygeline as sole replacement fluid in plasma exchange. Concentrations are expressed in g/l and ranges given in parentheses

	Polygeline (20 exchanges)			Plasma protein fraction (6 exchanges)		
	Total protein	Albumin	Globulin	Total protein	Albumin	Globulin
Before exchange	57 (71-43)	31 (41-20)	26 (30-19)	58 (65-40)	32 (38-18)	26 (29-22)
One hour after exchange	43 (55-30)	17 (28-8)	26 (35-21)	46 (57-35)	36 (42-36)	10 (15-6)
15 hours after exchange	47 (60-33)	21 (32-14)	26 (33-16)	49 (58-33)	33 (38-21)	16 (24-12)
4-7 days after exchange	55 (65-42)	30 (36-18)	25 (29-19)	54 (58-49)	31 (38-17)	23 (32-19)

plasma exchange the total protein concentration remained stable in both groups but the albumin concentration fell appreciably in the group given polygeline. This had recovered almost completely at 4-7 days. Haemoglobin concentration, white cell count, and platelet count remained stable in the two groups during plasma treatment, but coagulation factors, fibrinogen concentrations, and C3 and C4 concentrations fell equally with both solutions with complete recovery at 4-7 days. Serum immunoglobulin concentrations appeared to be reduced equally with both solutions but concurrent immunosuppression prevented a quantitative comparison and affected their concentrations.

Comment

Polygeline is a gelatin product of molecular weight 35 000 and a half life in the circulation of 5-10 hours. Using this material as sole replacement fluid 2½-litre plasma exchanges were performed successfully at intervals of 4-7 days. No evidence of hypoalbuminaemic hypovolaemia or postural hypotension occurred even though the serum albumin concentration in one patient fell as low as 8 g/l with no ill effects. Low albumin concentrations may be a problem if plasma exchange is contemplated at very short intervals, but an infusion of 1-2 units of plasma protein fraction at the end of the procedure may circumvent this problem (unpublished observations).⁴ Our results suggest that patients on weekly plasma exchanges do not need infusion of plasma protein fraction.

The serial reduction in immunoglobulin concentrations with repeated plasma exchange and immunosuppression, and the fall in complement, coagulation factors, and fibrinogen concentrations with each exchange are similar to those found by other workers.^{2,3} Polygeline has been reported to cause allergic skin reactions and, rarely, bronchospasm but only when the solution is infused rapidly. An urticarial reaction occurred in one of our patients on two separate occasions but was completely controlled and reversed by slowing the infusion rate.

Ideal protocols for the use of plasma exchange in various diseases have not yet been worked out. One factor limiting evaluation of plasma exchange is the high cost and limited availability of suitable replacement solutions. Polygeline is readily available and currently costs about £3.00 per 500 ml. In selected patients it seems to be

a safe substitute for plasma protein fraction and deserves further evaluation.

¹ Anonymous. Plasma exchange. *Lancet* 1980;ii:241-2.

² Keller AJ, Urbaniak SJ. Intensive plasma exchange on the cell separator: effects on serum immunoglobulins and complement components. *Br J Haematol* 1978;38:531-40.

³ Bayer WL, Farrates FB, Summers T, Belcher C. Coagulation studies after plasma exchange with plasma protein fraction and lactated Ringer's solution. In: Goldman JN, Lowenthal RM, eds. *Leucocytes: separation, collection and transfusion*. New York: Academic Press, 1975: 551-60.

⁴ Ibister JP. Fluid replacement during plasmapheresis. In: Biggs JC, chairman. *Clinical application of blood, plasma and plasma substitutes*. Macquarie University, Australia: Hoechst, 1977.

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Epidural morphine for ischaemic rest pain

Drowsiness and confusion often result when opiate analgesia is used to control severe rest pain in patients awaiting definitive treatment for ischaemia of the legs. To avoid these side effects we gave morphine by the epidural route, a procedure that is reportedly particularly effective in alleviating chronic pain.¹ The efficacy of this method of giving morphine is probably due to an action on specific receptors in the substantia gelatinosa.² Rapid penetration of the dura by morphine seems likely, as pain relief usually occurs within a few minutes of injection.¹ There is no loss of sensation or motor activity in the blocked segments.¹ A pin prick on the foot continues to feel sharp. This is a clear advantage over the effect of local anaesthetic agents given into the epidural space, which cause profound loss of sensation and power. Patients receiving epidural morphine analgesia may therefore go about their normal ambulant routine without risk of damaging an anaesthetised, chronically ischaemic limb. In addition, neither sympathetic blockade with risk of hypotension nor respiratory depression occurs with small doses. Cannulae have been left in situ without harm for up to 10 days.³

Changes in pain and duration of sleep at night produced by epidural morphine, showing mean values (and ranges)

	Pain score (cm)	Sleep at night (hours)
Before epidural analgesia started . .	8.28* (4-10)	3.25† (0-8)
After epidural analgesia started . .	0.94* (0-2)	6.93† (6-8)

Student's paired *t* test: **p* < 0.001; †*p* < 0.001.

Patients, methods, and results

We studied 16 patients with severe ischaemic rest pain that was poorly controlled by either dihydrocodeine or buprenorphine. An epidural cannula was inserted at the third to fourth lumbar interspace and connected to a bacterial filter at the shoulder. It was held in place by waterproof adhesive tape. Two millilitres of 1% plain lignocaine was injected down the catheter, followed several minutes later by 2 mg preservative-free morphine sulphate diluted in 10 ml isotonic saline. "Top-ups" were given when the patient felt the pain returning. While the cannula was in place patients were encouraged to walk about. Analgesia was continued during investigations before arterial grafting or amputation. Daytime pain relief was provided entirely by the epidural route. Occasionally, at night, oral analgesics were given if staff were not available to replenish the epidural. Immediately before operation the cannula was removed and the tip sent for bacteriological investigation. Pain was assessed using a 10 cm linear analogue scale⁴ once before and once after insertion of the epidural cannula. Changes in the number of hours' sleep at night and subjective changes in the temperature of the foot were also recorded.

Pain relief (table) was found to have reached its maximum within a few minutes. Before the planned end point nine cannulae had fallen out or become blocked or soiled. The mean time for which the cannula was retained was