

Klebsiella meningitis—report of nine cases

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SUMMARY During a serious epidemic of chest and urinary infections due to *Klebsiella aerogenes* in a neurosurgical unit, several patients developed klebsiella meningitis after trauma or surgery. Despite all attempts to control the epidemic and treat the meningitis with antibiotics, eight of the nine patients died. It was not until all antibiotics used to treat respiratory and urinary infections had been totally withdrawn that no further patients developed klebsiella meningitis.

Recent advances in antibiotic therapy have resulted in a great reduction in mortality from many infections and pyogenic meningitis is no exception. *Klebsiella* species are an uncommon cause of pyogenic meningitis, but this infection still carries a high mortality. This paper reports nine patients in a neurosurgical unit who developed this form of meningitis within one year. Only one patient survived.

In recent years an increasing number of hospital epidemics due to antibiotic-resistant Gram-negative bacilli have been reported (*Lancet*, 1966;

Lancet, 1970). Such outbreaks in neurosurgical units may result in patients developing meningitis or serious wound infections which may endanger life (Ayliffe, Lowbury, Hamilton, Small, Asheshov, and Parker, 1965).

Until 1971, the Glasgow Institute of Neurological Sciences was situated at Killearn Hospital, some 16 miles from Glasgow, and during the winter of 1967-68, antibiotic-resistant coliform organisms producing mucoid colonies, later identified as *Klebsiella aerogenes*, were isolated from sputum and urine specimens in increasing numbers. By July 1968, this organism could be recovered from the sputum of 12% of the

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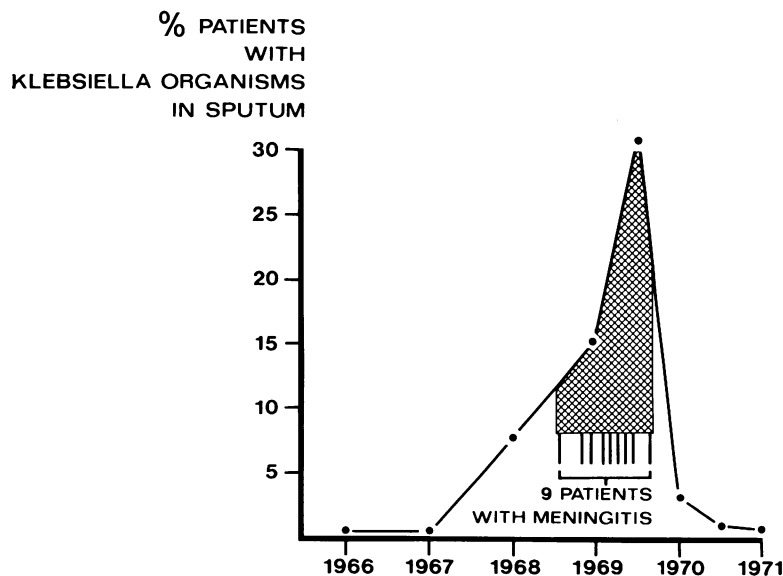


FIGURE Occurrence of meningitis in relation to isolation of klebsiella organisms from sputum.

patients in the intensive care ward (Figure). Full realization of the seriousness of the problem came with the death from klebsiella meningitis of a 12 year old boy admitted with cerebrospinal fluid (CSF) rhinorrhoea after a moderately severe head injury.

PATIENTS

There were six male and three female patients; two were children, one a young adult and the remaining six adults aged from 45 to 60 years (Table). Three patients (cases 1, 2, and 8) had sustained serious head injuries with compound fractures of the skull involving sphenoidal or frontal air sinuses. Two patients (cases 7 and 9) had undergone aneurysm surgery and at both procedures mucosa was breached during the approach: the frontal sinus at frontotemporal craniotomy for a middle cerebral aneurysm and the pharyngeal mucosa at a transcervical approach to a basilar aneurysm. Two patients (cases 3 and 5) developed meningitis after operations for benign intracranial tumours—an acoustic neuroma and a pituitary adenoma. The remaining two patients (cases 4 and 6) had relatively minor procedures—a ventriculoperitoneal shunt for hydrocephalus and stereotaxic surgery for Parkinsonism.

Three patients (cases 3, 4, and 5) had localized wound infections at the operative site in addition to the meningitis. *Klebsiella* was persistently isolated from the sputum and throat of one patient (case 9) during the period of four weeks between operation and development of meningitis, but it was only found in the sputum or throat of five patients and also the urine of two of these patients only in the 48 hours preceding clinical recognition of the meningitis. Blood cultures were taken from three patients during the 48 hours after meningitis was diagnosed. One (from case 9) was sterile but from the other two (from cases 3 and 4), *Kl. aerogenes* was isolated.

DEVELOPMENT OF MENINGITIS

In all but one patient, persistent pyrexia of 39–40° C developed within the 24 hours before recognition of meningitis: the remaining patient (case 8), however, had an intermittent fever for a week. The time between the presumed penetration of the dural defect (at injury or surgery) by *Kl. aerogenes* and the development of meningitis varied from three to 10 days in all but one patient. In this exception (case 9) the period was four weeks. Only five patients had neck stiffness or Kernig's sign before the diagnosis was proven at lumbar puncture. The clinical presentation was in

TABLE
CLINICAL DETAILS OF NINE PATIENTS

No.	Sex	Age (yr)	Diagnosis	Suspected portal of entry	Wound infection	Time to develop (days)	CSF (cells/cu.mm)		Sugar (mg/100 ml.)	Klebsiella isolated before		Prophylactic anti-biotics	If treated	Reason for no treatment	Cure	Survival (days)
							Lumbar	Ventric.		Sputum	Urine					
1	M	12	Head injury	Fracture Frontal sinus		7	5,000	4,000	0	+ve		+		+	56	
2	M	46	Head injury	Fracture Sphenoidal sinus		7	?	850	?	+ve		+	died early		0	
3	F	56	Acoustic neuroma	Postoperative	+	4	1,300	no tap	?	+ve		+			5	
4	F	2	Hydrocephalus	Postoperative	+	3	?	3,900	0			+			30	
5	M	59	Pituitary adenoma	Postoperative	+	10	7,000	25,000	?	+ve		+			19	
6	M	48	Parkinson's disease	Postoperative		unknown	1,300	90	35					diagnosed at p.m. died early	0	
7	M	47	Middle cerebral aneurysm	Postoperative mucosal breach		7	2,700	no tap	15						0	
8	M	21	Head injury	Fracture Frontal sinus		9	3,600	no tap	0	+ve		+	died early		0	
9	F	52	Basilar aneurysm	Postoperative mucosal breach		31	6,700	125	0	+ve		+		+	alive	

fact as varied as any other purulent meningitis in neurosurgical patients, and we concur with Thompson, Williams, Williams, and Anderson (1952) that the clinical features of *klebsiella meningitis* are indistinguishable from any other type.

When the diagnosis was substantiated by examination of the CSF, the initial white cell counts ranged from 1,300 to 7,000 cells per cu.mm. Sugar determinations were made on the CSF of six of the patients and results were all low, and, in fact, sugar was absent in four. Ventricular taps confirmed ventriculitis in all six patients who had this examination and ventricular CSF white cell counts ranged from 90 to 25,000 cells per cu.mm. Gram-stained films showed large numbers of polymorphs and Gram-negative bacilli. Culture yielded a heavy growth of lactose fermenting coliform organisms which produced mucoid colonies. Full biochemical investigation proved that they were *Kl. aerogenes*. In one patient (case 6) there was an increasing CSF leucocytosis but organisms were not seen in the smears nor were they isolated in culture until necropsy.

CHEMOTHERAPY

PROPHYLACTIC At the time of this epidemic, no defined policy restricting the use of antibiotics had been formulated. It was common practice to prescribe routinely broad-spectrum antibiotics to patients thought to be at high risk of meningeal infection after suspected dural breaches at the site of compound fractures or when the upper respiratory tract mucosa was opened at craniotomy. The most commonly used antibiotic regime was the combination of ampicillin and cloxacillin. Of the seven patients given prophylactic chemotherapy, two were given additional intramuscular colistin and despite the fact that all strains of *Kl. aerogenes* were sensitive *in vitro* to this drug, both patients developed meningitis after eight days of administration at normal dosage.

THERAPEUTIC Although the strains of *Kl. aerogenes* isolated differed in their sensitivity to many antibiotics, all proved to be sensitive to both gentamicin and colistin. The therapy for adults who were treated was standardized as follows:

Systemic
 / Gentamicin: 40 mg twice daily*
 \ Colistin: 1 mega unit 4-hourly

* The recommended dose of gentamicin is now 80 mg three times a day.

Intrathecal
 / Gentamicin: 2 mg
 \ Colistin: 50,000 units

} Twice daily for two days followed by once daily

(half of the dosage into a ventricle and half into the lumbar theca).

RESULTS OF TREATMENT

Only five patients were treated. Of the remaining four, three were diagnosed only within a few hours of death so that no more than one dose of colistin and gentamicin could be given and in the other case (case 6) the diagnosis was made only at necropsy.

Three of the patients who were treated died five, 30, and 19 days after isolation of the organism from the CSF (cases 3, 4, and 5). In these patients, the CSF became sterile within four days but it remained purulent. In the other two treated patients (cases 1 and 9) lumbar and ventricular CSF rapidly became sterile and the cell counts steadily fell to below 20 cells per cu.mm. One of these patients recovered (case 9) but the other finally died of pneumonia while remaining unconscious a month after the meningitis had subsided.

Necropsy was performed on six of the eight patients who died. All had florid meningitis with tenacious pus in the subarachnoid space over the convexities and filling the basal cisterns. In addition, four of them had evidence of persisting ventriculitis, two had subdural abscesses, and one had encephalitis. Three of the patients had herniation of the unci or cerebellar tonsils indicating raised intracranial pressure.

DISCUSSION

INCIDENCE *Klebsiella* species have been reported as an uncommon cause of purulent meningitis in several series. Ransmeyer and Major (1943) investigating the literature found that this was the causal organism of only three patients out of a total of 3,714 cases of purulent meningitis. In reviews of published cases, *klebsiella meningitis* was twice as common in men as in women. It usually affected infants or adults and was most uncommon between the ages of 3 and 20 years (Ransmeyer and Major, 1943; Thompson *et al.*, 1952). A 12 year old boy was

the only patient within this age range in this series and we found the same sex ratio.

PORTAL OF ENTRY Thompson *et al.* (1952) in a comprehensive review of all the known reported cases at that time observed that the most common primary foci of klebsiella infection were infections of the middle ear, mastoid, nasal sinuses, lungs, and wounds, and they concluded that this organism is rarely a primary invader of the meninges. When blood cultures were taken, 70% were positive.

In this series, we isolated the organism from the sputum or throat before or at about the same time as from the CSF in five patients, suggesting a spread from the upper respiratory tract. It is a matter of conjecture as to whether the organisms reached the meninges from the respiratory tract by direct spread (as probably in cases 1, 2, 7, 8, and 9).

It is possible that in the other cases transmission may have been mediated by the blood stream as is normal in meningococcal meningitis. Genest, Bingham, and Hamilton (1963) reported a patient with klebsiella urinary infection with presumed blood stream spread after urethral dilatations to infect bilateral chronic subdural haematomata. Septicaemia was recognized in two of the three patients on whom blood culture had been performed, but since these cultures had not been taken until after the onset of meningitis, this investigation does not clarify the route of spread.

In a neurosurgical unit, the risk of severe infection of the ventricles and meninges by Gram negative bacilli appears inseparable from operative procedures (Newman and Holt, 1967). Spivack, Eisenberg, Weiss, and Flippin (1957) reported one patient who developed klebsiella meningitis after a craniotomy at which the frontal sinus mucosa which was already infected with the organism was breached. Lewin (1948) reported an incidence of meningitis of 10% complicating a series of wartime penetrating head wounds and found a quarter of these to be due to Gram negative bacilli but none to *Klebsiella*.

BACTERIAL ENVIRONMENT The incidence of klebsiella meningitis appeared to be directly related to the number of patients whose respiratory tracts were colonized by the organism. There

appeared to be a critical level of about 10% above which meningitis occurred, and as soon as the isolation rate fell below this level there were no further meningeal infections (Figure).

Regular routine bacteriological monitoring within an intensive care area can give warning of an impending outbreak of infection. This organism may have been transmitted via the air from patients with tracheobronchitis (Price and Sleight, 1970) and all attempts to isolate infected patients from those at high risk should be enforced. Recent information regarding the epidemiology of *Klebsiella* infections (*Lancet*, 1971) suggests that gastrointestinal colonization with *Klebsiella* precedes infection and faeces may be an important reservoir in an epidemic situation. Shooter, Faiers, Cooke, Breden, and O'Farrell (1971) have shown that in hospital patients some of the intestinal Gram negative bacilli, including *Klebsiella*, originate in their food.

PROPHYLAXIS The isolation of *Klebsiella aerogenes* from sputum, nose and throat was recognized in one patient to indicate the potential risk of meningitis (case 9). Nevertheless prophylaxis by systemically and locally given antibiotics failed to prevent migration to the meninges. The failure of systemic colistin to prevent meningitis may well be due to the fact that, as with many antibiotics, they fail to attain therapeutic levels in the CSF when the meninges are normal (Boger and Gavin, 1961). Price and Impey (1971) record that, even when colistin is administered in five times the normal dose to non-meningitic patients, CSF levels are much lower than concurrent muscle and serum levels. Boger and Gavin (1961) found the mean colistin levels in lumbar CSF and serum to be similar (0.27 µg/ml. and 0.35 µg/ml. respectively) six hours after a single dose of 500,000 u. Patients on continuous very high dosage of colistin (26 mega units a day) attained a mean lumbar CSF level of 2.6 µg/ml. compared with the mean serum level of 71 µg/ml. The brain levels (mean 10 µg/g) compared more favourably with the concurrent muscle levels (mean 43 µg/g).

All attempts at chemoprophylaxis of klebsiella meningitis failed and the epidemic was controlled only when all antibiotics, both therapeutic and prophylactic, were withdrawn. This resulted in the organism virtually disappearing from the

unit and a considerable reduction in the overall infection rate (Price and Sleight, 1970). When an epidemic develops, the prescribing policy for antibiotics requires to be reviewed.

However, in the non-epidemic situation when infection with resistant Gram negative bacilli is not feared, it is probably justifiable to practise antibiotic prophylaxis whenever there is a break of dura mater resulting in a communication with the upper respiratory tract.

If the organism has also colonized or infected the respiratory or urinary tracts, it is reasonable to consider using colistin in very high dosage to eliminate the reservoirs within the patients and thus prevent reinfection. If so, renal function should be carefully monitored but nephrotoxicity is reversible (Price and Graham, 1970).

TREATMENT

We do not feel confident to give advice concerning the treatment of patients when reporting a series with such a very high mortality. When no antibiotics were available, all patients with this infection died (Thompson *et al.*, 1952). With the introduction of sulphonamides, streptomycin, chloramphenicol, and tetracycline, the overall mortality had fallen to only 50% (Soscia, Di Benedetto, and Crocco, 1974). Spivack *et al.* (1957) commented that one reason for the high mortality was the fact that the disease was often fulminating. Newman and Holt (1967) published a series of four infants with klebsiella meningitis who all survived as a result of systemic and intraventricular gentamicin.

Although early recognition of meningitis is not always easy, there must be no delay in instituting adequate chemotherapy as soon as the diagnosis has been substantiated by microscopic examination of the CSF. We believe that the most aggressive therapeutic regime using both colistin and gentamicin in conventional dosage by systemic, lumbar thecal and intraventricular routes is essential, and perhaps this is the regime of choice for meningitis caused by hospital strains of coliform organisms before *in vitro* sensitivities are available. Marsden and Hyde (1962) reported some success in treating infants with meningitis due to Gram negative organisms with colistin.

Pus associated with klebsiella infections is

characteristically tenacious and it has been suggested that this prevents adequate antibiotic penetration and may explain why the organism may be sensitive to an antibiotic *in vitro* but resistant *in vivo*.

In retrospect, we believe that six of those who died might have survived if they had not developed meningitis, although four of them would probably have been permanently disabled with dysphasia or hemiparesis. The other two would have died even if meningitis had not supervened.

We are aware that we have recommended a therapeutic regime, although eight of our nine patients died. We are comforted to find that Spivack *et al.* (1957) in reporting the largest single series believed that sulphonamide was the drug of choice, although 10 of their 11 patients succumbed.

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