Rifampicin in pneumococcal meningoencephalitis

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Abstract
The cases are reported of two infants with pneumococcal meningitis in whom initial antibiotic treatment was ineffective despite the organisms being sensitive to the drugs used. A clinical and radiological diagnosis of meningoencephalitis was made. A rapid improvement followed the addition of rifampicin treatment.

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Pneumococcal meningitis is a life threatening disease with an incidence of 1–3 in 100 000.1 Mortality may be as high as 30%. A large proportion of survivors have significant neurological impairment.2 Pneumococcal meningitis is often treated with β lactam antibiotics such as penicillin or cefotaxime.3 Among the many serious complications of pneumococcal meningitis is direct bacterial invasion of brain tissue, termed 'meningoencephalitis' or 'cerebritis'. This may present as persistent drowsiness, coma, confusion, convulsions, and focal neurological signs. In severe cases characteristic features may be seen by computed tomography. These findings have a significant association with persistent abnormal neurological signs and particularly subsequent epilepsy.4

Rifampicin has its major use in the treatment of tuberculosis infection, including tuberculous meningitis, and has a wide spectrum of activity against Gram positive organisms. Rifampicin is highly lipid soluble and penetrates cell membranes well,5 achieving high concentrations of cerebrospinal fluid, even in the absence of inflamed meninges. As a result it has been recommended for use in staphylococcal or listerial central nervous system infection or in cases of an infected ventriculoperitoneal shunt, in which there may be little or no meningeval inflammation.6,7 Rifampicin has also been used in combination treatment for meningitis caused by brucella and flavobacterium species.8,9

We report the cases of two infants with proved pneumococcal meningitis with organisms shown to be sensitive to β lactam antibiotics and in whom clinical and radiological evidence of severe meningoencephalitis did not resolve while receiving β lactam antibiotic treatment. In both infants the addition of rifampicin was followed by a striking clinical improvement.

Case reports
CASE 1
A previously well 4 week old male infant was admitted with a 24 hour history of poor feeding, vomiting, and irritability. He had not received antibiotic treatment before admission. On examination he was pyrexial (38-2°C) and irritable.

Initial investigations were as follows: haemoglobin 115 g/l, white cell count 6·0·10⁹/l (neutrophils 3·3), and platelets 440·10⁹/l. Plasma electrolytes were normal. Microscopy of lumbar cerebrospinal fluid showed white cell count 960·10⁶/l, red cell count 415·10⁶/l, and numerous Gram positive cocci. He was treated with intravenous cefotaxime (200 mg/kg/day), netilmicin (7·5 mg/kg/day), and dexamethasone (0·15 mg/kg every six hours for four days).

Culture of cerebrospinal fluid confirmed a pure growth of Streptococcus pneumoniae sensitive to cefotaxime by disc susceptibility testing. The infant remained pyrexial and irritable. Forty eight hours after admission he had several episodes of hypotonia and decreased responsiveness. Repeat electrolyte and calcium measurements were normal. An electroencephalogram confirmed widespread epileptic activity. Computed tomography of his brain showed ventriculitis and encephalitis, but no evidence of raised intracranial pressure. The convulsions were difficult to control, only partially responding to intravenous phenobarbital and an infusion of paraldehyde.

Eight days after admission he remained pyrexial (38-7°C) (fig 1) and irritable on 77-79

Figure 1 Maximum daily temperature during hospital admission of the two patients. The addition of rifampicin was closely followed by a rapid resolution of pyrexia as part of a marked clinical improvement.
chloramphenicol (100 mg/kg/day), and
dexamethasone (0-2 mg/kg every six hours
for five doses). His condition stabilised
and penicillin was stopped after 36 hours. On day
four of this admission he had a number of
generalised and left sided focal seizures.
Computed tomography showed meningo-
encephalitis and a small infarct in the right
internal capsule. Antibiotic treatment was
changed to intravenous ceftaxime alone
(200 mg/kg/day). His clinical status remained
poor with continuing fever, irritability, and
occasional fits despite phenytoin and
phenobarbitone.

On day 12 ceftaxime was discontinued.
Twenty four hours later he deteriorated with a
recurrence of high fever and increased fits.
Repeat computed tomography confirmed
persistent cerebritis (fig 2). Cefotaxime was
restarted with the addition of intravenous
rifampicin (20 mg/kg/day in two divided
doses). He made a rapid recovery with his
temperature falling to normal within 36 hours
and a complete cessation of his fits (fig 1).
He was maintained on intravenous antibiotics for
a further three weeks before taking rifampicin and co-trimoxazole by mouth for
two weeks.

On discharge he had marked left hemi-
paresis and a mild right sided weakness.
Repeat computed tomography showed generalised cerebral atrophy with resolution of
the appearances of cerebritis.

**Discussion**

These cases show a clear clinical improvement
in severe pneumococcal meningoencephalitis
with rifampicin treatment. This followed the
failure of a prolonged course of treatment
with antibiotics to which the pneumococcal
isolates were sensitive. A previous report of
pneumococcal meningitis in the presence of a
ventriculoperitoneal shunt describes similar
findings. Another case described by Peters,
Pizer, Millar with benzylpenicillin and
ceftaxime for nine days was ineffective,
but after the addition of rifampicin the child
made a rapid recovery without removal of the
shunt.

We believe our patients are not typical in
that the degree of cerebritis was much greater
than the characteristically mild disorder seen in
many cases of bacterial meningitis. This fact
may partially explain the dramatic response
achieved with rifampicin because of the high
cerebrospinal fluid levels and excellent tissue
penetration it exhibits, even in the absence of
marked meningeval inflammation. Another
possible explanation for the efficacy of
rifampicin may have been the persistence of
bacteria within host cells which provide an
effective barrier to β lactam antibiotic
treatment. In this situation the intracellular
penetration of rifampicin may have allowed it
to be effective in eradicating infection when
in presence of cell wall deficient bacteria or
1 forms. Rifampicin is effective against cell

**CASE 2**

A previously healthy 8 month old infant
was admitted after a prolonged generalised
convulsion. He had been irritable, sleepy, and
vomiting intermittently for 48 hours before the
convulsion. He was pyrexial (38-6°C with
generalised poor tone but no focal neurological
deficits. He continued to have fits despite
rectal diazepam and intravenous phenytoin
(10 mg/kg), but his seizures were eventually
controlled with a paraldehyde infusion.

Cerebrospinal fluid examination showed
a white cell count of 260×10^6/l (90%
neutrophils) and numerous Gram positive
cocci later confirmed as pneumococci sensitive
to benzylpenicillin, cefotaxime, and chloram-
phenicol on disc susceptibility testing. He was
treated with benzylpenicillin (200 mg/kg/day),

handling, with occasional convulsive move-
ments. Repeat lumbar puncture showed
persistent cerebrospinal fluid neutrophilia but
no organisms on Gram staining and no growth
on culture. Repeat computed tomography
showed persisting ventriculitis and cerebritis.

In view of the unsatisfactory response to
treatment, rifampicin (20 mg/kg/day, given in
two divided doses) was added intravenously on
the 13th day after admission. The next day a
dramatic clinical improvement was noted with
decreased convulsions, improved feeding, and
a more normal cry. His temperature settled to
normal within 36 hours for the first time since
admission (fig 1). He continued to improve
while receiving intravenous rifampicin for nine
days, followed by rifampicin by mouth for
eight days. On discharge on day 27 he was
smiling, fixing, following with his eyes, and
moving his limbs appropriately, except for
decreased use of his right arm.

**Figure 2** Contrast computed tomogram through
midventricular level in patient 2. The scan shows
enhancement of the ependyma and ring enhancement in the
low attenuation area adjacent to the right lateral ventricile.
The appearances are compatible with cerebritis and
ventriculitis.
Rifampicin in pneumococcal meningoencephalitis

wall deficient bacteria and may have eradicated cell wall deficient pneumococci in these two patients.

We conclude that in pneumococcal meningitis when β-lactam antibiotics are ineffective, the diagnosis of meningoencephalitis should be considered. In this situation rifampicin may be a useful addition to the treatment.

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