LETTERS TO THE EDITOR

Antibiotic treatment of suspected neonatal meningitis

SIR,—The annotation on antibiotic treatment of suspected neonatal meningitis seems to demonstrate that optimal treatment of this thankfully rare disorder is still not clear.[1] The suggested array of antibiotic treatment and combined routes of administration may provide cover against a wide range of organisms, but is such treatment in the best interests of every patient? In a sick hypotensive infant who may already have compromised renal function the combination of aminoglycoside and cephalosporin may exacerbate the problem. To state that 'Gentamicin should be used primarily to treat the associated septicaemia' is rather puzzling, as the implication is that cephalosporins are incapable of doing this. Is there any evidence to suggest that cefotaxime is ineffective in the treatment of bacteraemia in neonates?

I am concerned by the conviction of the authors in their management proposals. To begin a paragraph stating 'there is no doubt in our minds that intraventricular treatment should be used' and end it with 'there has been no study of intraventricular treatment . . . and little information on the ventricular drug concentration achieved after systemic treatment alone in dilated ventricles' is perhaps a little rash in view of the finding of significantly increased mortality after intraventricular treatment in the American study.[2]

The conclusion of McCracken and colleagues was that 'intraventricular therapy cannot be recommended for the routine management of neonatal meningitis caused by Gram negative enteric bacilli'. In the absence of a further randomised multicentre trial it is surely ill advised to recommend the adoption of this invasive and potentially dangerous mode of treatment as the standard treatment in neonatal Gram negative meningitis with ventricular dilatation.

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1 Gandy G, Rennie J. Antibiotic treatment of suspected neonatal meningitis. *Arch Dis Child* 1990;65:1–2.
2 McCracken GH Jr, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram negative bacillary meningitis of infancy. Report of the Second Neonatal Meningitis Cooperative Study Group. *Lancet* 1980;i:787–91.

SIR,—The main thrust of the annotation on antibiotic treatment of neonatal meningitis is the recommendation that antibiotics should be used intraventricularly as well as intravenously, particularly in the babies infected with Gram negative enteric organisms.[1] The authors mention the only significant study in the field, that of McCracken *et al* (1980),[2] only to dismiss its findings (there was a higher mortality in the group treated with intraventricular therapy) on the grounds that many of the infants had salmonella infection and were treated relatively late. This interpretation does not take into account recent advances in our understanding of the pathophysiology of meningitis, and is likely to lead to a simplistic approach to clinical management. It is now known that the inflammatory response in meningitis (and in many other infective conditions) is mediated through the release of cytokines, particularly tumour necrosis factor and interleukin-1, from cells after their exposure to bacterial endotoxin and other cell wall material. Interleukin-1 concentrations in the cerebrospinal fluid correlate well with the degree of meningeal inflammation and with the outcome.[3] Ventricular cerebrospinal fluid samples from the 1970s study performed by McCracken and his colleagues were stored in the deep freeze at the time, and their endotoxin and cytokine concentrations have recently been examined by Mustafa *et al* (1989).[4] They found increased endotoxin and very much higher interleukin-1 concentrations in the cerebrospinal fluid of the group treated with intraventricular antibiotics than in those only treated intravenously; mean endotoxin concentrations of 78 ng/ml in the intraventricular group compared with 22 ng/ml in those given intravenous treatment alone. Similarly, mean interleukin-1 concentrations as high as 5024 pg/ml in the patients given intraventricular gentamicin contrasted with mean concentrations of 87 pg/ml in patients treated with intravenous antibiotics alone. This effect is likely to be due to bacterial lysis, releasing endotoxin and other bacterial cell wall products by very high local concentrations of intraventricular gentamicin. The resulting cytokine production would appreciably exacerbate the inflammatory response within the ventricles. Thus although intraventricular antibiotics may be appropriate treatment in neonatal meningitis (although there is little firm evidence either way), it is important to modulate the resultant inflammatory response as well as to kill the bacteria. Considerable recent work, particularly from McCracken's group, has shown that dexamethasone can do this both in the experimental animal and in children with meningitis.[5] Until we recognise that the treatment of meningitis should include the suppression of excessive inflammation as well as the destruction of the pathogen we are unlikely to improve the prognosis in this serious and distressing disease.

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1 Gandy G, Rennie J. Antibiotic treatment of suspected neonatal meningitis. *Arch Dis Child* 1990;65:1–2.
2 McCracken GH Jr, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy. Report of the Second Neonatal Meningitis Cooperative Study Group. *Lancet* 1980;i:787–91.
3 McCracken GH Jr, Mustafa MM, Ramilo O, Olsen KD, Risser RC. Cerebrospinal fluid IL-1beta and TNF concentrations and outcome from neonatal gram-negative enteric bacillary meningitis. *Pediatr Infect Dis* 1989;8:155–9.
4 Mustafa MM, Mertsola J, Ramilo O, Saez-Llorens X, Risser RC, McCracken GH Jr. Increased endotoxin and interleukin 1beta concentrations in cerebrospinal fluid of infants with coliform meningitis and ventriculitis associated with intraventricular gentamicin therapy. *J Infect Dis* 1989;160:891–5.
5 Lebel MH, Freij BJ, Syrogiannopoulos GA, *et al*. Dexamethasone therapy for bacterial meningitis. *N Engl J Med* 1988;319:964–71.

Drs Rennie and Gandy comment:
Thank you for giving us the opportunity to reply to the correspondence regarding our editorial. Opinions regarding the benefits of intraventricular treatment in neonatal Gram negative meningitis are likely to continue to differ for some time: our recommendations constitute what we consider to be sensible guidelines for the management of this serious and rare disease. We remain of the opinion, shared with Pearse and Roberton,[1] that a ventricular tap should be performed if the ventricles are large or the infant is failing to respond to treatment after 24 hours. Intraventricular treatment should be given via a Rickham reservoir to babies with ventriculitis. We do not avoid this treatment because of the conclusions of the Neonatal Meningitis Cooperative Study Group because patients were enrolled in this study more than 10 years ago, before the widespread availability of cranial ultrasound or the third generation cephalosporins. Much of the discussion pertaining to this work has been well rehearsed before,[2] including the fact that only 20 cases were actually neonates suffering from *Escherichia coli* meningitis.

The combination of cefotaxime with another drug such as gentamicin[3] was suggested because of the evidence in favour of synergism, the improved outlook in granulocytopenic patients with Gram negative sepsis after dual treatment, and to combat the emergence of resistance. The advice of our microbiologists has always been to start treatment with a dual regime to obtain rapid bacterial killing. We use a single agent when the baby is improving and sensitivity results are available. Ceftriaxone monotherapy seems promising in adults and may prove useful in the newborn. The potential for renal toxicity is precisely the type of complication that led us to suggest transfer of such cases to centres with intensive care facilities.

Dr Tarlow's suggestion that neonatologists should consider high dose dexamethasone is an interesting one and we are aware of the evidence suggesting a reduction in neurological sequelae in older children, most of whom were suffering from haemophilus infection.[4] Trials of dexamethasone treatment in neonatal meningitis are planned.[5] The dose suggested is large and high dose steroid treatment has proved detrimental in shock. This may be more of a problem for the neonate with Gram negative meningitis than it has been in the general paediatric population.

1 Pearse R, Roberton NRC. Infection in the newborn. In: Roberton NRC, ed. *Textbook of neonatology*. London: Churchill Livingstone, 1987.
2 Warren RE, Roberton NRC. Intraventricular gentamicin in neonates. *Lancet* 1980;ii:252.
3 Allen JD, Meollering RC. Management of infection caused by gram negative bacteria: the role of antimicrobial combinations. *Rev Inf Dis* 1985;7:S559–71.
4 Havens PL, Wendenberger KJ, Hoffman GM, Lee MB, Chusid MJ. Corticosteroids as adjunctive therapy in bacterial meningitis. *Am J Dis Child* 1989;143:1051–5.
5 McCracken GH Jr, Lebel MH. Dexamethasone therapy for bacterial meningitis in infants and children. *Am J Dis Child* 1989;143:287–9.

When should the coeliac patient have an intestinal biopsy?

SIR,—Gluten challenges and intestinal biopsies are stressful procedures both for coeliac patients and for the doctors dealing with them. While we recognise that the time has