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A Randomised Prospective Comparison of Cefotaxime versus Netilmicin/Penicillin for Treatment of Suspected Neonatal Sepsis

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Summary

In an open prospective study performed in 2 neonatal units, infants with suspected neonatal sepsis (SNS) of unknown microbial cause were randomly allocated to receive treatment with either cefotaxime (CTX) or netilmicin plus penicillin (N + P). 236 patients were entered into the trial, of whom 222 were evaluable. The number of 'definitely' and 'probably' infected babies was similar in both groups. There was no difference in clinical outcome between patients in the 2 treatment groups and no side effects were recorded for either of the antibiotic regimens.

Antibiotic sensitivity testing of bacterial isolates from peripheral sites showed almost universal sensitivity of potential pathogens to both antibiotic regimens at the start of treatment in all infants. Thereafter, organisms resistant to CTX were isolated from patients in both *treatment groups, possibly reflecting the antibiotic sensitivity profile of the colonising bacteria in both neonatal units.*

The results of this study indicate that either CTX or N + P are suitable, in our units, for the 'blind' treatment of early SNS. In units where listerial infections are prevalent, specific cover should be added to CTX. For SNS developing after admission, the choice of antibiotics will depend upon the background antibiotic sensitivity profile of the colonising bacteria.

The use of broad spectrum antibiotics for the early treatment of suspected neonatal microbial infection is well established (Editorial 1979; Siegel & McCracken 1981). Antibiotics may be prescribed to treat suspected sepsis in newborn infants for several reasons. The neonatal immune system is immature, particularly in those infants born before term (Miller 1977), and there is, therefore, a high likelihood that abnormal clinical signs are due to infection. However, the signs of sepsis tend to be nonspecific and the clinical presentation of conditions such as hyaline membrane disease may be indistinguishable from that of pulmonary infection or septicaemia (Ablow et al. 1976). In addition, sick neonates are often subjected to invasive procedures, such as endotracheal intubation and the insertion of chest drains, that facilitate entry of pathogenic bacteria. Finally, antibiotic treatment tends

to be started early in neonates because infection can become overwhelming within a very short period, long before culture results become available.

The bacteria most commonly implicated in neonatal sepsis are Gram-negative bacilli, group B *Streptococcus* and staphylococci (Siegel & McCracken 1981; Vesikari et al. 1985).

For many years the standard antibiotic regimen for the treatment of suspected neonatal sepsis (SNS) in neonatal intensive care units (NICUs) and special care baby units (SCBUs) has tended to be an aminoglycoside with penicillin or ampicillin (Klaus & Fanaroff 1979). Although such combinations provide good protection against a wide range of organisms, aminoglycosides may be associated with important adverse effects (Blumer & Reed 1983) and the frequent monitoring of blood levels is mandatory; these are significant disadvantages, since the majority of treated babies do not have proven sepsis (Philip & Hewitt 1980). Also, after several years' use of such standard regimens the 'resident' organisms of a unit may become resistant (Hall et al. 1986). Effective, but safe, alternatives to the aminoglycoside/penicillin combination are, therefore, desirable.

Although there have been relatively few comparative trials, reports have indicated that broad spectrum penicillins such as piperacillin (Placzek et al. 1983) and third generation cephalosporins such as cefotaxime (de Louvois et al. 1982; Kafetzis et al. 1982) and ceftazidime (Elias-Jones 1985; Low et al. 1985) are suitable alternatives.

After the introduction of cefotaxime, with or without penicillin, as the standard antibiotic treatment for suspected neonatal sepsis on the SCBU in Southampton (Hall et al. 1986) a formal evaluation of the efficacy and potential adverse effects of the change in treatment was undertaken.

1. Methods

The study was carried out in two SCBUs in England that are separated geographically by about 120 miles. Cefotaxime had been used as a first-line antibiotic in the management of suspected neonatal sepsis for almost 4 years in one of the units (Southampton) and as a regular alternative to gentamicin plus penicillin in the other (Chatham).

1.1 Design

The study was designed as an open, randomised prospective comparison of 2 antibiotic regimens for the treatment of suspected neonatal sepsis. Consecutively presenting babies were randomly allocated to 1 of the 2 treatment regimens according to a balanced randomisation sequence having a block size of 4. Allocation to treatment group was stratified according to birthweight: those weighing 1500g or more at birth were randomised using a separate schedule from those weighing less than 1500g.

One regimen consisted of cefotaxime alone, given intravenously in a dose of 25 mg/kg twice daily, increasing to a maximum of 75 mg/kg if severe sepsis was suspected. The other regimen comprised intravenous netilmicin 3 mg/kg twice daily, together with intravenous penicillin 60 mg/kg twice daily. The dosage of netilmicin was subsequently adjusted as indicated by blood levels which were routinely taken immediately before and 30 minutes after the third dose of netilmicin. Treatment was discontinued after 2 days if deep bacterial cultures were sterile and infection was no longer suspected. If sepsis was still suspected or proven at 2 days, treatment was continued, usually for a minimum of 5 days, until the clinical and bacteriological signs had resolved or unless there were clinical or bacteriological reasons for changing to a different antibiotic regimen.

1.2 Bacteriological Testing

Bacteriological screening tests on entry to the study included surface swab cultures (throat, nose, rectum and umbilicus for all; some also had ear and axillary swabs at the discretion of medical staff), gastric aspirate for those admitted immediately after delivery, blood cultures (aerobic and anaerobic), urine culture and, where clinically indicated, cerebrospinal fluid (CSF) culture. Surface cultures were repeated at 2 days and at the end of treatment;

blood, urine and CSF cultures were repeated only if clinically indicated.

Sensitivity testing was performed by the Stokes method and 30μg cefotaxime discs, 10U penicillin discs (25μg for urinary isolates) and 10μg netilmicin discs. The control strain for Gram-positive isolates was the Oxford *Staphylococcus* and, for Gram-negative isolates, *Escherichia coli* NCTC 10418. Blood was also collected for the detection of group B streptococcal antigen (Baker & Rench 1983; Webb & Baker 1980).

1.3 Haematological and Biochemical Testing

The following blood tests were routinely performed on entry to the study: haemoglobin and full blood count; differential white cell count; c-reactive protein (quantitative assessment); urea and electrolytes; creatinine. These tests were repeated at 2 days and, when appropriate, 5 days. Blood pH, pCO_2, bicarbonate and pO_2 were also measured at trial entry. It was intended that liver function tests should be performed at similar intervals but, because of limited availability of blood, these measurements were possible in only some of the trial patients. Statistical analysis was performed by chi-squared and Student's t-tests, as indicated.

Table I. Indicators of sepsis

Risk factors
Maternal factors
Maternal pyrexia
Positive maternal bacteriological cultures
Obstetric factors
Prolonged rupture of membranes
Offensive liquor amnii
Instrumental delivery
Neonatal factors
Preterm delivery
Intrauterine growth retardation
Birth asphyxia
Ventilator therapy
Umbilical catheter
Venous long-line
Drip site ulcer
Certain non-lethal congenital anomalies
Abnormal clinical features
Nursing/medical staff concern
Unexplained tachypnoea or dyspnoea
Abnormal chest x-ray
Unstable temperature
Apnoea/bradycardia
Unexplained metabolic acidosis
Unexplained sudden collapse
Disseminated intravascular coagulation

2. *Patients*

Newborn infants up to the age of 4 weeks were eligible for entry to the trial if bacterial infection with an unknown organism was suspected. The main clinical indicators of sepsis present in the trial patients are shown in table I. The following were excluded:

- infants with a congenital abnormality incompatible with life;
- infants with suspected bacterial meningitis;
- infants born to mothers who had received antibiotics within 48 hours of delivery;
- infants who had received antibiotics within the previous 48 hours;
- infants known to be colonised, or previously infected with, an organism resistant to one of the trial antibiotics;
- infants with proven *Pseudomonas* infection;
- infants with known renal impairment (serum creatinine > 120 μmol/L);
- infants with known hepatocellular pathology.

Additionally, any infant known to have had an adverse reaction to either a cephalosporin, aminoglycoside or penicillin would have been excluded but, in practice, no such infant was encountered.

Clinical information was recorded routinely and daily for all patients, including relevant maternal antenatal history, type of delivery, sex, weight, gestational age, details of any previous episodes of sepsis, peak and trough daily temperature, concurrent medications and any other medical conditions affecting either mother or infant. At the end of treatment, each patient's status with regard to infection was classified as follows:

Definite Systemic Infection: clinical features

compatible with severe infection, associated with a bacterial growth on culture of blood or urine.

Definite Local Infection: signs of inflammation at a superficial site such as the umbilicus or the skin overlying the site of insertion of an intravenous cannula, in association with bacterial growth from a swab of the site.

Probable Infection: a clinical diagnosis of infection without positive 'deep' bacterial cultures but with supporting evidence of infection in the form of a positive 'sepsis screen', consisting of the presence of at least 2 of the following: chest x-ray suggestive of pneumonia; total white cell count < 5000 per mm^3; immature : total neutrophil count > 0.2; c-reactive protein above the reference range for the laboratory; presence of group B streptococcal antigen in the blood.

Not Proven: initial clinical suspicion of infection unsupported by positive deep cultures or by a positive sepsis screen.

3. Results

3.1 Population

236 babies were entered into the study, of whom 14 were later withdrawn: 8 did not fulfil the inclusion criteria, either because no signs of sepsis were present or because a lethal congenital abnormality was subsequently diagnosed; 2 had been previously included in the study; 2 were born to mothers who had received antibiotic treatment within 48 hours of birth; 1 was prescribed incorrect antibiotic treatment; 1 had renal impairment. 222 babies were, therefore, included in the analysis; 111 were in the cefotaxime (CTX) treatment group and 111 were in the netilmicin and penicillin (N + P) treatment group. 99 babies were entered from Southampton and 123 from Chatham. 3.5% of the babies were classified as being definitely infected and a further 15% were probably infected.

Table II shows the demographic details of the study patients. There were no statistically significant differences between the 2 groups for the parameters listed.

Table III gives a breakdown of the numbers of relevant investigations included in the sepsis screen obtained from patients in the 2 study groups. There was no statistically significant difference between the 2 groups in the number of diagnostic investigations performed.

Table II. Patient details

	CTX group	N + P group
No. entered	111	111
Birthweight[a] (g)	2285 ± 1018	2190 ± 992
Gestational age[a] (weeks)	34 ± 5	34 ± 5
Chronological age[a] (days)	1 ± 2	1 ± 3
Sex		
male	63	69
female	48	42
Delivery		
breech	4	4
instrumental	13	15
caesarean section	37	45
Previous antibiotics	2	2
Assisted ventilation	24	21

a Mean ± standard deviation.

Abbreviations: CTX = cefotaxime; N + P = netilmicin + penicillin.

Table III. Analysis of the sepsis screen

Investigation	CTX group[a]	N + P group[a]
C-reactive protein level	90 (81)	90 (81)
Total white cell count	111 (100)	110 (99)
% Band forms	91 (82)	92 (83)
Group B streptococcal antigen	95 (86)	94 (85)

a No. of patients for whom a day 0 result is available (% of total patients in group).

Abbreviations: CTX = cefotaxime; N + P = netilmicin + penicillin.

3.2 Efficacy

3.2.1 Clinical Categories and Outcome

The sepsis classification for babies in the 2 treatment groups is shown in table IV. There was no significant difference in efficacy between treatment groups for any of the 4 categories of sepsis.

Table IV. Sepsis classification by treatment group

Sepsis category	CTX group[a]	N + P group[a]
Definite (systemic)	2 (2)	3 (3)
Definite (local)	3 (3)	0 (0)
Probable	16 (14)	18 (16)
Not proven	90 (81)	90 (81)

a No. (% of patients in treatment group).

Abbreviations: CTX = cefotaxime; N + P = netilmicin + penicillin.

Table V. Clinical outcome for patients with definite sepsis

Organism(s)	Site	Treatment group	Outcom
Streptococcus group B	Blood	CTX	Cure
Staphylococcus epidermidis	Blood	N + P	Cure
Staphylococcus epidermidis	IV line site	CTX	Cure
Staphylococcus aureus	Urine	CTX	Cure
Escherichia coli *Streptococcus viridans*	Umbilicus	CTX	Cure
Proteus mirabilis	Umbilicus	CTX	Cure
Haemophilus parainfluenzae	Blood	N + P	Cure
Klebsiella oxytoca	Blood	N + P	Cure

Abbreviations: CTX = cefotaxime; N + P = netilmicin + penicillin; IV = intravenous.

Definite Sepsis

The clinical outcome for the 8 babies classified as having definite systemic or local infection is presented in table V.

No baby in the definite category died and the antibiotic treatment was not changed from that selected by randomisation in any case.

Probable Sepsis

Table VI shows the clinical outcome for babies classified as having probable sepsis. A satisfactory outcome was achieved in 87% of the cefotaxime treated group and in 78% of the netilmicin + penicillin group. The babies who died were all of less than 1500g birthweight and all had signs of severe hyaline membrane disease, with or without periventricular haemorrhage. The significance of sepsis in these infants is impossible to assess but none was colonised with organisms resistant to the antibiotics with which they were being treated.

The randomly allocated antibiotic treatment of 3 of the babies in this group was changed after 2 or 3 days. In 1, N + P treatment was replaced by chloramphenicol because *Haemophilus influenzae* was grown from peripheral swabs; however, this organism was sensitive to netilmicin and the baby had clinically improved by the time the change in treatment was made. In the other 2 the antibiotics were changed to provide specific cover against any possible staphylococcal infection, although no evidence of infection with this organism was found in either infant.

Not Proven Sepsis

Table VII shows the outcome for babies with unproven sepsis. The overall rates of satisfactory outcome were 87 and 94% for the 2 groups, respectively. Once again, all of the babies who died weighed less than 1500g at birth and all had signs of severe hyaline membrane disease.

Table VI. Outcome for patients with probable sepsis

	CTX group	N + P group
No. of babies	16	18
No. died	1 (6)	2 (11)
Antibiotics changed	1 (6)	2 (11)
Satisfactory outcome on initial antibiotics	14 (87)	14 (78)

Abbreviations: CTX = cefotaxime; N + P = netilmicin + penicillin.

Table VII. Outcome for patients with unproven sepsis

	CTX group	N + P group
No. of babies	90	90
No. died	5 (6%)	4 (4%)
Antibiotics changed	8 (9%)	1 (1%)
Satisfactory outcome on initial antibiotics	82 (87%)	85 (94%)

Abbreviations: CTX = cefotaxime; N + P = netilmicin + penicillin.

In this category the initial antibiotic treatment was changed in 8 babies in the cefotaxime group for the following reasons: 2 developed signs of necrotising enterocolitis after 5 or 6 days, 4 became more severely ill for reasons subsequently shown to be unrelated to sepsis and in 2 the antibiotic treatment was changed to provide specific cover against *Listeria monocytogenes* and *Staphylococcus aureus*, respectively, although neither organism was isolated from these patients. Treatment was changed in only 1 of those from the N + P group to provide specific cover against *Staphylococcus aureus*, which had been grown from peripheral swabs; however, this organism was sensitive to netilmicin, with which the baby was being treated.

3.2.2 Antibiotic Sensitivity Data

All isolates from the relevant sites among babies in the definite local or systemic sepsis groups were sensitive to both cefotaxime and netilmicin. For the other 2 groups, combined sensitivity data are presented for organisms isolated from peripheral sites in tables VIII and IX. In these tables, the term 'Gram-negative rods' is used to describe all Gram-negative bacilli and includes *E. coli, Pseudomonas* species, *Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Proteus* species, *H. influenzae, Klebsiella* species, *Serratia marcescens* and unidentified Gram-negative rods.

The most common known bacterial pathogens for newborn infants admitted to our units during the first few days of life are group B streptococci, Gram-negative rods and staphylococci. The group B *Streptococcus* was not isolated from any study infant in either of the units after day 0. *Listeria monocytogenes*, which is known to be an important and common neonatal pathogen in some parts of the world, was not isolated from any of the infants in this study.

4. Safety

Details concerning renal, liver and haematological function tests assessed before and at the end of antibiotic treatment are shown in tables X and XI. There was no statistically significant difference between the treatment groups for any of the changes observed. In addition to these investigations, blood pH, base excess, sodium and potassium were recorded before and after treatment and no differences were found between the 2 groups. Urinary protein and micro-protein excretion were also monitored; full analysis of these data will be reported in a future publication. Only 2 cases of necrotising enterocolitis occurred in study patients during treatment and both were receiving CTX. A further 8 study patients were diagnosed as having necrotising enterocolitis at a later stage during their admission; 1 had been treated with CTX and 7 had received N + P.

Table VIII. Day 0 isolates from peripheral sites and antibiotic sensitivities

Organism (type)	No. of babies with organism	No. of isolates	No. (%) of isolates sensitive to	
			CTX	N + P[a]
Gram-negative rods	34	62	59/59 (100)	56/56 (100)
Group B *Streptococcus*	12	22	20/20 (100)	21/21 (100)
Streptococcus pneumoniae	4	12	12/12 (100)	12/12 (100)
α-Haemolytic *Streptococcus*	7	11	10/10 (100)	7/10 (70)
Other streptococci	26	47	9/9 (100)	8/9 (89)
Staphylococcus aureus	8	14	12/12 (100)	11/11 (100)
Other staphylococci[b]	11	18	16/17 (94)	17/17 (100)

a Organism sensitive to at least 1 of the 2 antibiotics.

b Excludes *Staphylococcus epidermidis.*

Abbreviations: CTX = cefotaxime; N = netilmicin.

Table IX. Antibiotic sensitivities of Gram-negative rods and staphylococcal isolates after day 0 of treatment

Organism	CTX treatment group				N + P treatment group			
	day 2/3 no. sensitive to:		day 4-10		day 2/3 no. sensitive to:		day 4-10	
	CTX	N	CTX	N	CTX	N	CTX	N
Gram-negative rods	9/12 (75%)	12/12 (100%)	5/12 (42%)	12/12 (100%)	30/30 (100%)	29/30 (97%)	20/28 (71%)	26/28 (93%)
Staphylococci	4/4 (100%)	3/3 (100%)	4/5 (80%)	5/5 (100%)	5/5 (100%)	3/3 (100%)	2/5 (40%)	2/4 (50%)

Abbreviations: CTX = cefotaxime; N = netilmicin; P = penicillin.

Table X. Renal and hepatic function tests[a] before and at end of antibiotic treatment

Test	CTX group		N + P group	
	before	at end	before	at end
Blood urea (mmol/L)	3.7 ± 1.8 (n = 108)	2.8 ± 2.1 (n = 101)	4.0 ± 3.0 (n = 109)	3.0 ± 2.0 (n = 104)
Blood creatinine (mmol/L)	90.3 ± 34.7 (n = 34)	63.3 ± 25.0 (n = 44)	87.0 ± 27.6 (n = 34)	72.9 ± 24.7 (n = 41)
Total proteins (g/L)	49.1 ± 11.1 (n = 57)	52.0 ± 9.0 (n = 68)	46.3 ± 8.4 (n = 54)	53.6 ± 8.5 (n = 70)
Aspartate amino transferase (Units/L)	68.4 ± 34.8 (n = 62)	49.1 ± 31.2 (n = 73)	71.9 ± 53.6 (n = 61)	44.8 ± 42.1 (n = 81)
Bilirubin (μmol/L)	65.4 ± 42.3 (n = 97)	157 ± 69.7 (n = 99)	64.4 ± 45.9 (n = 92)	136.4 ± 63.5 (n = 100)

a Mean ± standard deviation.

Abbreviations: CTX = cefotaxime; N + P = netilmicin + penicillin; n = no. of patients tested.

No side effects arising from either treatment regimen were recognised.

5. Discussion

The 2 neonatal units involved in this study had no links with each other before undertaking the project and neither unit changed its usual practice in the indications for antibiotic treatment of suspected neonatal sepsis, for the purpose of the investigation. The units are separated by a distance of over 100 miles and each was staffed with doctors who had worked in hospitals elsewhere within the United Kingdom. It is likely, therefore, that the indications for antibiotic treatment described in this study are reasonably representative of those used by many other neonatal units within the United Kingdom.

The patients in the 2 treatment groups were comparable in all respects (table II). In both Chatham and Southampton the proportion of treated babies who had proven infection was almost identical and extremely low (4 and 3%, respectively).

Table XI. Haematological tests[a] before and at end of antibiotic treatment

Test	CTX group		N + P group	
	before	at end	before	at end
Red cell count ($\times 10^{12}$/L)	4.5 ± 0.7 (n = 111)	4.5 ± 0.8 (n = 101)	4.4 ± 0.6 (n = 109)	4.4 ± 0.8 (n = 104)
White cell count ($\times 10^{9}$/L)	14.1 ± 7.3 (n = 111)	10.8 ± 5.9 (n = 101)	14.1 ± 8.7 (n = 110)	12.4 ± 6.2 (n = 105)
Neutrophil count (%)	52.3 ± 18.5 (n = 100)	47.2 ± 14.8 (n = 95)	53.1 ± 19.4 (n = 98)	47.4 ± 15.2 (n = 98)
Platelet count ($\times 10^{9}$/L)	255 ± 82 (n = 107)	277 ± 130 (n = 99)	252 ± 94 (n = 109)	280 ± 133 (n = 101)

a Mean ± standard deviation.

Abbreviations: CTX = cefotaxime group; N + P = netilmicin + penicillin; n = no. of patients tested.

There are well-known difficulties in establishing the diagnosis of serious infection such as septicaemia in the newborn, because only limited amounts of blood and other bodily secretions can be spared for microbiological analysis. A sepsis screen may help in identifying babies who are probably infected but it is impossible to validate such screening procedures in babies with negative blood or other deep cultures.

The parameters used for the sepsis screen in the present study are somewhat arbitrary since we did not have access to measurements of certain acute phase reactants such as haptoglobins, as used in other studies (Philip 1981). However, despite inadequacies of data collection (some measurements of CRP and band cell counts were not obtained), it is noteworthy that the proportion of probably infected neonates in both centres was identical (15%).

The bacteria most commonly implicated in the causation of serious early neonatal sepsis are Gram-negative rods (principally *E. coli*), group B streptococci and staphylococci. Almost all such organisms grown from peripheral swabs of babies in this study were sensitive to both of the antibiotic regimens (table VIII). In terms of bacterial sensitivity, therefore, the use of either regimen would have been appropriate in most instances where serious sepsis was suspected but the causative organism was unknown.

This particularly applies to treatment within the first 1 or 2 days of life, and most babies included in this study were less than 48 hours old at entry; any sepsis present was likely, therefore, to have resulted from organisms acquired during the process of delivery. Such organisms would be expected to have a different pattern of antibiotic susceptibility from those acquired after admission to a neonatal intensive care unit. Table IX indicates that there was an increase in the number of organisms that were resistant to cefotaxime after admission; this applied to babies treated with netilmicin + penicillin as well as those treated with cefotaxime.

Cefotaxime had been used for some time in both units whereas netilmicin had not, and organisms resistant to cefotaxime may have been available to colonise babies after admission to either unit. Thus, although either regimen appears to be suitable for most babies at the time of entry to a unit the choice of blind antibiotic treatment for severe suspected neonatal sepsis after admission should take into account the prevailing antibiotic sensitivity patterns.

In addition, it is known that *Listeria monocytogenes* is relatively insensitive to cefotaxime (Neu & Labthavikul 1982). This organism is rare in this country and it was not encountered in either the

Chatham or the Southampton unit during the course of this study. However, in units where listeriosis commonly occurs cefotaxime monotherapy would not be an appropriate choice.

Diagnostic methodology notwithstanding, the majority of treated infants in this study were not actually infected. In such circumstances it is essential that the antibiotics used to cover any possible sepsis should be both effective and safe. Neither regimen appeared to have any adverse effect on the relevant liver or renal function tests or on the haematological parameters investigated. A practical advantage of cefotaxime over the aminoglycosides is that the lack of known toxicity means that there is no need for serum antibiotic levels to be checked, particularly in the presence of abnormal renal function. Further studies are required to determine the extent to which these antibiotics exert any adverse influence on blood coagulation mechanisms or on auditory function.

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