

## ORIGINAL ARTICLE

# The effect of HIV infection on paediatric bacterial meningitis in Blantyre, Malawi

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**Aim:** To compare presentation, progress, and outcome of acute bacterial meningitis in HIV seropositive and seronegative children.

**Methods:** A double blind randomised placebo controlled study of the use of dexamethasone as adjuvant therapy in acute bacterial meningitis, in children aged 2 months to 13 years, was carried out from July 1997 to March 2001. A total of 598 children were enrolled, of whom 459 were tested for HIV serostatus.

**Results:** Of the 459 children, 34% were HIV seropositive. Their presentation was similar to HIV seronegative children but more were shocked on arrival at hospital (33/157 v 12/302), and more had a focus of infection (85/157 v 57/302). HIV positive children had a higher incidence of *Streptococcus pneumoniae* infections (52% v 32%). Sixty four cases relapsed; 67% were in HIV positive patients. The mortality in HIV positive children was 65% compared with 36% in HIV negative children. The number of survivors in each group was similar. Hearing loss was more common in HIV negative than HIV positive children (66.3% v 47.2%). Steroid therapy had no influence on meningitis in HIV positive children, but the mortality in HIV negative children was 61% in children given steroids, and 39% in those who did not receive steroids.

**Conclusion:** HIV seropositive children who develop bacterial meningitis have a high mortality and are prone to recurrent disease. There is an urgent need to prevent both primary and recurrent infections.

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Bacterial meningitis is ten times more common in children in developing than in developed countries.<sup>1</sup> In resource poor countries the case fatality rate is high (12–50%) compared with richer countries (<5%), and a third of all survivors are left with sequelae.<sup>1–6</sup>

In many resource poor countries the prevalence of human immunodeficiency virus type 1 (HIV) infection among children is increasing. HIV infection makes a child more prone to invasive bacterial infections, including bacterial meningitis.

We wished to know whether the presentation of bacterial meningitis, the course of the illness, or the outcome were different in HIV infected and uninfected children.

The Queen Elizabeth Central Hospital (QECH) is an 1100 bedded government referral and teaching hospital in Blantyre, Malawi. The paediatric department has 250 beds with up to 310 inpatients. In the paediatric accident and emergency unit more than 90 000 children are seen each year, of whom 12 000 are admitted. A prevalence study of HIV infection rates for inpatients was carried out over a two week period in the malaria season of 2000. Children below 18 months of age who were seropositive had HIV PCR tests done to confirm their status. An overall HIV infection rate of 18.3% was found for all admissions regardless of diagnosis.<sup>7</sup> In an audit of children admitted to the nutrition unit it was found that 62% of marasmic children and 21.7% of those with kwashiorkor were HIV infected.<sup>8</sup> On the tuberculosis (TB) ward the seroprevalence was 70.6% in those suspected of TB and who agreed to be tested. In confirmed or "probable" cases of pulmonary tuberculosis HIV infection rates were 57.8%.<sup>9</sup>

Gastroenteritis, pneumonia, TB, and malaria are the most common causes of hospital admissions. In a previous study 2.7% of all admissions were due to bacterial meningitis.<sup>5</sup>

Malnutrition plays a significant underlying role in all the problems of children requiring admission.

Children with HIV related illnesses are treated appropriately, but anti-retroviral medicines are not available. Infants and children are not routinely tested for HIV serological status.

## METHODS

From July 1997 to March 2001 we conducted a double blind randomised placebo controlled study of the role of dexamethasone as an adjuvant therapy in the treatment of bacterial meningitis in children aged 2 months to 13 years.<sup>6</sup> Meningitis was defined as the presence of  $\geq 100$  white cells per mm<sup>3</sup>, predominantly granulocytes, in an admission sample of cerebrospinal fluid (CSF), or a positive Gram stain showing bacteria in CSF, or the culture of bacteria from CSF. Children who had received parenteral broad spectrum antibiotics up to 24 hours prior to admission were excluded from the study.

## Procedure

All study children had a complete history taken and were fully examined and weighed. A lumbar puncture was done and if meningitis was suspected by the naked eye appearance of the CSF sample, an intravenous line was established. Blood samples were taken for full blood count, malaria parasites (thick film), plasma glucose and electrolytes, and blood culture. Blood was not cultured if the CSF report was already available and confirmed the presence of bacteria on Gram stain. Sera and red cell pellets were stored. Patients were randomised to receive either dexamethasone (0.4 mg/kg intravenously 12 hourly for 48 hours) or placebo 5–10

minutes before antibiotic doses for the first two days of a 10 day course of antibiotics.

### Randomisation

Randomisation was done in blocks of 10, with the randomisation code held by the clinical monitor in a sealed envelope. Vials of dexamethasone or placebo were identical, labelled with only the study number, and contained 1 ml of clear liquid. The placebo vials contained water for injection, the active vials contained 5 mg of dexamethasone. Neither those who gave clinical care to the patients nor the patients' guardians were aware of the contents of the vials. All managements, outcome assessments, and data analysis were done without breaking the code.

Chloramphenicol (100 mg/kg/24 h) and benzylpenicillin (200 000 iu/kg/24 h) were the first-line antibiotics given. When CSF cultures and sensitivities were known, antibiotic therapy was continued or altered accordingly. During the study 39 children with Gram negative bacilli seen on the Gram stain of the CSF specimen were started directly on ceftriaxone as there was known to be increasing resistance of some *Haemophilus influenzae* type b to chloramphenicol. An ultrasound scan of the head was done if the child's fontanelle was still patent, either for clinical indications, or before discharge from hospital. A full physical examination including head circumference measurement, neurological function, and hearing and visual assessments were done prior to discharge from hospital and at 1 and 6 months after discharge. If the child had made a complete recovery from meningitis, was old enough to be properly assessed, and lived far from the hospital, follow up was not carried out. If the child had sequelae that required further management beyond 6 months, follow up was continued. Of the 348 survivors, 36 (10%) were not reviewed, 73 (21%) were seen 1 month, 33 (9%) 1–6 months, and 242 (69.5%)  $\geq$ 6 months post-discharge from hospital.

The results and detailed methodology of this study have been previously reported.<sup>6</sup> HIV testing was undertaken with parental agreement and accompanied by pre- and post-test counselling. Ethical permission for the study was given by the National Health Sciences Research Committee.

### Laboratory methods

CSF samples were examined microscopically for total cell count and white cell differential count. A Gram stain was done on all samples that were cloudy or contained more than 8 WBC/mm<sup>3</sup>. After centrifugation, the deposits were cultured on sheep blood agar (SBA) and haemophilus test medium (HTM), both incubated in a candle jar at 37°C for 48 hours; 5 ml brain heart infusion broth with 1% Vitox was added to the remaining deposit for enrichment culture. This broth was incubated for 48 hours, and then the centrifuged deposit was cultured on SBA and HTM plates which were incubated for 48 hours as for the direct cultures.

Blood cultures were done using a manual method; a maximum blood volume of 2 ml was added to a single blood culture bottle (20 ml brain heart infusion broth containing sodium polyanethol sulphate, E&O Laboratories, UK). Bottles were incubated overnight at 37°C before venting. Cultures were examined macroscopically every day, followed by Gram staining if turbid or haemolysed. Subcultures and direct susceptibility testing were performed as directed by the Gram stain findings. Routine subcultures on sheep blood agar were performed for all bottles after 18–24 hours, 36–48 hours, and 7 days. All plates were incubated in a candle jar, and examined after 24 and 48 hours incubation.

Isolates were identified according to standard techniques,<sup>10</sup> including optochin susceptibility, seroagglutination for *Haemophilus influenzae* type b and salmonellae, and biochemical

tests. Antibiotic susceptibilities were determined by disc diffusion on Mueller-Hinton agar, interpreted using the NCCLS guidelines.<sup>11</sup> For pneumococci, penicillin susceptibility was assessed with a screening technique using a 1  $\mu$ g oxacillin disc. Minimum inhibitory concentrations were not performed for any isolate.

### HIV tests

Serum samples were tested by at least two of the following tests: Serodia-HIV particle agglutination (Fujirebio Inc., Mast Diagnostics, UK), HIVSPOT (Genelabs Diagnostics, Singapore), Determine-HIV (Abbott Laboratories, USA), Capillus-HIV (Cambridge Diagnostics, Ireland). Discordant tests were confirmed either by a third test or an in-house HIV PCR. Nested PCR was used for detection of the long terminal repeat of HIV. The primary PCR was performed using proviral oligonucleotides 5'-ACCAGRTYTGAGCCTGGGAGCT and 5'-CCTGTTCGGCGCCACTGCTAGAGATTTT and using 5'-TGAGCCTGGGAGCTCTCTGGCT and 5'-CTGAGGGATCTCTAGDYA CCAGAGT for the secondary reaction. Both reactions were run for 35 cycles of 94°C for 30 seconds, 46°C for 30 seconds, 72°C for 30 seconds, with a final extension of 72°C for 10 minutes. Children below 18 months of age with a positive antibody test were confirmed with the HIV PCR test.

### Data

Data were entered in a Microsoft Excel file. This was double checked and analysed with Epi Info.6.

All 2 $\times$ 2 tables were analysed using Yates's correction of Pearson's  $\chi^2$  statistic. Time to clearance of fever was analysed using the Mann-Whitney U test. Models were selected in multiple logistic regression using a forward selection procedure. Significance tests were performed using likelihood ratio tests. A natural log transformation was applied to age (months). Odds ratios (OR) with 95% confidence intervals (CI) were estimated using the data for all patients with the selected variables, using the estimated standard errors.

## RESULTS

### Presentation

A total of 598 cases of meningitis were enrolled, of whom 459 were tested for HIV status. Of the 139 not tested, 100 were enrolled before permission was granted by the ethics committee to request the tests, 33 were inadvertently not asked or tested, five guardians refused permission for the test, and in one case no appropriate guardian was available to give permission. A total of 157 (34%) of the 459 tested were HIV infected. These children did not differ in age from the HIV uninfected children (table 1). The HIV infected children more commonly had generalised signs of HIV infection such as lymphadenopathy, hepatosplenomegaly, and a lower weight for age. On presentation the HIV infected and uninfected children had similar lengths of history of fever. Similar numbers in each group were admitted with a history of seizures or with a low coma score. The HIV infected patients were more likely to be in shock, or have a focus of infection (85/157 v 57/302,  $p < 0.0001$ ; OR 5.07, 95% CI 3.2 to 7.96) (table 1). Thirty nine of the 85 (46%) infections in HIV infected children were due to *Streptococcus pneumoniae* compared to 11 of 57 (19%) in uninfected children ( $p = 0.002$ ; RR 2.38, 95% CI 1.33 to 4.24). In the HIV infected children *S pneumoniae* infections mainly affected ears ( $n = 20/32$ ) or the chest ( $n = 10/18$ ). In the uninfected children 6 of 24 ear infections, and 2 of 8 chest infections were due to *S pneumoniae*. Foci of infection due to *Haemophilus influenzae* were found in both groups of children (10/85 HIV infected v 12/52 uninfected,  $p = 0.1$ ).

**Table 1** Findings on presentation of bacterial meningitis in different HIV status groups

HIV seropositivity	HIV+ (%)	HIV- (%)	Significant differences between HIV+ and HIV- groups
Number of children	157	302	
Median age (months) [range]	12 [2–168]	12 [2–164]	
Male:female	47:53	60:40	
Median % wt for age [range]	73 [39–126]	81 [39–123]	
Median fever (days) [range]	3 [0–60]	3 [0–30]	
≤2 days fever	76 (48)	114 (38)	
History of seizures	94 (60)	132 (44)	p=0.001, OR 1.92 (1.27 to 2.90)
Focal fits (%of fits)	19(12)	29(22)	p=0.5, OR 1.3 (0.67 to 2.49)
Not sucking	90 (57)	128 (42)	p=0.03
Prior antibiotics	73 (46)	101 (33)	
Ear infection	32 (20)	24 (8)	p=0.0002, OR 2.97 (1.61 to 5.48)
Focus of infection	85 (54)	57 (19)	p=0.0001, OR 5.07 (3.2 to 7.96)
Coma score ≤2	67 (43)	111 (37)	p=0.26
Skin rash	18 (11)	11 (4)	p=0.02, OR 3.43 (1.49 to 7.99)
Generalised LN++	32 (20)	12 (4)	p<0.00001, OR 6.19 (2.95 to 13.18)
Hepatomegaly	65 (41)	51 (17)	p<0.00001, OR 3.48 (2.19 to 5.52)
Splenomegaly	43 (27)	59 (19.5)	p=0.07, OR 1.4 (1 to 1.97)
Shock	33 (21)	12 (4)	p<0.00001, OR 6.43 (3.08 to 13.69)
Mean blood glucose (mmol/l) [range]	5.6 [0–37]	5.9 [0–13]	
Median temp (°C) [range]	38 [34–41]	38.4 [35–40.8]	
Median haematocrit (mg/l) [range]	290 [160–450]	300 [70–500]	
Malaria parasites +	(13.4)	(16.4)	
<i>H influenzae</i>	32 (20)	98 (32)	p=0.009, OR 0.53 (0.33 to 0.86)
<i>S pneumoniae</i>	92 (58)	98 (32)	p<0.0001, OR 2.95 (1.94 to 4.48)
<i>N meningitidis</i>	4 (2)	32 (10.5)	p=0.004, OR 0.22 (0.06 to 0.67)
Salmonellae spp.	10 (6)	14 (5)	p=0.56, OR 1.4 (0.56 to 3.45)
No growth	14 (9)	50 (16.5)	p=0.035, OR 0.49 (0.25 to 0.96)
Other	5 (3)	10 (3)	p=0.8

**Table 2** Progress in hospital in different HIV serostatus groups

HIV seropositivity	HIV+	HIV-	Differences between HIV+ and HIV-
Number of children	157	302	
Median time (h) for temp ≤37°C ≥24 h [range]	33 [6–264]	24 [1–456]	
Number requiring anticonvulsant therapy	74 (47%)	119 (39%)	p=0.135
Ultrasound scan of head done	28	82	
Abnormal findings on ultrasound	13 (46%)	34 (41%)	p=0.8
Number requiring 2nd line antibiotic therapy	43 (27%)	114 (38%)	p=0.03
Subdural/abscess tapped*	3 (2%)	6 (2%)	p=0.6
Blood transfusions†	3 (2%)	6 (2%)	p=0.6

\*Includes two brain abscesses (one ventricular tap (*S pneumoniae*) and one necrotic post-infarct abscess (*E coli*).  
†Transfusions given on admission or during stay in hospital.

### Causes of meningitis

The same bacteria caused meningitis in the two groups of children but in HIV infected children the proportion of cases caused by *Streptococcus pneumoniae* was significantly greater than in the uninfected group (table 1).

### Progress in hospital

HIV infected children who were febrile took longer to become afebrile than uninfected children. In other respects the illness progressed similarly in both patient groups. A similar number required anticonvulsants, blood transfusions, or a change in antibiotic therapy. Abnormal results from ultrasound scans of the brain were also similar (table 2).

### Recurrence of meningitis

Of the 598 episodes of meningitis, 64 were recurrent. Forty four (68%) recurrences were in HIV infected children, 13 (20%) in HIV uninfected children, and eight (12.5%) in children in whom HIV was not tested. The relative risk of recurrence in HIV infected children (44/157) compared with

HIV uninfected children (13/302) was 6.4 (3.5 to 11.5) (p<0.00001).

Twenty eight (44%) cases were due to *S pneumoniae*, and 17 (26.5%) were due to salmonellae species (table 3). In the cases due to *S pneumoniae*, 18 (64.2%) were HIV positive, five

**Table 3** Recurrent meningitis

Cause	Serostatus		
	HIV+	HIV-	Total
<i>Streptococcus pneumoniae</i>	18	5	23
<i>Salmonella</i> spp.	12	5	17
Unrecorded*	7	0	7
<i>Haemophilus influenzae</i> b	2	2	4
No growth	3	0	3
<i>Neisseria meningitidis</i>	0	1	1
<i>E coli</i>	1	0	1
Total	43	13	56

\*No results available; episode of meningitis managed elsewhere.

were negative, and five were not tested for HIV serology. The relative risk of recurrence for pneumococcal meningitis in HIV positive children (18/93) compared with HIV negative children (5/99) was 3.8 (1.5 to 9.9) ( $p < 0.005$ ).

Seventy per cent of the cases caused by a *Salmonella* sp., were HIV infected (table 3). The recurrences after the first episode of *Salmonella* sp. meningitis were from 7 days to 3 months. Recurrent *S pneumoniae* meningitis occurred from 2 weeks to 2 years after the first episode; only two episodes occurred  $< 2$  months after the first infection. In two cases of *S pneumoniae* meningitis the recurrence was due to another bacterium (one *E coli* and one *H influenzae*). All the *Salmonella* sp. infections had recurrences of the same bacteria. The time between infections was unaffected by the HIV serostatus of the child.

Recurrent episodes of infection were not caused by bacteria more resistant to chloramphenicol and/or penicillin than with the first infection. In two recurrent cases, one each of *S pneumoniae* and *H influenzae* type b, the bacteria had acquired chloramphenicol resistance that was apparent on in vitro testing of the isolate from the recurrent infection. Of these two cases one child was HIV infected and one was uninfected.

### Outcome

The outcome was significantly worse in the children who were HIV infected; in the study period, 102 of 157 (65%) died compared with 109 of 302 (36%) HIV uninfected children ( $p < 0.00001$ ; RR 1.8 (1.49 to 2.17)). In HIV infected children, 94 of 157 (59.8%) deaths were directly attributable to meningitis compared with 103 of 302 (34%) in uninfected patients ( $p < 0.0000002$ ; RR 1.76 (1.43 to 2.15)). The HIV infected children who died were more malnourished than the HIV infected survivors ( $p = 0.015$ ). A logistic regression model shows that for a 10% reduction on weight for age (WFA) the odds of death are estimated to be increased by a factor of 1.275 (95% CI 104 to 155). Among survivors the overall likelihood of having sequelae was unaffected by HIV status (30/55 HIV+  $v$  88/193 HIV-,  $p = 0.83$ ). Neurological sequelae were found in 21/55 (38%) HIV infected survivors versus 55/107 (51.4%) in HIV uninfected surviving children ( $p = 0.15$ ). The pattern of hearing loss in the two groups of survivors was similar but was less common in HIV infected than uninfected survivors (26/55 (47.2%)  $v$  71/107 (66.3%),  $p = 0.029$ ). Hearing loss was equally profound in both groups. The types of neurological sequelae were similar in each group except that hydrocephalus was found in 5/107 HIV uninfected survivors and in no HIV infected survivors (table 4).

### The role of steroids and HIV status on outcome

Outcome with full recovery, death, or residual sequelae was uninfluenced by the use of steroids as adjuvant therapy in HIV infected children. In HIV infected patients receiving adjuvant dexamethasone therapy the case fatality rate was 52% (38/73) compared with 39% (62/159) in HIV uninfected patients ( $p = 0.08$ ; RR 1.33 (1.0 to 1.79)) (table 5).

### Laboratory results in HIV infected and uninfected patients

The blood glucose level on admission and the number of children with malaria parasitaemia was similar in each group. The peripheral white cell count was similar with a median of 12 (range 1–70)  $\times 10^6/\text{mm}^3$  in HIV uninfected children and 10.8 (range 1–70)  $\times 10^6/\text{mm}^3$  in infected children. The white cell count in CSF varied widely but the median count in the infected group was 1925 (range 0– $> 100\,000$ )/ $\text{mm}^3$  and in the uninfected group was 840 (range 0–100 000)/ $\text{mm}^3$  ( $p = 0.83$ ). The total peripheral lymphocyte count was not different in the HIV positive (mean

lymphocyte count 33 642/ $\text{mm}^3$ ) and HIV negative groups (mean lymphocyte count 36 944/ $\text{mm}^3$ ). The total lymphocyte count was not significantly different in the group of HIV infected children who died and the group that survived ( $p = 0.51$ ).

### Bacterial resistance to first line antibiotics

There was no overall difference in bacterial resistance on in vitro testing by HIV status, with the exception of pneumococci from HIV infected patients, of which fewer were resistant to chloramphenicol than those in HIV uninfected patients (3%  $v$  16%,  $p = 0.006$ ) (table 6).

Fifteen per cent of *H influenzae* infections (15/99) and 13% (13/97) of *S pneumoniae* infections in HIV negative children were fully sensitive to the antibiotics against which routine testing is carried out (penicillin, ampicillin, chloramphenicol, gentamicin, cotrimoxazole, cefaclor, and erythromycin). In HIV infected children, 12.5% (4/32) of *H influenzae* infections and 4.4% (4/89) of *S pneumoniae* infections were fully sensitive to the antibiotics against which they were screened (table 6).

Of the children who had received known prior antibiotics, 31 of 73 (42%) HIV infected children had received penicillin compared with 59 of 104 (58%) uninfected children ( $p = 0.04$ ). Cotrimoxazole had been given to 23 (31.5%) of the HIV positive versus 16 (16%) of the seronegative group ( $p = 0.03$ ). Very few had received chloramphenicol (10/73  $v$  14/101) ( $p = 0.9$ ).

### DISCUSSION

In this study HIV infected children with bacterial meningitis were more likely to die than uninfected children (59.8%  $v$  34%,  $p < 0.00001$ ). Fifteen per cent (24/157) of HIV infected patients made a full recovery compared with 91/302 (30%) in the uninfected group ( $p < 0.001$ ). Children who survived with sequelae had the same types of problems regardless of HIV status. Hearing loss was similar but less common in the HIV infected group. Steroids marginally increased the case fatality rate in HIV uninfected children ( $p = 0.08$ ) but not the incidence of sequelae in either group. Recurrence could not be attributed to drug resistance. Sensitivity patterns of bacteria were similar between groups for the first and for the recurrent infections. We were unable to distinguish between recrudescence infections and new infections (recurrences occurred between 2 weeks and 18 months after the first infection), and it is possible that the greater recurrence rate in the HIV infected group simply reflects a greater susceptibility to invasive bacterial disease. More HIV infected children presented with foci of infection (54%  $v$  19%,  $p < 0.0001$ ) than uninfected patients and more of the foci were due to *S pneumoniae* (46%  $v$  19%). More children were in shock (21%  $v$  4%) on arrival to hospital, but in other ways they were no sicker on arrival than HIV uninfected children.

HIV infected children took longer to become afebrile, but the number who needed anticonvulsants, second line antibiotics, or blood transfusions did not differ from uninfected patients. The total lymphocyte count did not predict outcome in HIV seropositive children. The total lymphocyte count has been used as a surrogate marker for CD4 count. This has been shown to be useful (though not very specific or sensitive) as an indicator for starting HAART therapy in HIV positive adults.<sup>12 13</sup> It is yet to be seen if this is true in childhood and in an endemic malarial area where white cell counts are depressed by malarial infections. Our children had a severe infection which would acutely affect the peripheral white cell count and reduce the predictive value of a total lymphocyte count.

Poor nutrition is associated with a poor outcome from meningitis, and a low weight for age was associated with a

**Table 4** Outcome by different causative agents and HIV serostatus

	Causative agent (%)													
	Overall (n = 459)		S pneumoniae (n = 192)		H influenzae (n = 131)		N meningitidis (n = 36)		Salmonella spp (n = 24)		No growth (n = 64)		Other (n = 13)	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Number of children	157	302	93	99	32	99	4	32	10	14	14	50	4	9
Died in hospital	88	89	48	39	21	26	0	1	8	7	9	12	1	4
Died after discharge of meningitis problem	6	14	4	4	0	5	2	0	0	2	1	2	1	0
Died after discharge of non-meningitis illness	8	6	4	3	0	1	0	0	1	0	0	1	1	0
Survivors with full recovery*	27 (17)	92 (30)	18	17	5	30	1	22	0	0	3	21	1	2
Total with sequelae* (%)	30 (19)	88 (29)	17	34	6	27	3	8	2	5	1	11	1	3
All neuro problems†	21	55	7	16	5	17	3	3	1	2	0	9	2	1
All with hearing loss	26	71	18	27	1	21	3	9	3	4	3	8	0	2
Hearing normal	24	103	14	21	8	35	1	20	0	1	1	23	0	3
Bilateral loss	12	35	8	16	1	7	1	2	1	3	1	5	0	2
Bilateral reduction	6	7	4	3	0	2	1	1	1	0	0	1	0	0
Unilateral loss	1	14	1	8	0	2	0	3	0	1	0	0	0	0
Unilateral reduction	1	5	0	0	0	3	1	2	0	0	0	0	0	0
Conductive loss	6	10	5	0	0	7	0	1	0	0	1	2	0	0
Inconclusive tests*	10	19	5	3	2	11	0	1	0	1	1	3	2	0
Not tested	3	14	2	5	0	3	0	1	0	0	1	4	0	1

\*Includes 8 too young for testing and seen when oto-evoked emission test not available, 15 neurologically damaged and seen when oto-evoked emission test not available, 1 child uncooperative, 1 history and findings incompatible, 1 unknown.  
 †Excludes hearing problems.

**Table 5** Role of HIV status on outcome in steroid treated and placebo groups

	HIV status	Total (%)	Steroids	No steroids
Total	+	157	73 (46)	84 (53.5)
Alive and well	+	27 (17)	13 (48)	14 (50)
Died	+	94 (60)	38 (52)	56 (67), p=0.08 (RR 0.6 to 1.02)
Sequelae	+	30 (19)	18 (60)	12 (40)
?	+	6	4	2
Total	-	302	159 (53)	143 (47)
Alive and well	-	92 (30)	43 (27)	49 (59)
Died	-	103 (34)	62 (61)	40 (39), p=0.05 (RR 0.99 to 2.75)*
Sequelae	-	88 (29)	39 (44)	49 (56)
?	-	20	15	5

Died: only includes meningitis related deaths.

\*No other significant differences found between the groups.

**Table 6** Pattern of bacterial resistance to first line antibiotics used in meningitis

	Resistance to antibiotics (%)		
	Serostatus	Total chloramphenicol	Penicillin
HIV+	139	14 (10)	40 (29)
HIV-	247	40 (16)	86 (35)
HIV + <i>H influenzae</i>	32	5 (16)	9 (28)
HIV - <i>H influenzae</i>	99	17 (17)	55 (55.5)
HIV + <i>S pneumoniae</i>	89	3 (3.3)*	19 (21)
HIV - <i>S pneumoniae</i>	97	16 (16)*	14 (14)
HIV + <i>Salmonella</i> sp.	10	4 (40)	10 (100)†
HIV - <i>Salmonella</i> sp.	15	3 (20)	13 (89)†

\*p=0.006, †p=0.05; no other significant differences.

poor outcome our study.<sup>5 6 14</sup> The HIV infected patients who died were significantly more wasted than the children who survived (p = 0.015).

In a literature review of bacterial meningitis in children who are HIV infected in developing countries, only a few reports focused on this problem. Madhi *et al* in South Africa reviewed their admissions for bacterial meningitis over a two year period (March 1997 to February 1999) and found that 62 (42%) of the 147 cases were HIV infected. The mortality was 30.6% compared with 11.8% in HIV uninfected children. The causes of bacterial meningitis were *S pneumoniae* in 74.2% of HIV infected children versus 12.9% in HIV uninfected children. *H influenzae* caused meningitis in 42.3% of HIV uninfected children versus 29.4% in HIV infected children.<sup>14</sup> The same group of researchers reported that in a study of pneumococcal infections it was noted that *S pneumoniae* meningitis was significantly more common in HIV infected children than uninfected children (p = 0.003) and 64% of systemic pneumococcal infections in patients below the age of 12 years were in HIV infected patients.<sup>15</sup> In that study, unlike in ours, shock was found to be more common in HIV uninfected children with systemic *S pneumoniae* infections than in HIV infected children (p = 0.0003). This group report that systemic pneumococcal infections are 40 times more likely in HIV infected than uninfected patients.<sup>16</sup> In post-mortem examinations carried out on HIV infected children in Cote D'Ivoire, bacterial meningitis was no more common in HIV infected than HIV uninfected children.<sup>17</sup> Several studies, which include and were predominantly about adults, note the rise in meningitis incidence and the predominance of cryptococcal meningitis, TB meningitis, and lymphocytic meningitis in AIDS patients.<sup>18-20</sup> In Soweto bacterial meningitis caused 22.5% of meningitis in HIV positive (adult) patients.<sup>19</sup> In Harare pyogenic meningitis accounted for 16% of cases of meningitis, of whom 81% were HIV positive.<sup>18</sup> During the time of this study we had one case of childhood

cryptococcal meningitis and six cases of confirmed TB meningitis.

In South Africa Madhi *et al* reported a rise in penicillin resistance of *S pneumoniae* infections in HIV infected patients compared with uninfected patients (46% v 28%, p = 0.009). Cotrimoxazole resistance was 44.5% in HIV infected and 19% in HIV uninfected patients.<sup>15</sup> We found 21% resistance to penicillin in HIV infected patients and 14% resistance in uninfected patients with *S pneumoniae* meningitis. Cotrimoxazole resistance is high (>80%) in both groups of patients, and only 4.4% of all infections in HIV infected children were fully sensitive to routine antibiotic screening (Lorna Wilson; personal communication). However, chloramphenicol resistance was less in HIV infected patients than uninfected patients (p = 0.006) (table 6).

Children who are HIV infected are prone to develop systemic bacterial infections, including meningitis, and have a high mortality. In our experience, if they recover from meningitis the likelihood of a recurrent infection is high. There is clearly a need to prevent both primary and recurrent infections. We do not know if prophylactic antibiotics would be helpful, and if so, which antibiotic to choose as cotrimoxazole resistance is widespread in our setting. After one episode of bacterial meningitis, should all HIV infected children be given monthly injections of benzathine penicillin to try to prevent recurrence? The use of conjugate vaccines against *H influenzae* type b and *S pneumoniae* looks more promising and needs to be evaluated in HIV infected children as soon as possible.<sup>21-25</sup>

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# PostScript

## VIDEO REVIEW

### Chronic fatigue syndrome: a clinical view

Audiovisual Department, Southampton University, 2003.

This is an excellent video which I would highly recommend to anyone who deals with young people and adults with chronic fatigue syndrome (CFS): not only will health professionals find it a useful resource but teachers and families too. The treatment approach of the team in Southampton is presented in a clear and coherent way and the choice of articulate patients and parents to explain the illness and its impact on their lives is particularly helpful. In a logical way the video goes through the causes of CFS and making the diagnosis. A large section of the video is concerned with the treatment programme, stressing the importance of team work and engaging with the family to ensure that they are "on board" with the treatment. Drug usage and symptom relief are discussed, as are the use of complementary therapies. The focus of the treatment in Southampton is graded rehabilitation and cognitive behaviour therapy, and I believe that some patient groups will not rest easy with some of the aspects of care advocated by the Southampton group. At the end of the video is a section on prognosis and discharge.

Some aspect of the video I found disappointing. For example, it suggests that 2% of young people are affected by CFS and that the sex distribution is equal, but the reason for this statement is not discussed and does not accord with published data. The recent RCPCH/RCGP community based survey suggests a prevalence of 0.066%, two thirds of whom were girls. The consequence of this was to make me feel that if they had got this wrong, what else was wrong in the video? The video tended to avoid some of the contentious aspects of CFS management with which many paediatricians have most difficulty; although education is discussed, there is no mention of the pros and cons of home tuition. Rightly the video stresses the importance of engaging with the whole family, but there is no mention of what to do when the relationship between the family and the therapeutic team breaks down. The role of social services and child protection issues are also not dealt with. It would have been very helpful to have some advice on the management of the very severely affected bed ridden individual; as it is those patients who are the most taxing in terms of treatment.

Technically, the video is well produced with clear sound and pictures. There are not any glaring continuity problems, though the posterisation of some of the images was a little bit annoying. I wonder in 2003 whether production in DVD format would have been appropriate, with chapter headings for each section, allowing the viewer to jump to their areas of interest.

Despite my reservations above, this is an excellent resource which would be of value in

any departmental library. It should also find a place in the school health service as an information resource for school nurses and teachers.

D W Beverley

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## LETTERS

### Community growth monitoring in practice

The aim of routine growth monitoring (GM) of school age children is to identify children with the so-called "silent" conditions. These include growth hormone deficiency, hypothyroidism, and Turner's syndrome. Using the UK 1990 nine centile growth charts it has been recommended that all children with heights less than the 0.4th centile should be referred to growth clinics for further assessment.<sup>1</sup> We evaluated a district GM programme fulfilling this criterion, to assess its outcome.

A total of 89.6% (3465/3864) of children in the 1999-2000 reception class (mean age 4.83 years) had their height and weight measured by school health nurses. The mean height of all the children was 108 cm with a mean height standard deviation score of 0.052; 18/3465 children (0.5%) had heights less than the 0.4th centile. Fourteen of these children have now been assessed. Table 1 shows their diagnoses.

In our programme, 50% (7/14) of children with heights less than the 0.4th centile in whom a diagnosis has been made had an organic disorder. This is a better yield than either the Wessex growth study<sup>2</sup> (which used height <3rd centile as criteria for further assessment) or the Oxford Growth study<sup>3</sup> (which used height <2SD). The percentage of children with heights below the "cut off" that had an organic disorder in those studies were 18% and 43% respectively.

Our programme detected two children with idiopathic growth hormone deficiency (IGHD). This is more than would be expected given that the prevalence of IGHD is 1:4018.<sup>4</sup> There were no children with Turner's syndrome in our cohort. This may be because of our sample size as the prevalence of Turner's syndrome is 1:2500 female live births.<sup>4</sup> It could however be that using the 0.4th centile as referral criterion is too strict as a proportion of children with Turner's syndrome will

be taller than the 0.4th centile at this age. In the Wessex Growth study, two children identified with "silent disease" had heights above the 0.4th centile.<sup>5</sup>

In our programme, although a new significant diagnosis was made in 0.1% (4/3465) of the cohort, we remain concerned that the 0.4th centile "cut off" may be too strict.

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## The collusion of anonymity in paediatrics

One of the thankless, if necessary tasks of the NHS general practitioner is to sort and summarise incoming GP records of patients new to the practice.

While carrying out this noble duty, we looked at the records of an 11 year old patient with cerebral palsy who, in his brief life had seen 15 consultants, one research fellow, one clinical assistant, one senior medical officer, one clinical fellow, one principal health physician, and six registrars on 62 different occasions in 10 different specialties. At one point the patient was under the care of two

**Table 1** Diagnoses of children with heights less than the 0.4th centile

	Newly identified by programme	Diagnosed prior to programme
Autoimmune hypothyroidism	1	0
Idiopathic growth hormone deficiency	2	0
Intrauterine growth retardation	1 (with major psychosocial problems)	1
Batter's syndrome	0	1
Cystic fibrosis	0	1
Familial short stature	5	2
Total	9	5

community paediatricians simultaneously. In an orthopaedic clinic, the patient saw six differently named doctors on six clinic visits. Along with the medical appointments, there were up to seven clinic visits a week for other clinicians: physiotherapists, speech and language therapy, health visitor, psychology, occupational therapy, wheelchair assessment, and other.

This case illustrates a number of important issues for consideration by specialists, who may be tempted to refer:

- Dilution of responsibility—vital decisions are made without anyone feeling fully responsible for them; the “collusion of anonymity” described by Balint.<sup>1</sup>
- Increased burden of care on the parents of a disabled child; the sheer physical and time effort required in getting a disabled child to a clinic and then waiting for the specialist can be imagined.
- The potential for confusion of opinions between specialists in the same field.
- In this case, the lack of any obvious medical benefit from many of the multiple cross-referrals.

We hope that paediatricians will consider carefully the need for cross-referral and the need for a single point of contact for the parent of the disabled child.

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**Reference**

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**The Seville effect**

For some, football is more a religion than a sport. This can impact on families in multiple ways. One such quasi-religious event was the UEFA Cup Final between Glasgow Celtic and Porto (21 May 2003). An estimated 85 000 Celtic supporters converged on Seville for the UEFA Cup Final.

While doing two paediatric clinics on the day of the Cup Final I noted that the “did not attend” (DNA) rate at these clinics was well above normal, being 58.4% and 58%.

My hypothesis was that this quasi-religious event was being put before children’s health, shown by their failure to attend paediatric clinics. I decided to look at the DNA rates at Glasgow’s tertiary paediatric hospital, Yorkhill Hospital and the paediatric department of a large District General Hospital Trust, Ayrshire and Arran NHS Trust. The DNA rates at identical clinics the week before and after the Cup Final were analysed to allow appropriate comparison. The mean DNA rate was 14.58% on the day of the UEFA Cup Final, 17.38% on 14 May and 19.06% on 28 May. This in fact shows a trend towards attendance on the day of the UEFA Cup Final but this did not reach significance (p = 0.3). Reassuringly this refutes the hypothesis that Glaswegians will put football before their child’s health.

The breakdown of the subspecialty DNA rates had some interesting results. The

**Table 1** Number of non-attenders in three subspecialties

Department	14 May	21 May	28 May
General paediatric clinic	4/36 (11.1%)	16/50 (32%)	11/41 (26.8%)
Nephrology clinic	7/43 (16.3%)	8/31 (25.8%)	1/16 (6.3%)
Respiratory clinic	1/13 (7.7%)	2/6 (33.3%)	1/12 (8.3%)
Total	12/92 (13%)	26/87 (29.9%)	13/69 (18.8%)

haematology clinics, for example, had the lowest DNA rates, with an average of 5.9% (5/54 and 1/42 on 14 and 28 May respectively) not attending on the dates before and after the Cup Final. The DNA rate on the day of the Cup Final was 2/39 (5.1%). Other specialties including general medical paediatric, nephrology, and respiratory clinics showed a very different picture (table 1). When comparing the average DNA rate at these clinics with that on 21 May, there was a significant increase in failure to attend (p = 0.019%).

From this we can say that despite the huge exodus of football followers in the West of Scotland that occurred on the day of the UEFA Cup Final, the attendance rate at paediatric clinics in the West of Scotland was better on the day of the Cup than normal. This is very reassuring in this football frenzied area. However, it may be said that certain paediatric illnesses were treated with less importance.

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**Nephrotic syndrome relapse: need for a better evidence based definition**

Despite the occurrence of relapses, steroid sensitive nephrotic syndrome (SSNS) has a good long term prognosis. As it often heralds a clinical relapse, significant proteinuria (+++ or more on albustix) for ≥3 consecutive days (simplified as P3D in this letter) defines a relapse, resulting in steroid therapy before the onset of oedema. Proteinuria may be triggered by viral infections<sup>1</sup> and does not always develop into a relapse.<sup>2</sup>

We have observed 24 consecutive episodes of asymptomatic P3D, without oedema, occurring during a viral illness, in four children (two boys, two girls, age range 2–5 years) known to have SSNS. In eight of these episodes, the families refused to rush with steroid therapy; serum albumin level remained >30 g/l in the three where measured, and the proteinuria resolved between 5 and 10 days. Sixteen other episodes occurred in three children, who were treated as relapses; all three were later labelled as frequent relapsers and started on long term steroid therapy. None required renal biopsy. One child required cyclophosphamide and two required levamisole therapy; a rash occurred in one. None could be vaccinated against varicella while on steroid therapy; all required varicella zoster immunoglobulin injections after contact with chickenpox,

and one child developed varicella while on steroids and required acyclovir therapy.

In this series, 33% (exact binomial 95% confidence intervals 15% to 55%) of the P3D episodes were not relapses: there was no hypoalbuminaemia or oedema, and they resolved spontaneously within 5–10 days. We cannot ascertain how many of the remaining episodes were genuine relapses, as some may well have also resolved spontaneously after a few days. Although not blinded or controlled, this observational study challenges the current definition of relapse by the sole presence of P3D, confirming studies where up to one third of such episodes did not develop into a relapse and where waiting 10 days before starting therapy did not influence the course.<sup>2</sup> Defining a relapse only by P3D may therefore lead to unnecessarily treating 15–55% of affected children, and may cumulatively lead to over-diagnosing frequent relapses, resulting in unnecessary renal biopsy, prolonged steroid courses, and therapy with cyclophosphamide, cyclosporin, and levamisole, with their potential side effects.

As the natural history of isolated proteinuria in children with SSNS remains largely unknown, there is a clear and urgent need for larger prospective controlled studies in order to define relapses more accurately.

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**CORRECTION**

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Molyneux E, Forsyth H, Tembo M, et al. The effect of HIV infection on paediatric bacterial meningitis in Blantyre, Malawi (*Arch Dis Child* 2003;**88**:1112–18). The authors would like to apologise for an error in the results section of the abstract of this paper. The sentence “the number of survivors in each group was similar” should have been omitted prior to publication.