LETTERS TO THE EDITOR

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P Schneider  
V Greene  
J Kanold  
J-P Vannier

Fludarabine in the treatment of an active phase of a familial haemophagocytic lymphohistiocytosis

Editor,—Familial haemophagocytic lymphohistiocytosis (FHL) is a lethal disease with an uncontrolled activation of T lymphocytes and macrophages due to a perforin gene defect.1 The only current curative treatment is bone marrow transplantation. However, favourable outcome is associated with clinical remission status at the time of the procedure.1 Unfortunately, the use of steroids, etoposide (VP16), cyclosporin A, and antithymocyte globulins alone or in association frequently fails to control recurrent active phases.

BL, a 2 month old boy, was admitted in June 1999 for an active phase of FHL. His elder brother had died of FHL. The diagnosis was established on clinical (vomiting, fever, pallor, hepatosplenomegaly) and biological features (pancytopenia, hypertrophic-keratodermia (3.82 mmol/l), haemodilution, hypofibrinemia (0.65 g/l), a moderate eleva-
tion of aspartate transaminase (2N) and haemophagocytosis on bone marrow aspi-
rate). There was no clinical evidence of immunodeficiency in patients treated with fludarabine lymphohistiocytosis. 


Visceral leishmaniasis: also beware of these deceptive microbes in non-endemic countries!

Editor,—We read with interest the report by Grech et al.2 From their population based study, it seems that the annual incidence of visceral leishmaniasis (VL) declined considerably in Malta as a result of the eradication of stray dogs. VL is still endemic around the Mediterranean Sea and sporadic cases are reported in children living in Northern Europe. It seems likely that with increasing tourism the incidence of VL will also increase in areas where until recently this condition would not even be thought of. During the last 18 months, we have diagnosed three children with VL. As the presentation features can be fairly dramatic and physicians in Northern Europe are not always alert to the possibility of this condition, we would like to call attention again to the possibility of VL in non-endemic countries.

The main clinical features of the patients are shown in table 1. All three children presented with spiking high fevers, anorexia, hepatitis-splenomegaly, and pancytopenia. The onset of symptoms was insidious and it took 3–12 weeks to establish the diagnosis. In all three patients this was achieved through bone marrow aspiration and the demonstration of the typical amastigotes in macrophages. The diagnosis was further confirmed through the demonstration of antibodies to the leishmania parasite. All three patients needed erythrocyte transfusions and patient three also needed platelet transfusions. A 5–10 day course of liposomal amphotericin-B was given to all three children. The treatment was well tolerated, and they all became afebrile within a week. Pancytopenia subsided over the ensuing 2–3 weeks and the children gradually returned to normal activity.

Visceral leishmaniasis is a neglected tropical disease that is endemic in areas where until recently this condition was underdiagnosed. Strong serological and parasitological evidence supports the existence of this condition, we would like to call attention again to the possibility of VL in children travelling from Northern Europe might be because they have no transplacental immunity against the parasite and are therefore more prone to develop this condition than local children. There is much in common between the presentation features of the haemophagocytic syndromes and VL. It is noteworthy that all three of our patients showed signs of macrophage activation and haemophagocytosis was observed in their bone marrow smears. With increased awareness of this condition by physicians in non-endemic countries, the time required to reach the correct diagnosis and institute treatment should be reduced.

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>6</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Holiday destination where infected</td>
<td>South of France</td>
<td>Elba</td>
<td>South of Spain</td>
</tr>
<tr>
<td>Interval from exposure to appearance of symptoms (months)</td>
<td>7</td>
<td>12</td>
<td>6–18</td>
</tr>
<tr>
<td>Interval between appearance of symptoms and diagnosis (weeks)</td>
<td>6</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Hepatomegaly (%)</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Splenomegaly (%)</td>
<td>10</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Hb (mmol/l)</td>
<td>2.9</td>
<td>3.0</td>
<td>4.1</td>
</tr>
<tr>
<td>WBC (×10⁹/l)</td>
<td>4.5</td>
<td>3.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Platelets (×10¹²/l)</td>
<td>47</td>
<td>107</td>
<td>10</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>10813</td>
<td>260</td>
<td>4612</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>4779</td>
<td>914</td>
<td>1761</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>5.64</td>
<td>6.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Serum IgG (g/l)</td>
<td>13.9</td>
<td>15.6</td>
<td>36</td>
</tr>
</tbody>
</table>

LDH = lactate dehydrogenase


...
I have explored the validity of this assay for use in supernatants of fecal homogenates in children with cystic fibrosis and found it wanting. Recovery of a 500 pg/ml spike of IL-8 progressively increased from 41% in samples which were a 12-fold dilution of faeces to 180% in samples which were a 120 000-fold dilution of faeces, when used according to manufacturer’s instructions. Prediluting the samples 50/50 in newborn calf serum, and using call of serum for further dilutions gave this assay (R&D catalogue no DB8000) mean (SD) spike recovery of 92.1 (12.5%) and coefficients of variation of 3.46% (intra-assay) and 6.85% (interassay). Without knowledge of the IL-8-ELISA validation data of Smyth et al, I assume that this assay returns similarly spuriously high IL-8 concentrations in polyethylene glycol based wholegut lavage fluid to my 120 000-fold dilution fecal supernatant. The absence of a significant difference between CF patients and controls in their IL-antitrypsin output suggests that intestinal inflammation was not present in the CF patients. Overestimation of the WGLF IL-8 concentration would explain the apparently implausibly large volumes of swallowed sputum that the authors estimate would be required to account for their findings. In this study which could not turn the mucous layer escalator, but did dramatically increase the rate of intestinal transit and exclude exogenous pancreatic enzymes, swallowed sputum is the most likely explanation for the results.

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Intestinal inflammation in cystic fibrosis

EDITORS,—Following their studies of whole gut lavage fluid, Smyth et al have suggested that a non-idiosyncratic intestinal inflammation occurs constitutively in patients with cystic fibrosis (CF), as a consequence of a proinflammatory effect of the patient’s CFT1R mutations. They reported marginally elevated excretion of IgG, IgM, interleukin 1 (IL-1), neutrophil elastase, and eosinophil cationic protein, and much more significant increase in excretion of IL-8 and albumin, but no increase in excretion of α1 antitrypsin or α1 antichymotrypsin. In this study where lavage fluid was admistered continuously, and intestinal effluent was collected in discrete samples, pooling of the effluent before analysis would have allowed small differences in calculated inflammatory mediator outputs to be interpreted as representative of gastrointestinal output. Of all the inflammatory markers presented, only IL-8 shows a range of cytokte outputs in CF patients with or without fibroscopic colonoscopy that did not extend into the range seen in controls, in these non-parametric databases. The author’s evidence for intestinal inflammation therefore relies heavily on the validity of their IL-8 Quantikine assay (R&D Minneapolis) protocol.

I have explored the validity of this assay for use in supernatants of fecal homogenates in children with cystic fibrosis and found it wanting. Recovery of a 500 pg/ml spike of IL-8 progressively increased from 41% in samples which were a 12-fold dilution of faeces to 180% in samples which were a 120 000-fold dilution of faeces, when used according to manufacturer’s instructions. Prediluting the samples 50/50 in newborn calf serum, and using call of serum for further dilutions gave this assay (R&D catalogue no DB8000) mean (SD) spike recovery of 92.1 (12.5%) and coefficients of variation of 3.46% (intra-assay) and 6.85% (interassay). Without knowledge of the IL-8-ELISA validation data of Smyth et al, I assume that this assay returns similarly spuriously high IL-8 concentrations in polyethylene glycol based wholegut lavage fluid to my 120 000-fold dilution fecal supernatant. The absence of a significant difference between CF patients and controls in their IL-antitrypsin output suggests that intestinal inflammation was not present in the CF patients. Overestimation of the WGLF IL-8 concentration would explain the apparently implausibly large volumes of swallowed sputum that the authors estimate would be required to account for their findings. In this study which could not turn the mucous layer escalator, but did dramatically increase the rate of intestinal transit and exclude exogenous pancreatic enzymes, swallowed sputum is the most likely explanation for the results.

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Intestinal inflammation in cystic fibrosis: an alternative hypothesis

EDITORS,—I was interested by the report of Smyth and colleagues on the finding of markers of intestinal inflammation in whole gut lavage in patients with cystic fibrosis. As the α1 antitrypsin levels were not elevated when compared to controls, perhaps another hypothesis needs to be considered. Conceivably the inflammatory markers are not increased within the bowel, but rather, they are not degraded due to the lack of intestinal enzymes, α1 antitrypsin, which is resistant to proteolytic enzyme activity, would not be affected by such a phenomenon and, therefore, would be the same in patients with cystic fibrosis and controls. Perhaps the authors would need to resort to the somewhat dated technique of radio labelled albumin to definitively answer this question.

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Intestinal inflammation in cystic fibrosis

EDITORS,—We thank Dr Briars for his recent comments and are aware of his opinions regarding the potential source of the intestinal cytokines that we discussed in paper, including reference to his previous paper.1 We do not agree that our data is dependant upon IL-8 alone. We have shown statistically significant differences for a whole range of proteins and types of assays. Due to the small number of proteins and types of assays that we have performed, we have not carried out the extensive experiments for IL-8, as reported by Dr Briars. We do know that the polyethylene glycol, a key constituent of the lavage fluid, does not affect the IL-8 assay. There are two reasons why variable recovery is unlikely to be a major factor in our results. Firstly, by collecting whole gut lavage, any intestinal secretions present, including bile, intestinal transit and exclusion of exogenous pancreatic enzymes, swallowed sputum is the most likely explanation for the results.

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Lumbar puncture should not be performed in meningococcal disease

**Editor,—I was dismayed to see your publication of the letter by Dr Sam regarding the role of lumbar puncture in meningococcal disease.** While fully understanding the need to get as much information as possible, the benefits of isolating the causative organism need to be weighed against the risk of causing clinical deterioration in a patient who may have coagulase negative meningococcal disease and raised intracranial pressure, both of which are recognised contraindications to lumbar puncture. There are clear and recognised risks of performing this procedure in such patients.

The potential benefits of lumbar puncture include making a diagnosis of meningitis and isolation of the organism for epidemiological and sensitivity testing. In the UK the typical haemorrhagic rash of meningococcal infection is pathognomonic of the disease and should be treated as such prospectively, until further confirmatory evidence is available. With polymerase chain reaction (PCR) of meningococcal DNA in blood allowing up to 100% sensitivity for diagnosis in the first 24 hours of illness, there is little to be gained from looking for bacteria or cells in the cerebrospinal fluid (CSF). The antibiotic regimen is no different for either meningococcal meningitis or septicaemia, with seven days of a third generation cephalosporin being the treatment of choice because of improved CSF penetration. There are no reports of meningococcal resistance to this treatment in the UK, so performance of a lumbar puncture for bacterial sensitivity testing appears to be unnecessary.

Prospective therapy while awaiting results of culture or PCR from blood seems to be a small price to pay in this life threatening illness. An analogy could be drawn from the management of epiglottitis. It is generally accepted that throat swabs should not be taken from children with epiglottitis until the child’s airway has been protected, because of the risk of clinical deterioration. It is time that textbooks of emergency paediatrics stated clearly that lumbar punctures on children with a haemorrhagic rash, and clinical signs of meningococcal meningitis should not be carried out until the clinical condition has been stabilised, and only if the procedure will add further valuable information that cannot be obtained elsewhere.

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**Prophylaxis for respiratory syncytial virus infection: missing the target**

**Editor,—**Two recent reports about hospitalisation for respiratory syncytial virus (RSV) infection in high risk infants have suggested that the introduction of prophylaxis may, potentially, be beneficial in certain subgroups. We would like to emphasise that the “bigger picture” also warrants further consideration.

During the winters of 1998–99 and 1999–2000, we reviewed our admissions who were RSV positive and had a Cambridge “CB” post code. “At risk” infants—that is, pretermers under 6 months of age, or those with bronchopulmonary dysplasia (BPD) under two years, were identified from the two winters (1998–99 and 1999–2000) was 5/51 (9.8%) and 4/62 (6.5%), respectively. Supposedly “low risk” infants accounted for 92% (66/72) and 90% (54/60) of our RSV related admissions for each winter. There were no deaths in any of the admissions including the two with BPD.

In the first winter, 10 intensive care bed days were needed, none in the “high risk” population. In the second winter, such infants used 12 out of 54 intensive care bed days. Finally, inpatient costs for RSV in “high risk” infants was about 10% and 15% of total RSV related hospital costs for the two winters respectively (see table).

Taken together, even if there were potential savings following the introduction of prophylaxis to specific subgroups, a target population—arguably equally in need of protection—is being overlooked. In fact, in our area, the potential effect of introducing prophylaxis would more than double health authority costs for RSV, with little impact on our so called “low risk” more major caseload.

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**Hajj and risk of blood borne infections**

**Editor,—**Annually, some two and a half million pilgrims congregate in the city of Mecca in Saudi Arabia to perform the Hajj (pilgrim-age), a religious duty for all adult Muslims who are physically and financially able. Because of the very large numbers of peoples from disparate regions, and the hostile climate of the Arabian Desert, the chances of disease are high. Heat exhaustion, sunstroke, and infectious diseases such as pneumonia and meningitis have traditionally caused the greatest disease burden.

One of the rites of the Hajj is for males to shave their heads, although trimming the hair is also acceptable. Most will choose the former, often in make-shift centres run by opportunistic barbers. A razor blade is commonly used, and may be used on several scalps before ultimately being discarded. The risks of blood borne infections such as HIV and hepatitis B and C are obvious, especially considering that many pilgrims come from regions of the world where such infections are endemic. Pilgrims should be aware of the potential dangers and be educated to insist on the use of a new blade. We would also strongly recommend that they be vaccinated against hepatitis B.

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**Table 1**
Potential cost of prophylaxis in the community

<table>
<thead>
<tr>
<th>Year</th>
<th>Low risk infants</th>
<th>High risk infants</th>
<th>Savings in “high risk”</th>
<th>Prophylaxis costs</th>
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<tbody>
<tr>
<td>1998–1999</td>
<td>£9340</td>
<td>£10455</td>
<td>£228</td>
<td>£31440</td>
</tr>
<tr>
<td>1999–2000</td>
<td>£97692</td>
<td>£15162</td>
<td>£5588</td>
<td>£16120</td>
</tr>
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</table>

£1 equals approximately $1.5 (November 2000).

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Hajj and risk of blood borne infections

A R GATRAD and A SHEIKH

Arch Dis Child 2001 84: 373
doi: 10.1136/adc.84.4.373h

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