

# Antibiotic resistant fever associated with herpes simplex virus infection in neutropenic patients with haematological malignancy

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**SUMMARY** The incidence of mucocutaneous herpes simplex virus infection confirmed by culture and occurring during febrile neutropenic episodes was determined in 43 patients with haematological malignancy. The outcome of 72 episodes of neutropenic fever was determined and correlated with the presence or absence of herpes simplex virus (HSV) infection. Twenty four patients had mucocutaneous HSV infection during at least one episode. In 24 episodes in which HSV was isolated only 12.5% of fevers responded to antibiotics and 75% of fevers were otherwise unexplained. Conversely, in 48 episodes of neutropenic fever in which HSV was not isolated 67% of fevers responded to antibiotics and only 8.3% were unexplained. The difference in incidence of antibiotic resistant fever in the two groups was significant. There was, therefore, a strong association between mucocutaneous HSV infection and antibiotic resistant fever in immunosuppressed neutropenic patients. As most HSV infections are the result of virus reactivation, establishing the HSV serological state of patients would identify those at risk of infection and hence those in whom the prophylactic use of acyclovir would be indicated.

Early treatment with broad spectrum bactericidal antibiotics reduces the morbidity and mortality from bacterial infection in neutropenic patients.<sup>1-4</sup> A significant proportion of febrile episodes which occur in neutropenic patients, however, fail to respond to broad spectrum antibiotics.<sup>1-4</sup> In these cases antibiotic resistant bacteria and invasive fungal and viral infections are sometimes identified.<sup>4</sup> Reactivation of herpes simplex virus (HSV) is increasingly recognised in patients with haematological malignancy,<sup>5,6</sup> and mucocutaneous infection is a major cause of morbidity in patients after bone marrow transplantation.<sup>7,8</sup> An association between HSV infection and prolonged fever in recipients of allogeneic bone marrow transplants has been suggested,<sup>8</sup> but HSV infection as a cause of persistent fever in neutropenic patients has not been confirmed. We therefore set out to determine the incidence of HSV infection in patients with haematological malignancy who were receiving intensive chemotherapy and to correlate this with the outcome of episodes of neutropenic fever.

## Patients and methods

The records of febrile neutropenic patients in whom throat swabs for virus culture had been taken at the onset of fever were examined for details of infection, fever, bacterial isolates and response to antibiotics.

Neutropenic fever was defined as a single recording of 39°C or greater, or two recordings of 38°C two hours apart in a patient with a neutrophil count of less than  $0.5 \times 10^9/l$ . Patients were examined for clinical signs of infection, and blood cultures were taken from a peripheral vein and central line if present. Throat and rectal swabs were taken for bacterial culture, and a throat swab in virus transport medium for virus culture was taken from all patients. Patients were then treated with parenteral antibiotics: piperacillin 4 g and gentamicin 80 mg four times a day each, and then appropriate antibiotics as indicated by bacterial isolates. If fever had not settled within 48 hours and bacterial cultures were negative, ceftazidime 2 g three times a day and vancomycin 500 mg twice a day were given and the response noted 48 to 72 hours later. Patients known to be allergic to penicillin were treated initially with ceftazidime and gentamicin. Patients not responding to two combinations of broad spectrum

antibiotics were considered to have antibiotic resistant fever. This definition of resistant fever excluded patients with intermittent fever associated with administration of blood products.

For the isolation of virus, swabs were collected in virus transport medium (2 ml Hanks's balanced salt solution with 1% bovine albumin). A volume of 100  $\mu$ l was inoculated into cultures of human amnion, Vero, or MRC-5 cells which were then rolled for seven to 10 days at 37°C. Those cultures showing a cytopathic effect characteristic of HSV were stored at -20°C. Serotyping of HSV was performed with the Imagen HSV direct immunofluorescence assay (Celltech Diagnostics Ltd).

Data were analysed by Fischer's exact test and the Mann-Whitney U test.

## Results

### INCIDENCE OF HERPES SIMPLEX VIRUS INFECTION

One hundred and sixty one throat swabs were taken during 72 episodes of neutropenic fever occurring in 43 patients. The diagnoses and the number of patients with at least one episode of HSV infection confirmed by culture are shown in table 1.

Cultures from 13 swabs were discarded because of contamination with either bacteria or fungi. Of the remaining 148 swabs, HSV was cultured from 52 (32% of all swabs). Positive HSV cultures were obtained during 24 episodes of neutropenic fever (mean number of positive swabs for each HSV infection = 2.2). In all cases patients were also lymphopenic ( $< 1.0 \times 10^9/l$ ). There was no correlation, however, between the incidence of HSV infection and the absolute lymphocyte count. Furthermore, there was no difference in lymphocyte counts at the time of infection in those patients with HSV ( $0.4 \times 10^9/l$ ) and those without HSV infection ( $0.5 \times 10^9/l$ ) ( $p = NS$  by Mann-

Whitney test). All HSV strains were serotyped as HSV type 1.

The same 43 patients had a further 152 surveillance throat swabs cultured for HSV when not febrile. Only 15 swabs from six patients grew HSV. None of the patients was febrile or neutropenic at the time swabs were taken, all but one were lymphopenic ( $< 1.0 \times 10^9/l$ ). These episodes were not associated with recent chemotherapy, five occurring in patients with active lymphoma and one following anti-lymphocyte globulin treatment for aplastic anaemia.

### RESPONSE OF NEUTROPENIC FEVER TO ANTIBACTERIAL TREATMENT AND RELATION TO HSV INFECTION

Seventy two episodes of neutropenic fever were recorded. HSV was isolated at the time of fever in 24 episodes (33%) and was not cultured in 48 (67%). One patient in each group died, giving an overall mortality of 3%.

Only three (12.5%) of the 24 febrile neutropenic episodes in which HSV was cultured responded to antibacterial treatment. Positive blood cultures were obtained on six occasions. On two occasions bacteria were resistant to the antibiotics administered. A single episode of fever responded to removal of an indwelling central venous catheter. One case of aspergillus, diagnosed serologically, was documented but intravenous amphotericin did not lead to resolution of the fever. Eighteen episodes (75%) of persistent fever were unexplained, apart from the presence of mucocutaneous HSV infection. Symptoms or signs suggestive of mucocutaneous HSV infection were recorded in only six of the 24 episodes.

In contrast, in 32 (67%) of the 48 episodes in which HSV was not isolated fever responded to either first or second line antibacterial treatment. Positive blood

Table 1 Diagnoses and number of patients with at least one episode of HSV infection confirmed by culture

Diagnosis	No of patients	No of patients with HSV infection
<b>Myeloid malignancies:</b>		
Acute myeloblastic leukaemia	14	6
Chronic myeloid leukaemia	2	0
Aplastic anaemia	1	1
<b>Lymphoid malignancies:</b>		
Acute lymphoblastic leukaemia	4	3
High grade non-Hodgkin's lymphoma	10	9
Chronic lymphocytic leukaemia	1	0
Hairy cell leukaemia	1	0
Myeloma	4	1
<b>Others:</b>		
Hodgkin's disease	6	4
<b>Totals</b>	<b>43</b>	<b>24</b>

Table 2 Outcome of 72 episodes of neutropenic fever with respect to results of HSV cultures

Outcome of neutropenic fever	No of episodes	
	Negative HSV culture	Positive HSV culture
Response to antibacterial treatment	32	3
Resistant bacteria	2	2
Response to removal of central venous catheter	2	1
Response to granulocyte transfusion	1	—
Response to surgical drainage of abscess	2	—
Culture confirmation or seroconversion to aspergillus and response to amphotericin	4	—
Confirmed by culture candida hepatitis	1	—
Unexplained fever	4	18
<b>Total</b>	<b>48</b>	<b>24</b>

cultures were obtained in 11 of the 48 episodes. In two the bacteria were resistant to the antibiotics administered. An identifiable cause of fever was found in a further 12 episodes (table 2). Four (8.3%) cases of unexplained fever remained.

In the presence of mucocutaneous HSV infection confirmed by culture 75% of neutropenic fevers either failed to respond to appropriate antibacterial treatment or remained unexplained, compared with only 8.3% in the absence of HSV infection ( $p < 0.001$ , Fischer's exact test).

## Discussion

Bacterial infection in neutropenic patients may be rapidly fatal, and as the results of bacterial cultures and hence antibiotic sensitivities are not immediately available patients are treated empirically with parental broad spectrum antibiotics. This approach has greatly reduced the mortality associated with episodes of neutropenic fever.<sup>1,4</sup> The mortality during neutropenic fever in our study was 3% and the incidence of documented bacteraemia was 24%, both of which are comparable with the data of previous studies.<sup>1-4</sup>

Herpes virus infections are common in immunosuppressed patients.<sup>5-10</sup> The rate of HSV reactivation in patients with high grade lymphoproliferative malignancy has been reported to be as high as 60%,<sup>11</sup> while a prospective point prevalence study in 29 patients with acute myeloblastic leukaemia showed a 34.5% HSV reactivation rate, with 40% of patients shedding HSV on at least one occasion.<sup>6</sup> In our study 52% of patients with haematological malignancy had at least one documented episode of HSV infection during episodes of neutropenic fever.

Our data suggest that in patients at risk of reactivation of HSV, infection is associated with lymphopenia rather than neutropenia. This observation is in keeping with known mechanisms of T cell mediated defence against HSV.<sup>9</sup> Among the lymphoid malignancies there were only two T cell high grade lymphomas and two cases of T cell acute lymphoblastic leukaemia. Most HSV infections, therefore, occurred in patients with B cell lymphomas. We suggest that this is because active HSV infection is associated with the severe lymphopenia associated with intensive chemotherapy rather than impairment of lymphocyte function associated with disease. As all the patients in this study were lymphopenic at times of neutropenia, neutropenic patients seem to be at risk of HSV infection by virtue of associated lymphopenia. Notably, fever was only associated with HSV infection in our patients when they were lymphopenic and neutropenic following intensive cytotoxic chemotherapy. At this time the integrity of mucous mem-

branes is also compromised and this may allow a portal of entry for organisms, particularly Gram positive bacteria.<sup>12,13</sup>

The high incidence of antibiotic resistant fever in neutropenic patients with HSV infection (87.5%), compared with those without (33%,  $p < 0.001$ ) indicates the importance of recognising HSV infection as a contributory factor in persistent fever in neutropenic patients. Symptoms or signs suggestive of HSV infection, such as mouth ulceration, gingivitis, sore throat and oesophagitis were not documented in 70% of cases confirmed by culture. Undue reliance should not be placed, therefore, on the clinical findings alone.

Although the incidence of disseminated HSV infection is low, the prophylactic administration of acyclovir to HSV antibody positive patients during neutropenia might reduce not only morbidity, related to mucosal ulceration, but also the incidence of antibiotic resistant fever. This study did not prospectively evaluate the response of fever to the therapeutic administration of acyclovir. In several prospective controlled studies, however, acyclovir has been shown to be effective in preventing HSV infection in patients with haematological malignancy. The pharmacokinetics of absorption of orally administered acyclovir do not seem to be significantly affected by gut toxicity,<sup>14</sup> and both oral<sup>7,11,14</sup> and intravenous<sup>8,15</sup> prophylaxis with acyclovir are effective. Furthermore, significant resistance to acyclovir has not been found in our patients, despite altered susceptibility to acyclovir during treatment of established HSV infection, and oral therapy should be adequate in most if not all patients.<sup>16</sup>

In conclusion, mucocutaneous HSV infection in immunosuppressed neutropenic patients is associated with antibiotic resistant fever. There is therefore a rational basis for the inclusion of acyclovir in the management of fever in these patients and its use may reduce that of intravenous amphotericin B and second line antibiotics. Because HSV infection is predominantly the result of virus reactivation, establishing the HSV seropositive state of patients would identify those at risk of infection and hence those in whom prophylaxis with acyclovir would be indicated.

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