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Response from Dr Hohenthal

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This response to the letter by Miall *et al* (*Bone Marrow Transplantation* 2002; **29**:6 541–542) was inadvertently omitted from the last issue of *Bone Marrow Transplantation*.

The report by Miall *et al* describes an interesting case of human parainfluenza type 4 virus (hPIV4) infection provoking many questions regarding the role of this virus as the causative agent of respiratory tract infections in the post-transplant setting. These issues involve the frequency and clinical severity of the hPIV4 disease as well as the need for rapid virological diagnostics in patients undergoing BMT.

The authors refer to our paper[1] on a cluster of nine patients with hPIV3 infection in a hematology unit during a 2-month period. This and additional recent reports[2,3] on outbreaks in BMT units demonstrate the clinical importance of hPIV3 as a nosocomial pathogen. In contrast, as pointed out by these authors, there are few documented cases of hPIV4 infection in immunocompromised patients. This may indicate that the virus is, indeed, uncommon or merely that it is seldom detected using the presently available diagnostic methods.

The clinical presentation of the patient described by Miall *et al* was severe with pleural and pericardial effusions, pneumonia and respiratory failure requiring continuous positive airway pressure support. It seems reasonable to assume that this patient might have benefitted from ribavirin therapy, if hPIV4 as the causative agent of infection had been identified early on. During the outbreak in our unit, ribavirin was administered in all four hPIV3-positive patients who had infiltrates on chest radiograph; all survived.[1] This is of note considering the high mortality rate of up to 50% previously reported in BMT recipients with lower respiratory tract infection caused by hPIV3.[4–6] Our experience supports the concept that it may be possible to avoid mortality from hPIV lower respiratory tract infection in BMT recipients and other hematological patients, provided that efforts are made to obtain a rapid etiological diagnosis. The clinical features do not reliably distinguish this syndrome from that caused by other respiratory pathogens.

The case described above does not include any data on or suspicion of potential transmission of hPIV4 from this patient to other patients in that unit. Neither are we aware of other reports on nosocomial transmission of hPIV4 among immunocompromised patients. Nevertheless, whenever hPIV is introduced into hospital, there is a danger of nosocomial viral transmission. hPIV3 is characterized by prolonged shedding: in BMT recipients, the shedding may continue for many months, even despite ribavirin treatment.[2] Some of our patients continued to shed the virus for several weeks.[1] We believe that the imminent outbreak in our unit was contained by nasopharyngeal sampling of patients and by prompt implementation of strict hygienic measures when a patient was shown to be positive for hPIV3 on antigen detection.

The main issue of Miall *et al* is to remind us that hPIV4 is not detected when currently available commercial immunofluorescent reagents are used for rapid diagnostics. On the other hand, an hPIV4 immunofluorescent reagent in monoclonal antibody form is not widely used. Moreover, there are data showing that hPIV4 is the most difficult hPIV to grow in cell culture, being rarely isolated despite relatively common serological evidence of infection.[7] These data clearly indicate that there is a need to develop and adopt new diagnostic methods for detection of hPIV4 in a clinical setting. Aguilar *et al*[7] have published an interesting paper showing that a multiplex reverse transcription-PCR (m-RT-PCR) assay was able to detect and differentiate all known hPIVs. This m-RT-PCR assay was more sensitive than either cell culture isolation or indirect immunofluorescence with monoclonal antibodies for the detection of hPIV infections. Among 64 hPIVs detected by this assay in 201 nasopharyngeal samples from pediatric patients hospitalized for lower respiratory tract infection, hPIV1 and hPIV3 were the most prevalent hPIVs, but hPIV4 was more frequent than hPIV2 (10 *vs* 7 isolates). Based on this and a few other studies[8] in which the presence of hPIV4 was confirmed by viral culture, it has been hypothesized that this infection may be more common than previously believed.

We totally agree with Miall *et al* in their conclusion that rapid methods used in virological diagnostics should also detect hPIV4. In addition to ensuring early commencement of specific antiviral therapy for severe lower respiratory tract infections caused by hPIV4, accurate diagnostics renders possible prompt implementation of hygiene measures to prevent nosocomial viral spread. Due to the potentially serious nature of hPIV infection in immunocompromised patients, this is especially important in BMT units.

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Allogeneic BMT for infantile acute leukemia: what is the optimal conditioning regimen?

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Leung *et al*[1] recently reported their results in 22 infants with acute leukemia or myelodysplasia who underwent allogeneic BMT. Patients received a radiation-containing regimen prior to BMT. The authors report a 5-year event-free survival of 45.5%.

Total body irradiation had been recognized to be associated with adverse effects on the growth and endrocrinologic status of BMT recipients. In a study concerning late effects of treatment in survivors of childhood AML, Leung *et al*[2] reported that younger age (at the time of diagnosis or initiation of radiation therapy) was a risk factor for development of academic difficulties and greater decrease in height. Furthermore, they concluded that those who received TBI and allogeneic BMT had an increased risk for development of growth hormone deficiency, hypothyroidism, hypogonadism, infertility and cataracts. Similarly, Cohen *et al*[3] concluded in their study of final height of patients who had undergone BMT during childhood that irradiation was one of the major factors for long-term height loss.

Regimens containing no radiation for conditioning of infants with acute leukemia prior to BMT have been reported to result in satisfactory outcomes. Marco *et al*[4] reported a 5-year disease free survival of 63% in 26 patients with infantile leukemia after BMT (eight allogeneic and 18 autologous), only one patient received TBI, the remainder received conditioning with chemotherapy only. Infants who had AML fared better than those with ALL (73% *vs* 56%, respectively, although *P* was not significant). On the other hand, our results have not been as rewarding at King Faisal Specialist hospital. Using chemotherapy only as conditioning prior to BMT, 12 infants with acute leukemia underwent allogeneic BMT between October 1993 and March 2001, five had acute lymphoblastic leukemia and seven had acute myeloid leukemia. The median age at BMT was 15.25 months (range, 9.5–23.5 months). All patients were in remission before BMT. All donors were HLA-identical (nine from siblings and three from a parent). Harvested bone marrows were not manipulated, the median CD34-positive cell count was 8×10^6/kg of recipient body weight (range, 0.63–15.4). The conditioning regimen in 11 patients consisted of busulphan (BU) at total dose of 12 mg/kg, cyclophosphamide (CY) at a total dose of 120 mg/kg, and etoposide at a total dose of 60 mg/kg. One patient received BU/CY only. At 45 months post-BMT, our event-free survival was 25%. When analyzed separately, however, the event-free survival for patients with AML was 45%. All patients with ALL died (three had relapse of their disease, one died of severe acute GVHD of the gut, and one died of pulmonary fibrosis).

When compared with our results, Leung's data suggest that the use of TBI may offer better results. We believe, however, that its role in the conditioning of infants undergoing BMT is still not clearly defined. Further multi-institutional randomized studies are required to clarify this controversial issue.

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