Graft-versus-host disease is a common complication of allogeneic bone marrow transplantation, consequent on disparity in histocompatibility antigens between donor and recipient. The extent of disease varies, but in the acute phase may involve skin, gut and liver, and signs include a maculopapular, erythematous skin rash, fever, diarrhoea, and jaundice. With liver involvement, laboratory investigation typically shows cholestasis, and, to a lesser extent, raised transaminases. Although the precise pathway of tissue damage remains unclear, engrafted donor T lymphocytes are central to pathogenesis, and treatment is by immune suppression, but the disorder remains a major cause of transplant related morbidity and mortality.

A similar disease, transfusion-associated graft-versus-host disease (TA-GvHD), may follow transfusion of blood products containing viable T cells, and although uncommon, this disorder has been described both in immune competent and immune suppressed individuals. The incidence is unknown, and as similar features may occur in at risk children due to other causes, it is possible that cases pass undiagnosed. Clinical features are similar to graft-versus-host disease after marrow transplantation, but pancytopenia has been a distinctive feature of TA-GvHD, and there is a higher mortality, although some individuals have recovered with supportive care and treatment with steroids, cyclosporin, and antilymphocyte antibodies.

TA-GvHD appears more likely if the donor is homozygous for one of the recipient HLA haplotypes, and this is particularly likely to occur with directed donations from first or second degree relatives, the provision of HLA matched platelets, and transfusion within a population with a high prevalence of shared HLA haplotypes.

Despite animal studies the minimum dose of T cells required to produce TA-GvHD in humans remains unknown and is likely to depend on several factors including HLA disparity between donor and recipient, and the degree of immunosuppression. Cases have followed transfusion with red cell, granulocytes and platelet packs, and fresh plasma, but coagulation concentrates, albumin solutions, and immunoglobulin preparations are all free of risk. Despite residual lymphocytes, there are insufficient data to indicate that fresh frozen plasma carries risk.

Children with TA-GvHD develop symptoms and signs up to one month after transfusion, but diagnosis may be delayed as individual clinical features are not specific, and similar signs occur in immune compromised patients due to infection or drug toxicity. On clinical suspicion, biopsy of affected tissue is recommended, and typical features in skin include T cell infiltrates in the upper dermis and demopidermal junction, vascular degeneration of epidermal basal cells, and dyskeratosis. A liver biopsy specimen may also show a lymphocytic infiltrate, with necrosis of small bile ducts and cholestasis. Further evidence for the diagnosis may be obtained by detection of donor lymphocytes within blood, from karyotype, by HLA typing, or DNA techniques, although circulating donor lymphocytes are not of themselves indicative of a disease process. Aberrant expression of HLA-DR antigens on epidermal keratinocytes has been described as a specific features of graft-versus-host disease.

Children at risk
Cases of TA-GvHD have generally been described among children with congenital abnormalities of cell mediated immunity, or during treatment for malignancy. In contrast, no cases have been reported after acquired T cell deficiency, including infection with HIV. In cancer treatment, the majority of cases have occurred during treatment of leukaemia and lymphoma, although due to small numbers it is not possible accurately to determine relative risk. There is, however, an impression that patients with Hodgkin’s disease are at higher risk than those with other malignancy, even in the absence of intensive treatment, and abnormal cell mediated immunity is a recognised feature in Hodgkin’s disease before treatment. Due to the intensive preparative regimens before bone marrow transplantation, and the prolonged immune suppression that follows an allograft, these children are considered high risk for TA-GvHD. Uncertainty exists regarding the period of risk after transplantation, and this is likely to be affected by many factors including the type of transplant, preparative regimen, time to full engraftment, and on-going immune suppressive treatment.

Newborn infants, especially if preterm, have evidence of reduced immune function, and are frequently transfused. TA-GvHD in this population is rare, and has usually been described in infants with congenital deficiency of cell mediated immunity, or after exchange transfusion. Among infants with immunodeficiency, the underlying disorder was usually undetected before transfusion. Further cases have resulted from standard transfusion of blood or platelets, and extracorporeal circulation in children with no evidence of an immunological disorder. Prior transfusion in utero may increase the risk with subsequent blood products, possibly due to immune modulation by lymphocytes transfused to the fetus. Directed donations from a parent, for example maternal platelets for babies with alloimmune thrombocytopenia, may also carry higher risk (see above).

Preventative measures
Prevention of TA-GvHD is currently dependent on irradiation of cellular blood products before transfusion, in order to abrogate T cell function. Other methods with potential for prevention such as removal of lymphocytes by leucocyte depletion filters, or inactivation by ultraviolet light are currently either inadequate or unproved, although further development of leucocyte filters may ultimately make filtration a feasible alternative. Although abrogation of T lymphocyte response in mixed lymphocyte culture may be achieved by irradiation doses over 500 cGy, TA-GvHD has followed transfusion of blood products irradiated at up to 2000 cGy, and as the dose delivered varies within an irradiation chamber, stipulated doses may not have been administered to the whole transfusion pack in these cases. Furthermore, doses of 1500–2000 cGy are associated with a 90% reduction in mitogen responsiveness, and remaining active T cells may effect TA-GvHD. Accordingly, the minimum dose should be at least 2500 cGy to all parts of the unit to be transfused. This recommendation takes account of changes in the recovery of transfused cells derived from irradiated packs, red cell, granulocyte and platelet function, and alterations in biochemistry. In particular, the increase in extracellular potassium associated with irradiation is unlikely.
Which children should receive irradiated blood products?

As TA-GvHD is rare, widespread irradiation of blood products is not justified in the United Kingdom, but it is possible to identify situations in which preventative measures are indicated. Directed donations and HLA matched platelets should always be irradiated, as these products may carry increased risk, and as granulocyte packs contain large numbers of lymphocytes, and are usually transfused to patients who are immunocompromised, preventative irradiation appears prudent.

Children undergoing bone marrow transplantation require irradiated products immediately before and during autologous stem cell harvest due to the risk of collecting donor lymphocytes in the procedure, and from the beginning of preparative treatment. It remains unclear at what stage after transplantation this policy may be relaxed, but at a pragmatic level, continuation until immune suppressive treatment has been discontinued for those undergoing an allograft, or for three months after an autograft, seems prudent. The risk may be extended in children with prolonged immunosuppression for any reason.

For children receiving standard cancer chemotherapy, the incidence of TA-GvHD is generally very low, but those with Hodgkin’s disease may be considered a higher risk group, and should therefore receive irradiated blood products from diagnosis. As TA-GvHD has rarely occurred during treatment for other malignancy, including leukaemia, irradiation is not currently recommended, but this situation remains under review.

Children with suspected as well as proved congenital defects of cellular immunity should only receive irradiated blood products, particularly as TA-GvHD has occurred in children with Di George syndrome who have undergone cardiac surgery before definitive diagnosis. Irradiated products are not presently indicated for children with HIV/AIDS, or isolated defects of humoral immunity.

Red cell and platelet packs selected for intrauterine transfusion should be irradiated, and as intrauterine transfusion may be associated with increased risk with subsequent transfusions in the newborn period, irradiation of blood products should continue for this group. There have been few cases after exchange transfusion alone, and irradiation cannot be considered essential in this setting. Current evidence does not indicate that preventative measures are required for other infants.

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