Is this really the current status of small bowel transplantation in the UK?

We read with interest the article on "The current status of small bowel transplantation in the UK and internationally" by Middleton *et al* (*Gut* 2005;54:1650–7). This is a timely article about the improving worldwide outcome following small bowel transplantation but does not fully reflect the status of small bowel transplantation in the UK. In the UK, the Department of Health through NSCAG (National Specialist Commissioning Advisory Group) recognises and funds three units for small bowel transplantation (2 adult centres—Addenbrooke's Hospital, Cambridge and St James Hospital, Leeds; and a single paediatric centre—Birmingham Children's Hospital (BCH)) since 1997. The majority of transplants in the UK to date have been carried out in children, which also reflects the international situation. Thirty eight intestinal transplants have been performed in children at BCH since 1993 compared with 14 transplants in the adult population in the last 15 years at two adult centres.

The paediatric experience has taught us many useful lessons which also benefit adult recipients, such as: reduction of graft size,¹ increased awareness of post-transplant infectious enteritis, and Epstein Barr virus (EBV) related post-transplant lymphoproliferative disease (PTLD), which are risk factors for death following small bowel transplantation in both adults and children.^{2,3}

Since the introduction of graft reduction techniques, we have performed 21 en bloc reduced combined liver and small bowel transplants, thus extending the donor pool and facilitating transplantation of small children from older donors.¹

In a recent report from the UCLA group, infectious enteritis (IE) with viruses (adenovirus, EBV, and rotavirus) and protozoa (giardia lamblia, cryptosporidium) has been reported in three adults and 10 children following small bowel transplantation. This is an underreported and underdiagnosed complication following intestinal transplantation. A high index of suspicion and prompt laboratory investigations are necessary to arrive at an early diagnosis as the clinical features can mimic acute cellular rejection (ACR) and the treatment of IE is very different to ACR.²

EBV related PTLD is seen more commonly in children who, unlike adults, are EBV seronegative pre-transplant, but also occurs in adults following small bowel transplantation.³ The diagnosis of EBV related PTLD is based on high viral EBV polymerase chain reaction (PCR) loads and histopathological examination. Treatment modalities such as reduction of immunosuppression, surgical resection for control of local complications, anti-CD20 monoclonal antibody (Rituximab), adoptive immunotherapy, and cytotoxic chemotherapy are helpful in the treatment of this invasive disease.⁴ Awareness about PTLD and serial EBV PCR monitoring has reduced the incidence of PTLD in the last decade.

In conclusion, this article does not acknowledge the contribution of the paediatric experience in this developing field.

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White cell scanning has a role in imaging small and large bowel

I enjoyed the article by Albert *et al* (*Gut* 2005;52:1721–7) comparing newly emerging imaging modalities for the assessment and detection of small bowel Crohn's disease, an area of the gastrointestinal tract that is often difficult to adequately image, assess, and biopsy.

However, their article failed to mention 99mTc HMPAO labelled white cell scanning as a method of imaging the small (and large) bowel. Planar white cell scintigraphy is a well established non-invasive method of assessing intestinal inflammation.¹ While histological assessment is considered to be the gold standard method of detecting intestinal inflammation, planar white cell scintigraphy accurately reflects disease extent and histological activity.² The new imaging methods discussed by Albert *et al* also suffer from this disadvantage of not allowing histological assessment.

In addition to planar white cell scanning, single photon emission computerised tomography white cell scanning has been shown to correlate very well with histology ($r = 0.8$, $p < 0.0001$) in subjects with active inflammatory bowel disease.³

We have previously shown that both white cell scanning techniques are valuable not only in assessing extent and severity of inflammation but in following up response to treatment in subjects with ulcerative colitis and Crohn's disease.^{4,5}

When evaluating newly emerging imaging techniques, it is vital not to forget previously established techniques.

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Seventeen years after successful small bowel transplantation: long term graft acceptance without immune tolerance

The first attempts at small bowel transplantation (SBT) in humans were disappointing^{1–3} and characterised by severe graft rejection in spite of initially encouraging experience in animals.^{3–5} Major difficulties were encountered as: (1) the intestine is an immune organ harbouring most immune competent cells of the body; and (2) it is particularly vulnerable to ischaemia, not allowing time consuming HLA matching prior to transplantation (Tx). Therefore, Tx of intestinal allografts into fully immune competent recipients results almost inescapably in terminal graft rejection. With the introduction of tacrolimus in the 1990s, this difficulty was partially overcome, improving small bowel graft survival rates (70% at one year post Tx).^{6–8} However, on follow up, a large number of grafts are still lost, raising the question of long term success and benefit after SBT. Here we present the first patient with a 17 year follow up after isolated SBT.

A Caucasian infant girl with extreme short bowel secondary to neonatal volvulus was transplanted with an isolated intestinal graft on 18 March 1989 at the age of five months.⁹ The iso-blood group O Rhesus positive transplant (two HLA class I and one class II mismatch, with negative T cell cross match) was derived from an anencephalic newborn girl. Immunosuppression was based on ciclosporin (CsA), prednisolone, azathioprine, and a single injection of rabbit antihuman thymocyte globulins (5 mg/kg) with an in situ flush of the SB graft with CsA. Four acute graft rejection episodes occurred, at days 82, 121, and 205, and 19 months post Tx, all of which responded favourably to medical therapy (OKT3, anti-interleukin 2 receptor monoclonal antibodies, or rabbit antihuman thymocyte globulin combined with steroid pulses and transient bowel rest). Eight months after SBT, the infant was weaned off parenteral nutrition. Further complications included CsA induced hypertrichosis, gingival hyperplasia, a moderately severe *Pneumocystis carinii* pneumonia at two months, and cytomegalovirus infection five years post-Tx. In 1998, nine years after SBT, the patient suffered another (fifth) rejection episode motivating a switch from CsA to tacrolimus that resulted in intestinal graft recovery. Since then, she has been leading a normal life (eating normally by mouth, 2–3 soft stools a day) without any further Tx related complications or hospital stays (except routine examinations evaluating graft function and monitoring for adverse reactions to IS, including tumour screening). Meanwhile, the girl has completed puberty (final height 160 cm (median percentile) and weight 45 kg (–1 SD)).

Figure 1 Ileal biopsy of the intestinal graft 15 years after small bowel transplantation, showing normal cytoarchitecture with long villi and well differentiated enterocytes (haematoxylin-eosin staining, $\times 200$). A mononuclear inflammatory infiltrate was seen within the lamina propria which was predominantly of a T cell nature (CD3, positive brown staining, $\times 200$). Some of these cells stained positive for CD4 and CD25 (merged immunofluorescence picture resulting in a yellow colour, $\times 800$).

Evaluation of graft function at 15.5 years post Tx showed a total energy absorption rate of 93% using calorimetric analyses (carbohydrates 94%, nitrogen 86%, and lipids 93%, with a daily oral caloric intake of 2300 kcal in 2005). On histology (fig 1), we observed normal intestinal cytoarchitecture and villi; however, the lamina propria was infiltrated with mononuclear, mainly CD3 positive T cells. Some of these cells stained positive for CD4/CD25, which indicates the presence of regulatory T cells within the lamina propria of the graft.

To date, one can expect SB graft survival of approximately 50% five years post SBT.⁷ No follow up data are available beyond five years. Here we show for the first time that it is possible to keep a functional intestinal graft for more than 17 years, with normal life quality. The ultimate goal in transplantation medicine is the development of complete immune tolerance towards a graft, which

guarantees long term survival, as recently proposed by Starzl and colleagues.¹⁰ Five rejection episodes as well as persistent inflammatory infiltrate in the graft in our patient clearly indicate lack of immune tolerance; however, the use of potent IS has allowed long term graft acceptance and function. The presence of regulatory T cells within this intestinal graft indicates some adaptive regulatory steps. Therefore, monitoring of regulatory T cells might help in elucidating the mechanisms underlying immune acceptance versus tolerance.

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