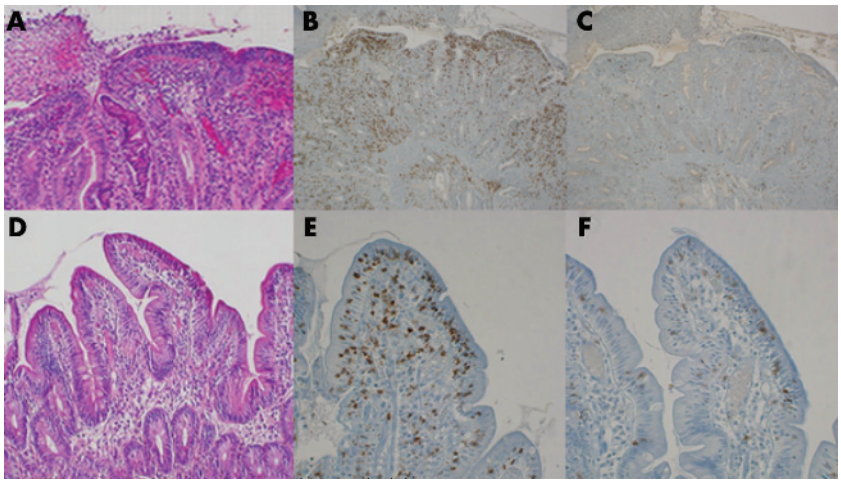

Figure 1 Jejunoileitis (A–C) on jejunal biopsy samples in July 2003, with total villous atrophy, ulceration, major intraepithelial lymphocyte infiltration (haemato-eosine-safran, A) widely expressing CD3 (immunoperoxidase, B) but rarely CD8 (immunoperoxidase, C). Villous regrowth (D–F) on jejunal biopsy samples in November 2004 after small bowel resection followed by combination treatment with pentostatine, budesonide, and a strict gluten free diet: no villous atrophy (hemato-eosine-safran, D), moderate CD3+ intraepithelial lymphocyte infiltrate (immunoperoxidase, E) with mixed CD8− and CD8+ populations (immunoperoxidase, F).

A severe but reversible refractory sprue

Original treatments, including corticosteroids, azathioprine, infliximab, ciclosporin, and interleukin 10 have been occasionally reported in refractory sprue patients with unsatisfactory results.[1–8] We report on the clinical and histological efficacy of anti-T chemotherapy (pentostatine) in a patient with a refractory sprue complicated by an ulcerative and stenotic jejunitis.

A 38 year old man diagnosed with refractory sprue in June 2002 developed ulcerative jejunitis in July 2003. Diagnosis led on the following: malabsorptive diarrhoea resistant to a gluten free diet (GFD); severe malnutrition (body mass index (BMI) 14.3 kg/m^2); albuminaemia 11 g/l; diffuse total villous atrophy associated with jejunal ulcerations and a major intestinal intraepithelial CD3+ CD8− T lymphocyte population (IEL) (fig 1A–C); clonal T cell receptor γ rearrangement; negative circulating antigliadin and antitransglutaminase IgA and IgG antibodies (total IgA and IgG were normal); hyposplenism; no intestinal stenosis; and jejunal ulcerations but no evidence of an enteropathy associated T cell lymphoma (EATL) on endoscopic videocapsule, enteroscopy, or laparoscopy with small bowel, liver, and lymph node biopsies.

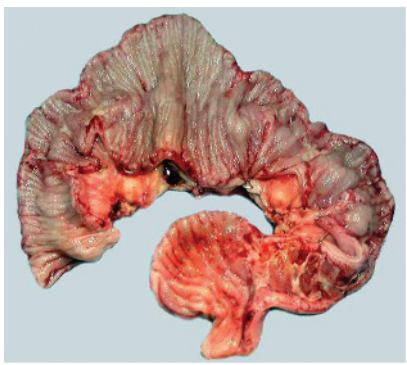

Figure 2 Stenosis and ulcerations (macroscopy, January 2004).

Total exclusive parenteral nutrition (PN), budesonide, and omeprazole (in an attempt to optimise jejunal release of enteric coated budesonide) led to a moderate improvement in September 2003 (BMI 15.4, albuminaemia 19 g/l, citrullinaemia 4 µmol/l (normal range 20–47))[9]. Strict GFD was reintroduced but intake remained low (800 kcal/day) because of nausea. Three jejunal stenosis were found and a 60 cm jejunal resection was performed in January 2004 (fig 2). Microscopic findings were similar to preoperative samples showing no sign of malignancy. Twelve infusions of pentostatine (Nipent 4 mg/m^2—that is, 6 mg every two weeks) were administrated from March to September 2004 with no side effects, together with trimethoprime/cotrimoxazole, budesonide, omeprazole, and a strict GFD.

At the end of the chemotherapy period, improvement was noticeable: no diarrhoea, weaned off PN since April 2004, BMI 20.7, albuminaemia 44 g/l, and citrullinaemia 14 µmol/l. Two months later entero computed tomography, small intestine follow through radiography, and push and retrograde enteroscopy were considered normal. Duodenal biopsies showed partial villous atrophy whereas jejunal biopsies had no villous atrophy with a mixed IEL CD8+/CD8− up to 40 per 100 epithelial cells (fig 1D–F) with a persistent clonal T cell receptor γ rearrangement; GFD, budesonide, and omeprazole were continued. In November 2005 he remained symptom free, BMI 20.0, with stable biological parameters, including albuminaemia 36 g/l and citrullinaemia 11 µmol/l.

Pentostatine (a nucleoside analogue inducing T cell depletion) is commonly used in hairy cell leukaemia[10] and chronic lymphoid leukaemia.[11] It has been tested in hepatosplenic gamma/delta T cell lymphoma with promising efficacy.[12] In eight patients with CD3+ CD8− refractory sprue treated with cladribine (another anti-T nucleoside analogue),[13] significant clinical improvement (weight gain, improvement in diarrhoea and hypoalbuminaemia) was noted in all but one case. Two patients showed histological improvement and a decrease in IEL. However, three patients died of EATL. In our patient treated with pentostatine and budesonide, tolerance was good and we observed a dramatic clinical and histological improvement, including not only villous regrowth but also reappearance of CD8+ T cell IEL. Because refractory sprue was fully reversible in this patient, as illustrated in fig 1, our original findings prompt us to propose this combination therapy for similar patients.

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Severe recurrent Crohn's disease of ileocolonic anastomosis and antimicrobial (anti-mycobacterial) therapy

Elliott *et al* (*Gut* 2005;**54**:1818–19) presented an interesting and clinically useful finding of successful treatment of a patient with severe Crohn's disease and circumferential narrowing of the ileocolonic anastomosis with 750 mg ciprofloxacin plus 400 mg metronidazole daily for almost three years, resulting in complete healing and opening up of the stenosed anastomosis.

The authors list a number of bacterial species known to be susceptible to these antibiotics. However, they have omitted perhaps the most important potential pathogen, *Mycobacterium avium* ss *paratuberculosis* (MAP), the leading candidate causal agent of Crohn's disease.[1 2] It is well known that ciprofloxacin exhibits marked activity against *Mycobacterium avium*.[3] It is also known that metronidazole can be bactericidal against dormant *M tuberculosis* in anaerobic conditions.[4] Although no such data are yet available concerning other mycobacteria, the role of metronidazole in affecting MAP cannot be excluded when these bacteria persist under anaerobic conditions. It is indeed very unlikely that the success of the metronidazole/ciprofloxacin combination had much to do with luminal flora bacteria but more likely it treated indolent tissue MAP, which may explain the need for prolonged therapy. We can be even more certain that luminal flora was not the only target of these antibiotics, especially ciprofloxacin, because more than 10 prolonged trials of various combinations of antituberculosis antibiotics were inactive against MAP, were active against luminal flora bacteria, yet still failed to improve the outcome of Crohn's disease.[5] On the other hand, in our experience[6] with specific anti-MAP treatment, we have reported five patients whose terminal ileal strictures returned to normal, an indication that prolonged targeted antimicrobial therapy is necessary to inhibit tissue MAP and its consequent inflammation and oedema.[6]

In retrospect it was difficult to accept that a chronic infection with a previously poorly known organism could cause such widespread gastroduodenal disease. In the pre-*Helicobacter* era, bismuth was thought to ''chelate with protein at an acid pH…may stimulate release of mucus''[7 8] when actually it was acting via a completely different mechanism, inhibiting growth of *Helicobacter pylori*. Similarly, in this case report, one could initially postulate that metronidazole in combination with ciprofloxacin exerts its effect by inhibiting local bowel flora. On closer examination it becomes more plausible that data presented in this case report supports involvement of MAP in the causation of inflammation, oedema, and stenosis in Crohn's disease and that prolonged anti-MAP treatment can progressively reduce inflammation.

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Complication rates of ablation therapies for hepatocellular carcinoma: a difficult comparison with an easy solution

We read the recent debate from Taipei (*Gut* 2005;**54**:1151–6) on which is the best image guided ablation therapy for hepatocellular carcinoma (HCC), proposed by Lin and colleagues[1] and Huo and colleagues.[2] This is an interesting topic for hepatologists and gastroenterologists.

The papers by Lin *et al* stated that in the treatment of HCC, radiofrequency (RFA) was superior to percutaneous ethanol injection (PEI) and percutaneous acetic acid injection (PAI) with respect to local recurrence, overall survival, and cancer free survival, but RFA also caused more major complications. In contrast, Huo *et al* stressed that PEI may still be the preferred ablation method for small HCC because the complication rate of RFA may be higher than previously assumed. In fact, the rate of death occurring with the two techniques was higher for RFA (0.3–0.5%) than for PEI (0.09%).[3 4] Moreover, Huo *et al* reinforced their point of view by emphasising that RFA is affected by a higher mortality (risk ratio of 10.6-fold) if the death rate is calculated on the basis of number of sessions of treatment.[3 4] The letter of Huo and colleagues,[2] demonstrates that lack of standardisation persists in the reporting results of ablation therapies. This is due to the use of non-uniform terms and different parameters to calculate the rate of complications.

Although the recent publication of the International Working Group on Image-guided Tumor Ablation[5] has standardised terminology, thus facilitating communication between investigators and improving comparison of the results of different ultrasound guided treatments, some doubts remain on which denominator should be used for the rate of complications: number of patients, number of sessions, number of ablations, or number of tumours?

As far as mortality is concerned, it is clear that death should be reported on a per patient basis. If instead we indicate the number of sessions as the denominator, as reported by Huo and colleagues,[2] then the technique which employs a higher number of sessions to achieve ablation obviously has a lower rate of complications, and this is particularly true when we compare PEI with RFA. As regards treatment related morbidity (that is, major (not death) and minor complications, as defined by the SIR classification[6]) it is more appropriate, in our opinion, to divide the number of complications by the number of ablated nodules (that is, cured).

Unlike the number of sessions, ablations, or tumours, the number of ablated nodules represents the main objective for all ablation techniques and only by using this parameter can we truly compare the incidence of complications that occur after RFA, PEI, or other image guided tumour ablation therapies.

In conclusion, we suggest using a sole parameter as the denominator (that is, number of ablated nodules), as the future for prevention and therapy for HCC will rest on comparative prospective studies based on dedicated databases.[7]

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