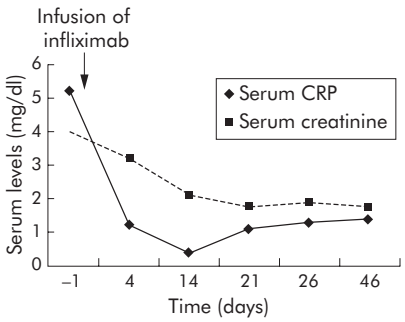

Figure 1 Serum C reactive protein (CRP) and creatinine levels of the patient after treatment with infliximab.

progression of renal dysfunction on 4 April 2004. This patient was diagnosed as having Crohn's disease with ileocolitis in 1990 based on clinical, endoscopic, and histological criteria. A small amount of proteinuria was observed in 1992, and AA type amyloid deposition was systemically detected in biopsy specimens from his colon, terminal ileum, stomach, duodenum, and kidney.[2] Before admission, he had been treated with elemental diet,[2] prednisolone, and dimethylsulphoxide. After admission, he underwent parental nutrition therapy. However, inflammatory parameters and renal function did not improve in two weeks, and we decided to use infliximab. He received an infusion of infliximab 5 mg/kg on 16 April 2004, and his renal function as well as C reactive protein dramatically improved (fig 1). Furthermore, serum amyloid protein level also decreased significantly (from 762 to 30.2 μg/ml) in 10 days. The Crohn's disease activity index (CDAI) of the patient decreased from 235.5 to 148.2 points in eight weeks.

Although the detailed mechanism is unknown, it is noteworthy that infliximab not only decreased serum amyloid protein level but also ameliorated the renal function of our patient with systemic AA amyloidosis associated with Crohn's disease. Therefore, we hope that clinical trials assessing the efficacy of infliximab in systemic amyloidosis associated with Crohn's disease will soon be conducted. There have been many patients with Crohn's disease who have suffered from severe and fatal extraintestinal complications. Infliximab may shed light on therapeutic strategies for such patients.

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Do baseline ALT levels predict complications of chronic hepatitis B?

We read with interest the paper by Yuen *et al* (*Gut* 2005;**54**:1610–4). This study included a large patient cohort with chronic hepatitis B and analysed the determinants predicting outcome. The authors concluded that low level viraemia and mildly elevated serum alanine aminotransferase (ALT) levels more commonly led to the development of complications. This conclusion however was not supported by their findings as the independent predictive factors were male sex, age, stigmata of chronic liver disease, and others, whereas serum ALT and hepatitis B virus (HBV) DNA levels were not.

It is questionable if patients with mildly elevated baseline ALT levels are truly associated with a higher risk of complications. As shown in fig 2 of their paper, the incidence of complications in the group with ALT >2–6× upper limit of normal (ULN) and the group with ALT >6×ULN was still significantly higher compared with the group with ALT <0.5×ULN that had the lowest risk of complications. More importantly, serum ALT level was not an independent risk factor predicting poor outcome in the Cox multivariate analysis, suggesting lower serum ALT and/or HBV DNA levels were only associated but not independent factors. Although HBV DNA levels were tested to correlate with clinical course, it should be noted that DNA levels were measured at different time points (21 patients before, nine at, and 80 after the complication developed) and this inhomogeneous information makes the analysis of the impact of HBV DNA level on disease course less useful. Interestingly, entirely different conclusions were reported from a recent study that prospectively investigated 4841 Taiwanese men who were HBV carriers.[1] A higher baseline HBV DNA level was associated with an increased risk of the development of hepatocellular carcinoma (HCC), with a risk ratio of up to 7.3-fold.[1] In addition, a positive baseline hepatitis B e antigen consistently predicted a higher risk of HCC.[1 2] The contrast between these studies can be best explained by the fact that patient data were collected at different time points in the natural history of chronic hepatitis B. In this regard, the necessity of serial multiple measurements of clinical parameters in patients with chronic hepatitis B has been emphasised to reveal important information associated with long term outcome.[3]

Another potential flaw in this study is that the authors defined ascites, spontaneous bacterial peritonitis, and encephalopathy as complications of chronic hepatitis B. It should be noted that these are rather late complications of cirrhosis and may not be directly related to HBV infection. As the time interval from silent cirrhosis to the development of complications may vary widely and many cirrhotic patients never develop significant cirrhosis related complications in their natural history, the complication should be defined as formation of cirrhosis or HCC which is directly linked with chronic HBV infection.

In summary, end points evaluated should be cirrhosis or HCC rather than cirrhosis related complications which are not directly related to HBV infection. Lower serum ALT and HBV DNA levels more likely reflect a later stage of chronic hepatitis B and are possibly associated with increasing age of these patients who may already have severe fibrosis or subclinical cirrhosis.

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Authors' reply

We would like to thank Dr Huo *et al* for their comments. The following are point by point responses to their comments.

(1) Serum alanine aminotransferase (ALT) levels were not considered in our analysis of prognostic factors because stratification into five groups rendered it too complicated for statistical calculation by multivariate analysis. In addition, we aimed to examine independently the differences in outcome in patients with different ALT levels, as elevated ALT level is the most commonly used criterion for initiation of treatment. As for HBV DNA levels, our conclusion was that development of cirrhosis was related to prolonged low level viraemia up to the time of development of complications. Baseline HBV DNA levels would be of little help in determining whether HBV DNA levels are important. A good example is high HBV DNA levels in children; this does not mean that they are at risk of cirrhotic complications when they are young.

(2) As is clearly shown in the table under fig 2, for patients with ALT <0.5× upper limit of normal (ULN), the risk of development of complications was significantly different from those with ALT 0.5–1×ULN. Also, the risk of development of complications was significant *lower* than patients with ALT >1–2×ULN and ALT >2–6×ULN. Clearly, ALT levels >1–2×ULN have the highest risk of complications.

We would like to stress that the "baseline HBV DNA levels" of the study of Yu *et al* were arbitrary,[1] taken at the particular time point the subjects were recruited on a completely random basis.

As for the study of Yang and colleagues,[2] hepatitis B e antigen (HBeAg) status was only measured on recruitment. It is not known what proportion of these patients had HBeAg seroconversion during the subsequent follow up of 92 359 patient years (that is, HBeAg/anti-HBe status was not known at the time of development of hepatocellular carcinoma).

(3) As for our specifically studying the late complications of cirrhosis, we consider this as one of the important and innovative aspects of our study, and not a flaw. Huo *et al* are wrong in saying that only the formation of cirrhosis or hepatocellular carcinoma is directly linked with chronic HBV infection. As the study of Liaw *et al* has elegantly shown, lowering viral replication can suppress the development of late complications of cirrhosis.[3] In fact, this exactly confirms the proposal of our study.

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Mannan binding lectin (MBL) gene polymorphisms are not associated with anti-*Saccharomyces cerevisiae* (ASCA) in patients with Crohn's disease

Recently, an association between the presence of antibodies to *Saccharomyces cerevisiae* (ASCA) and mutations in exon 1 and the promoter region of the mannan binding lectin (MBL) gene was described in 58 patients with Crohn's disease (CD).[1] A possible link between ASCA and MBL mutations in patients with CD is plausible. MBL is a component of the innate immune system that can bind to *S cerevisiae* and the serum concentration of MBL depends on structural mutations in exon 1 and promoter polymorphisms.

Table 1 Different mannan binding lectin (MBL) variants and the presence of anti-*Saccharomyces cerevisiae* (ASCA)

	Prevalence of ASCA (%)	p Value (χ^2 test)	Titres of ASCA (EU/ml)*	p Value (Kruskal-Wallis or Mann-Whitney U)
MBL exon 1 (codons 52, 54, 57)		0.62		0.82
A/A	54		4.12 (1.12-11.88)	
A/O	58		4.48 (1.46-10.18)	
O/O	67		5.31 (0.95-8.23)	
MBL promoter C-225G		0.61		0.55
Y/Y	55		4.37 (1.32-11.81)	
Y/X	52		3.61 (1.05-9.87)	
X/X	71		5.61 (3.25-6.41)	
MBL		0.27		0.43
Sufficient (A/A+YA/O)	53		3.64 (1.23-10.32)	
Insufficient (XA/O+O/O)	63		4.96 (0.92-10.45)	

*Values are median (interquartile range).
Wild-type alleles are designated A (structural alleles) and Y (promoter −225 allele). Mutant alleles are designated O (structural alleles) and X (promoter −225 allele).

We previously found no association between structural mutations in exon 1 of the MBL gene and susceptibility to CD.[2] In view of the recent report of Seibold and colleagues,[1] we were interested to see if we could confirm the reported association between ASCA and MBL mutations in a larger and independent cohort of CD patients. Three point mutations in exon 1 (codons 52, 54, and 57) and one polymorphism in the promoter region (C-225G) of the MBL gene were genotyped using polymerase chain reaction-restriction fragment length polymorphism or ARMS in a cohort of 241 CD patients. Statistical analysis was performed using SPSS 12.0 for Windows. The results are summarised in table1.

We found no association between the presence of ASCA and structural MBL mutations in exon 1 (codon 52, 54, and 57) ($p = 0.62$; χ^2). Similarly, we found no association between the presence of ASCA and MBL promoter polymorphism C-225G ($p = 0.61$; χ^2). Furthermore, no statistical difference was found between ASCA titre and MBL structural genotypes in exon 1 ($p = 0.82$; Kruskal-Wallis) and promoter polymorphism C-225G ($p = 0.55$; Kruskal-Wallis). Finally, no difference was found when we compared sufficient and insufficient MBL alleles towards either the presence or the titre of ASCA (see table1).

We found no association between the presence of ASCA and polymorphisms/mutations in the MBL gene in a large cohort of CD patients and conclude that the occurrence of ASCA is not related to MBL polymorphisms/mutations. This is in contrast with a previous report in which such an association was suggested.[1] Therefore, we consider the relationship between ASCA and MBL highly controversial.

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Dyspepsia is distinguishable from heartburn

This systematic, original, and large study from the Leuven group (*Gut* 2005;**54**:1370–6) proves what experienced physicians have appreciated for many years: that heartburn is a specific symptom that is easily identifiable by careful history or validated questionnaire; that heartburn is predictive of abnormal oesophageal acid exposure in approximately 75% of people with the symptom; and that it occurs in a minority of patients with typical or "true" dyspepsia, especially when the latter syndrome consists of symptoms other than pain or burning which occur after meal ingestion.

The heartburn prevalence of <20% in the typical dyspepsia group of Tack and colleagues (*Gut* 2005;**54**:1370–6) is consistent with the high rate of somatic symptoms in these patients and it is likely that it represents