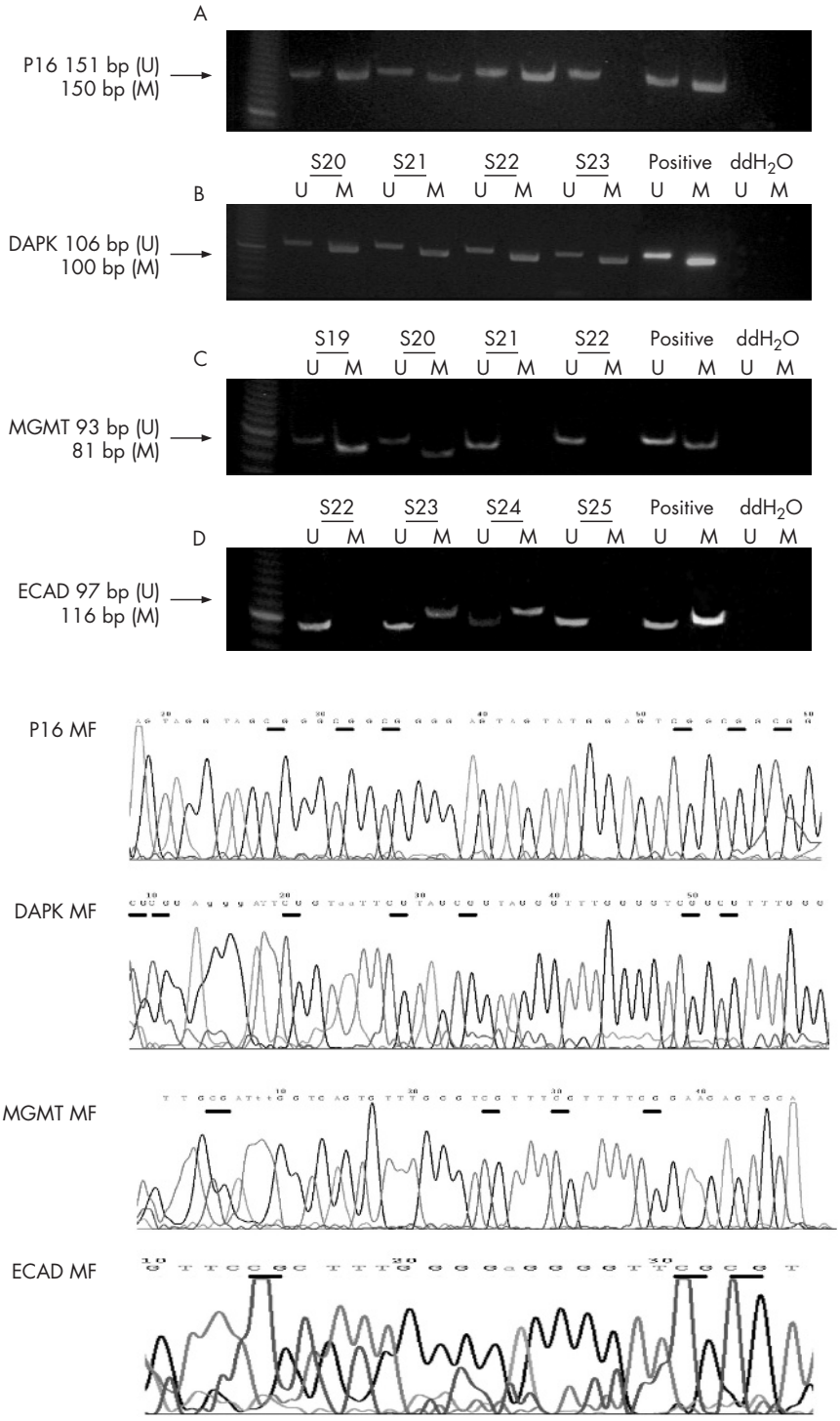

Figure 1 Examples of polymerase chain reaction products of P16, DAPK, E-cadherin (ECAD) and O^2-methyl-guanine methyl transferase (MGMT) genes. The lower panel shows segments of the methylated sequences of these gene products. Methylated cytosine residues that are unchanged are shown as underlined.

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Restricted use of albumin for spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) may precipitate deterioration of circulatory function with severe hepatic insufficiency, hepatic encephalopathy, and type-1 hepatorenal syndrome (HRS) and has 30% hospital mortality despite infection resolution.[1] Predictors of this acute-on-chronic liver failure include ascitic fluid concentrations of granulocytes and cytokines and renal and hepatic insufficiency at diagnosis.[1–3] Endotoxemia and the inflammatory response precipitate renal failure (RF) by accentuating splanchnic vasodilatation and impairing cardiac function.[3–5] Compensatory activation of the renin-angiotensin and sympathetic nervous systems further decrease renal perfusion. Volume expansion with albumin (1.5 g/kg day one, 1 g/kg day three) significantly reduces the incidence of HRS and hospital mortality.[2]

In the sole reported trial, only patients with serum bilirubin (bili) >68.4 μmol/l, blood urea nitrogen (BUN) >30 mg/dl or serum creatinine (Cr) >88.4 μmol/l appeared to benefit from albumin.[2] In this report we describe a therapeutic protocol involving 38 episodes in 28 patients at the Mount Sinai Medical Center New York and the Barcelona Hospital Clinic in which albumin (1.5 g/Kg on the day of diagnosis, 1 g/Kg on the third day; Human Albumin 25%, ZBL Bioplasma AG, Berne, Switzerland) was restricted to those at high risk for RF (bili > 68.4 μmol/l or Cr >88.4 μmol/l) (table 1). Diagnosis and treatment of SBP were based on established guidelines.[6] Cardiovascular and splanchnic hemodynamics and the activity of the renin-angiotensin system and inflammatory response were assessed in 6 low-risk cases from Barcelona at SBP diagnosis and resolution.[3 7 8]

Table 1 Clinical characteristics of patients at diagnosis of spontaneous bacterial peritonitis episodes who did receive (A) and who did not receive (B) albumin

	A (n = 26)	B (n = 18)	p Value
Age (years)	50 (32–70)	54 (38–74)	0.383
Sex (male/female)	12/14	12/6	0.179
Aetiology (HCV/other)	12/14	12/6	0.179
History of SBP (n/%)	15 (58%)	7 (39%)	0.220
SBP prophylaxis (n/%)	10 (39%)	6 (33%)	0.728
Community/hospital acquired SBP (n)	19/7	15/3	0.489
Mean arterial pressure (mm Hg)	78 (54–124)	88 (62–103)	0.046
Hepatic encephalopathy	23 (89%)	9 (50%)	0.007
Total bilirubin (μmol/l)	115 (12–395)	39 (14–67)	<0.001
Albumin (g/dl)	2.1 (1.5–3.5)	2.2 (0.8–4.1)	0.005
INR	2.3 (1.2–5.9)	1.7 (1.1–2.2)	0.002
BUN (mg/dl)	28.5 (7–74)	18 (5–48)	0.003
Creatinine (μmol/l)	124 (35–327)	80 (53–106)	0.001
White cell count ($\times 10^3/\mu L$)	9.4 (2.7–34.3)	7.5 (2.5–17.5)	0.010
Ascitic neutrophil count (/μL)	1464 (128–21794)	833 (90–8640)	0.062
Child-Pugh score	13 (9–15)	10 (8–12)	<0.001
MELD score	26 (14–42)	14 (6–18)	<0.001

BUN, blood urea nitrogen; HCV, Hepatitis C Virus; INR, interleukin; MELD, model end-stage liver disease; SBP, spontaneous bacterial peritonitis

Table 2 Systemic and splanchnic hemodynamics, endogenous vasoactive systems and interleukin 6 at spontaneous bacterial peritonitis diagnosis and resolution

	Diagnostic	Resolution	p Value
Cardiac index ($L/min/m^2$)	5.0 (3.3–6.4)	3.9 (3.7–5.3)	0.094
Systolic volume (ml)	93 (67–131)	83 (63–114)	0.188
Heart rate (bpm)	83 (71–127)	80 (58–112)	0.313
Right atrial pressure (mm Hg)	8 (4–11)	7 (5–11)	0.875
Pulmonary artery pressure (mm Hg)	17 (13–28)	18 (14–29)	0.438
Pulmonary capillary pressure (mm Hg)	11 (7–19)	11 (9–13)	0.625
Systemic vascular resistance ($dyn/s/cm^5$)	668 (467–1153)	852 (706–970)	0.438
Mean arterial pressure (mm Hg)	80 (70–89)	79 (67–88)	1.000
Wedged hepatic venous pressure (mm Hg)	32 (25–37)	31 (24–40)	0.875
Free hepatic venous pressure (mm Hg)	10 (8–14)	12 (6–15)	0.313
Hepatic venous pressure gradient (mm Hg)	20 (17–29)	19 (13–35)	0.625
Hepatic blood flow (l/min)	1.0 (0.5–1.7)	0.7 (0.4–2.0)	0.688
Plasma renin activity (ng/ml/h)	5.6 (0.5–8.1)	3.1 (0.1–5.8)	0.031
Norepinephrine (pg/ml)	257 (172–805)	255 (44–511)	0.156
Plasma IL6 (pg/ml)	65 (8–365)	16 (10–63)	0.625
Serum NOx (nmol/ml)	35 (24–40)	30 (21–55)	1.000
Ascitic fluid NOx (nmol/ml)	30 (12–68)	33 (32–93)	0.125

Nox, nitric oxide; IL, interleukin.

In the low-risk group (15 patients, 18 episodes), SBP resolved in all, and none developed RI. None of the 15 patients died. In the subgroup in which hemodynamic assessment was performed, the characteristic profile of severe portal hypertension and hyperdynamic circulation was present, and the only change at resolution was a decrease in plasma renin activity (table 2).

In the high-risk group (21 patients, 26 episodes), renal impairment (RI) was present in 12 patients (57%) and 15 episodes (58%). It resolved in 10 episodes, remained steady in three, and progressed in two. Among 11 episodes with normal renal function, it remained normal in nine and progressive RF developed in two. RF responded in two episodes to a vasoconstrictor (midodrine, noradrenaline) and albumin but subsequently recurred. In two episodes, RF developed after SBP resolution. The outcome in five (24%) patients (19% episodes) was death.

This study is the first to assess whether albumin is needed for all cases of SBP. Our results indicate that patients with bili <68.4 μmol/l and Cr <88.4 μmol/l can be treated without albumin. Hemodynamic deterioration did not develop in these low-risk episodes. Plasma renin activity, the most sensitive marker of effective arterial blood volume, also decreased, indicating improvement in effective hypovolemia and providing additional support for our proposal that albumin need not be administered to all patients. Although our results do not provide definite proof because of the absence of a control group, they do provide supportive evidence for the role for albumin in patients at high risk of acute-on-chronic liver failure. Fifteen of 26 high-risk episodes had RI at diagnosis. According to previous reports, 50% hospital mortality rate should have been expected.[2 9]

An explanation for the discriminative power of Cr and bili remains to be determined. Elevated levels prior to infection would indicate that patients with pre-existing advanced cirrhosis and impaired renal function are predisposed to the development of HRS. Alternatively, individual response to infection would be of pathophysiologic significance. Despite the beneficial effect of albumin, treatment of SBP is still not optimal, and RF may still develop. Whether co-administration of a vasoconstrictor would further prevent the development of RF remains to be determined.

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Long-term prospective pilot study with tranilast for the prevention of stricture progression in patients with Crohn's disease

Fibrosis and strictures are common and irreversible complications of Crohn's disease that potentially necessitate bowel resection. Tranilast, N-(3′,4′-dimethoxycinnamoyl) anthranilic acid, inhibits keloid scar formation through the inhibition of production of metalloproteinases and tissue inhibitor of metalloproteinase-1 from neutrophils.[1] Please check the phrase ''inhibition of … neutrophils'' is OK Tranilast has been shown to inhibit fibrosis in various experimental models.[2–4] Randomised, double-blind, placebo-controlled studies have shown substantial inhibition by tranilast of restenosis of coronary arteries.[5–7] A case report has demonstrated the efficacy of long-term administration of tranilast in inflammatory endobronchial stenosis.[8]

Between June 2001 and July 2005, 24 patients with quiescent Crohn's disease with non-symptomatic intestinal strictures were recruited. Baseline intestinal stricture was evaluated by small bowel barium enteroclysis, or Gastrografin® (Schering Aktiengesellschaft, Berlin, Germany) enteroclysis under endoscopic examination using a digital caliper (Digimatic® Caliper, Mitutoyo Corporation, Kawasaki, Japan). Patients were allocated using a random number table to receive tranilast 200 mg (2 tablets) after every meal, three times daily (tranilast group) or to a control group that did not receive the agent, and followed up prospectively. The primary endpoint was whether or not there was development of symptomatic stricture requiring hydrostatic balloon dilatation of the stricture or requiring surgical resection, which was quantified as the cumulative non-symptomatic stricture rate. The secondary endpoint used in this study was the diameter of the stricture, which was measured at the time of recruitment (basal diameter) and at the time of development of symptomatic stricture or at the latest follow-up (final diameter). Change in diameter during the follow-up period was assessed using the equation (final diameter-basal diameter/basal diameter) 100/month. The change in diameter was compared between groups (% change/month)

There was no significant difference in clinical backgrounds between the tranilast group and the control group (table 1). One patient in the tranilast group withdrew because of a reduced white blood cell count. During the observation period, one patient in the tranilast group and two in the control group received infliximab infusion, and two tranilast and one control patient had been taking oral prednisolone. Six tranilast and seven control patients had been taking immunomodulators (azathioprine or mercaptopurine there were no significant differences between groups for these factors.

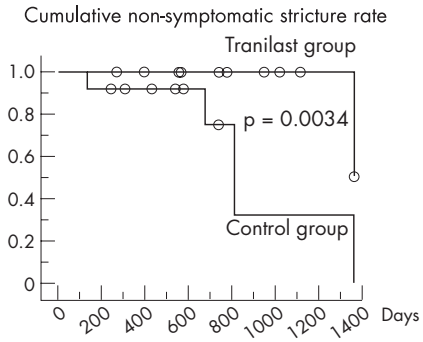

Figure 1 Cumulative non-symptomatic stricture rate with and without oral tranilast administration. Patients taking tranilast had a significantly higher non-symptomatic stricture rate compared with those not receiving this agent. The median observation period for the tranilast group was 782 (25th percentile 558, 75th percentile 1093) days, with a period of 559 (366, 738) days in the control group.

Hydrostatic balloon dilatation was done in one patient in the tranilast group and in five patients in the control group owing to the development of symptomatic stricture (fig 1, $p = 0.0034$). The median basal diameter of the stricture was 6.40 mm (25^{th} percentile 4.25, 75^{th} percentile 6.70) in the tranilast group and 6.35 mm (5.50, 7.25) in the control group ($p = 0.3837$). At follow-up, the diameter of the stricture was 5.60 mm (4.25, 11.23) in the tranilast group and 5.05 mm (4.30, 7.10) in the control group ($p = 0.1769$). Change in diameter during the follow-up period was 0.48% per month (–0.63, 3.18) in the tranilast group, compared with –0.86% per month (–2.11, 0.88) in the control group ($p = 0.2740$).

We found a preventive effect of tranilast on the development of symptomatic intestinal stricture in patients with Crohn's disease. Since there is no established effective medical therapy for intestinal stricture in Crohn's disease, long-term tranilast administration

Table 1 Clinical background of the patients

Characteristic	Tranilast group (n = 12)	Control group (n = 12)	p Value
Median age, years (25th and 75th percentile)	35.0 (26.5, 40.5)	37.5 (33.5, 46.5)	0.1183
Male/female	7/5	9/3	0.6650
Median disease duration, years (25th and 75th percentile)	7.3 (4.7, 10.5)	11.5 (6.5, 13.5)	0.2122
Location of the disease			
Ileitis	3	7	0.0892
Colitis	4	0	
Ileocolitis	5	5	
Behaviour of the disease			
Stricturing	7	4	>0.9999
Penetrating	5	5	
Location of stricture			
Ileum	7	8	>0.9999
Colon	5	4	

Differences between groups were analysed by one-way analysis of variance with Bonferroni's correction. χ^2 analysis was used for table analysis, and Fisher's exact test with Yates' correction was used. The cumulative non-symptomatic stricture rate was assessed by the life-table method employing Log rank (Mantel–Cox) analysis. P values less than 0.05 were considered significant.