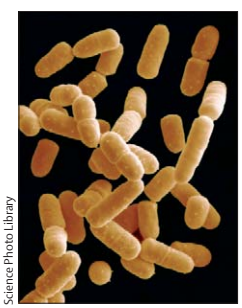

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bone and mineral metabolism, reduction of testosterone, and gynaecomastia—have been reported in adults.[2,3]

In children, CML is rare, imatinib is well tolerated, and molecular remission can be achieved. However, up until now, no information on the growth of children taking imatinib has been reported. The mechanism of transient growth deceleration in this case is uncertain. The patient had no history of medication that could interfere with growth, he had normal body proportions and appearance, no hypothyroidism, was not undernourished, had normal serum values of insulin-like growth factor 1, a radiograph of the left hand at 15 years showed a corresponding bone age, and the growth velocity eventually recovered. The timing of growth deceleration in relation to the start of imatinib administration suggests a possible causal relation. However, in the absence of provocative testing for growth hormone, random measurements are inconclusive, and a transient growth hormone deficiency cannot be excluded.

The reduction of the inhibin-B/FSH ratio could be attributable to KIT inhibition: FSH is increased when KIT in the testis is reduced, and point mutations in the *KIT* gene cause sterility in mice.[4] The patient had no history of cryptorchidism, was not hypogonadic, and had normal serum concentrations of luteinising hormone, ruling out alternative causes of the hormonal alterations seen. Overall, these findings suggest a probable causal relation between the reduced inhibin-B/FSH ratio and imatinib therapy.

Gynaecomastia is a recognised side-effect of imatinib in adults;[3] however, a clear-cut relation with imatinib cannot be established here.

Hypophosphataemia, hyperphosphaturia, mild calcium decreases, secondary hyperparathyroidism, and decreased markers of bone formation have been associated with imatinib treatment.[2] We uncovered no evidence that our patient had a personal or family history of endocrine diseases, renal diseases, inflammatory disorders, neurological diseases, congenital abnormalities, nor was taking medications that could alter BMD, suggesting a probable association between low BMD and imatinib. Young mice lacking the gene encoding the membrane-bound form of KIT ligand have reduced BMD owing to a prevalence of bone resorption.[5] This finding could also justify the trend towards high serum calcium and phosphate and the overt hypercalciuria seen in our patient. This pattern of disordered bone metabolism differs from that found in adults.[2] The most obvious explanation for is that our patient was treated during the period of the highest bone turnover.

The risk of CML recurrence makes it difficult to assess the effects of withdrawal of imatinib and to infer a stronger causal link between the intake of the drug and the adverse reactions seen. However, we strongly suspect that reduced BMD and reduction of the inhibin-B/FSH ratio are potential consequences of imatinib use in adolescent boys.

This study was supported by the Italian Ministry of University and Research (MIUR). We declare that we have no conflict of interest.

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Probiotic prophylaxis in predicted severe acute pancreatitis

The International Scientific Association for Probiotics and Prebiotics wishes to register serious concerns with the paper by Marc Besselink and colleagues (Feb 23, p 651).[1]

The term probiotic requires that a product has been adequately tested for safety and proven to confer a health benefit.[2] Ecologic 641 does not meet this requirement on the basis of published data. The inhibition of pathogens in vitro and reduced onset of pancreatitis in animals is not suitable justification for the use of this substance as a primary treatment for acute pancreatitis.[3] The failure to reduce C-reactive protein also illustrates that in-vitro immune modulation did not translate into a clinical anti-inflammatory effect.

The most disturbing part of this report is that the organ failure rate on the day of randomisation was significantly ($p<0·02$) higher in patients allocated to Ecologic 641 treatment (n=20) than those allocated to placebo (n=7). These pretreatment events correlate closely with mortality rates (24 *vs* 9 patients) and incidence of bowel ischaemia (9 *vs* 0). In the setting of acute pancreatitis, both organ failure and non-occlusive bowel ischaemia are parallel consequences of the haemodynamic disturbance.

The study showed no negative effect of Ecologic 641 with respect to the author-defined primary endpoint (infectious complications)[3]—a point not emphasised in their conclusions.

We strongly urge full disclosure of the medical condition, drugs administered, and timeline of event for all patients who succumbed. In addition, given the randomisation bias in terms of patients with organ failure, Besselink and colleagues should retract their conclusions that "probiotic prophylaxis...was associated with an increased risk of mortality".

We declare that we have no conflict of interest.

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We question Marc Besselink and colleagues' explanation for the gut ischaemia seen in eight of nine deaths in the probiotic group of their study.[1] They suggest that the increased bacterial load caused by probiotics resulted in greater oxygen demand and additional inflammation of the enterocytes.

However, if bacterial load were a causative factor, the effect would be cumulative. But all cases of gut ischaemia occurred within a few days of starting treatment, and no effect whatever was seen on the primary endpoints throughout the study. Additionally, there was a higher prevalence of gut-derived organisms in the probiotic group than the control group. By contrast, we[2] and others[3] have shown a specific reduction in gut-derived organisms with probiotics. These changes are likely to have been a consequence of intestinal hypoperfusion.

The prevalence of enteral-feeding-related bowel ischaemia can be as high as 3·5%.[4] It has been linked with jejunostomy feeding (all patients in this study had jejunostomies), occurs more commonly in patients on vasopressors (six of nine with ischaemia were on vasopressors), and can be related to the volumes given (in this study the goal rate was 125 kJ/kg, which is at the higher end of recommended intake). Besselink and colleagues do not provide data on how many patients achieved goal rate and whether or not any had signs of intolerance, which can be an early indicator of bowel ischaemia. Inadequate gut function, often manifested as intolerance to enteral nutrition, is becoming recognised as an important predictor of outcome.[5]

In our view, inadequate gut function in association with hypercaloric feeding in the presence of compromised gut perfusion is a more likely explanation for the episodes of gut ischaemia seen in this study.

We declare that we have no conflict of interest.

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Marc Besselink and colleagues[1] report small bowel ischaemia in nine patients with acute pancreatitis who received a high-dose lactic acid bacteria combination and jejunal feeding. Small bowel ischaemia has never before been reported with probiotics in clinical or animal trials.[2]

In fact, several of the trial conditions have not been previously tested—ie, the very high dose of probiotics (5×10^9 colony-forming units twice per day) and bypassing of the dilutional capacity of the stomach and duodenum by infusion of substrates and probiotics directly into the jejunum (in animals, probiotics were given gastrically[2]). The bolus injection might have led to bacterial concentrations in the small bowel 10–100 times higher than measured in clinical trials with healthy volunteers or patients.[3,4] Dose-response studies are needed.

The infusion delivered both bacteria and fibre, which might have led to fermentation (producing short-chain fatty acids, lactic acid, and carbon dioxide), resulting in bowel distension and increased oxygen demand. This substrate–bacteria interaction needs further study.

Pancreatitis is associated with impaired upper jejunal peristalsis. This might have increased the time of exposure to highly concentrated metabolites.

Finally, previous clinical trials have shown probiotics to reduce the risk of severe necrotising enterocolitis and mortality in preterm infants.[4] Besselink and colleagues do not specify whether the parts of the bowel not subjected to the bolus were necrotic.