Correspondence

bone and mineral metabolism, reduction of testosterone, and gynaecomastia—have been reported in adults.1,2

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.3 The patient had no history of cryptorchidism, was not hypogonad, 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;4 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.6 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.

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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).

The term probiotic requires that a product has been adequately tested for safety and proven to confer a health benefit.1 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.2 The failure to reduce C-reactive protein also illustrates that in-vitro immune stimulation 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 end-point (infectious complications)—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, we2 and others3 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 jejunalostomy feeding (all patients in this study had jejunosomies), 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’ 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.6

In fact, several of the trial conditions have not been previously tested—ie, the very high dose of probiotics (5×1010 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). 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.
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On the basis of all of the above points, one cannot conclude that probiotics in general present a risk in enteral feeding.

I declare that I have no conflict of interest.

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Authors’ reply

Gregor Reid and colleagues correctly cite the definition of a probiotic provided by the Food and Agriculture Organization and WHO: “Live microorganisms which when administered in adequate amounts confer a health benefit on the host”. This does not mean that if such a product shows negative effects in a new study in a different population, the product should no longer qualify as a probiotic. From now on we will refer to the product used as a “combination of probiotic strains” or “the combination” because the individual strains have shown beneficial effects in previous studies.

Contrary to Reid and colleagues’ suggestion, our combination was designed after rigorous selection studies. In several animal studies and smaller clinical studies, no negative effects of the combination were detected. As a consequence, we feel that it was probably not the combination but the administration of the combination together with the severity of the disease that was largely responsible for the effects obtained.

The implication that the increased mortality rate in the probiotics group was caused by a higher rate of organ failure on the day of randomisation in the study product group is incorrect. None of the baseline characteristics differed significantly between the groups. Furthermore, in a post-hoc subgroup analysis, having excluded patients with organ failure on the day of randomisation, mortality was still twice as high and bowel ischaemia was significantly more frequent in the group receiving the study product.

Bala Reddy and John MacFie propose “hypercaloric feeding” as a potential cause of bowel ischaemia. This was a post-hoc, quite heterogeneous, end- point and whether it was initiated by organ failure, inflammation, or other unknown factors is unclear. It is, however, unlikely that it was related to hypercaloric feeding as such, because the feeding regimen—jejunal infusion of multifeed nutrition—was identical in both groups and the administration of the study product, with a negligible caloric load, was the only difference.

Philippe Marteau raises concerns about the dose of probiotics, and we agree that studies on doses are indeed lacking. However, several trials, in patients with acute pancreatitis and patients scheduled for elective abdominal surgery, have used even higher doses of probiotics with a similar route of intrajejunal (bolus) administration. As for our alleged conclusion that probiotics in general present a risk in enteral feeding, we feel that this does not accurately reflect our cautious interpretation that probiotics can no longer be considered harmless under all conditions, especially in critically ill patients.

We declare that we have no conflict of interest.

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According to Marc Besselink and colleagues, the increase in mortality in patients with pancreatitis treated with probiotics was due to bowel ischaemia. It has been suggested that most small-bowel diseases have a common final pathogenic pathway. Accordingly, enterocytic damage by various assaults (biochemical, immunological, microbiological, vascular, etc) leads to an increase in intestinal permeability. This increased permeability results in a tissue reaction as luminal substances gain access to the mucosa where bacteria are the main neutrophil chemoattractant.

The prototype of this damage is enteropathy caused by non-steroidal anti-inflammatory drugs, but there are more than 30 situations in human beings in which an increase in intestinal permeability leads to a uniformity prevalent and severe enteropathy. These enteropathies cannot easily be distinguished from each other, even by enteroscopy or histologically (on which the changes resemble ischaemia). The inflammation can respond to antimicrobials (metronidazole), implicating resident commensal anaerobic bacteria in the pathogenesis.

The patients described by Besselink and colleagues had pancreatitis, and
many misused alcohol, were critically ill, and infected. All of these conditions are characterised by increased intestinal permeability and the effect is additive.\(^1\) Exposing an extremely leaky intestine to an additional bacterial load, albeit in apparently "friendly" probiotic form, seems to have led to severe intestinal damage.

All intestinal bacteria have the potential to cause disease if they are in the wrong place. Probiotics should only be contemplated if the integrity of the gastrointestinal tract is not severely compromised: there are no "good" intestinal bacteria, only less harmful ones.

We declare that we have no conflict of interest.

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Antibiotics for acute rhinosinusitis

The results of the meta-analysis by Jim Young and colleagues (March 15, p 908)\(^3\) are robust, but, for clinicians, a bit disappointing. The hope was that this effort would provide us fieldworkers with a set of subgroups that benefit more than others from antibiotic treatment. But the message is the same as it has been for years: acute sinusitis based on clinical symptoms will not be cured with antibiotics.

I am afraid that these findings will not stop us from prescribing antibiotics. We still believe that a subgroup that benefits exists. This idea is not an illusion. Lindbaek and colleagues\(^1\) showed that antibiotics were of great benefit in patients in primary care with acute sinusitis diagnosed by CT scanning (number needed to treat 3). However, the large effect seen for that study could at least partly have been attributable to chance. It was the only study in primary care with CT scanning as a selection criterion and replication of the findings would be useful. A further criticism might be that CT scanning is not a diagnostic tool in primary care.

More diagnostic research in primary care should be done first. Up until now there have been no studies with large numbers on diagnosis of sinusitis with CT scanning, sinus puncture, and clinical signs and symptoms.\(^2\) But the possibility that we might need CT scanning to identify a subgroup should be accepted.

Doctors are more at ease knowing who to treat and who not, as was shown with an identical meta-analysis on acute otitis media.\(^4\)

I declare that I have no conflict of interest.

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We welcome Jim Young and colleagues’ meta-analysis of individual patient data from studies investigating the value of antibiotics for acute rhinosinusitis.\(^1\) Combining the data from studies with similar patients, interventions, and outcomes can provide more precise estimates and thus resolve discussions with respect to contradicting outcomes of individual studies.

Comparing the overall results for the odds ratio calculated in their "classic" meta-analysis with the individual patient data meta-analysis shows highly similar point estimates and CIs (1·35, 95% CI 1·15–1·59, and 1·37, 1·13–1·66, respectively), both significant. However, the number needed to treat (NNT) calculated from the individual patient data turns out to include the point of no effect, and thus is not significant.

To our surprise, Young and colleagues do not address this discrepancy between the significant odds ratio and the non-significant NNT. For no apparent reason, they chose to give preference to the latter result in their Discussion. Moreover, the Summary only provides the NNT and ignores the odds ratio.

For reasons of transparancy, we suggest that Young and colleagues provide their arguments for making the choice they did. Ideally, this choice should have been made in their research protocol.

We declare that we have no conflict of interest.

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