The Editors welcome topical correspondence from readers relating to articles published in the Journal. Responses should be sent electronically via the BJS *website (www.bjs.co.uk). All letters will be reviewed and, if approved, appear on the website. A selection of these will be edited and published in the Journal. Letters must be no more than 250 words in length.*

Randomized clinical trial of short-term outcomes following purse-string *versus* conventional closure of ileostomy wounds (*Br J Surg* 2010; 97: 1511–1517)

Sir

I would like to congratulate the team from New South Wales on what was a very well designed study, especially their efforts to rigorously standardize aspects of patient care not directly linked to the two methods of ileostomy site closure under scrutiny.

It was unfortunate that the study could not be completed to its original population size as this would have proven that the reduced surgical-site infection (SSI) rate was not due to sampling error. It would also have enabled meaningful subgroup analysis and may have shown a benefit in using purse-string closure in obese patients.

A robust definition was used to identify SSIs, but with eight of the total of 12 SSIs being diagnosed in the community it would have been useful to know whether the medical officer responsible for prescribing antibiotic treatment also adhered to this definition.

Finally, and perhaps most importantly, no mention was given to the potential deleterious effects on quality of life that having a continually seeping wound and daily pack changes would cause those in the purse-string closure group. The rate of infection in linear closure may be approaching 40 per cent, but the wounds in the remaining 60 per cent needed no further attention except for suture removal. Even patients who develop a severe SSI need treatment not much different from that given as standard to the purse-string group, that is pack changes after the initial drainage. We think this is an additional important factor to consider when selecting the method of ileostomy closure.

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Author's reply: Randomized clinical trial of short-term outcomes following purse-string *versus* conventional closure of ileostomy wounds (*Br J Surg* 2010; 97: 1511–1517)

Sir

We thank Dr Moreton and his colleagues for their kind words and comments.

It is possible that the reduced infection rate was due to sampling error, and this highlights the concern with early cessation of trials. As always with randomized clinical trials there is balance between the perfect scientific approach and what is technically feasible. Our interim analysis was planned, and our unit was in the stages of changing its practice of routine defunctioning to a loop colostomy, rather than an ileostomy. The reason for this shift in practice was the high proportion of patients developing renal failure from ileostomies in our unit. We believe that the Australian environment (particularly over summer months, with an ageing surgical population and many patients requiring chemotherapy) makes a loop colostomy, despite its higher incidence of local problems such as prolapse and parastomal hernia, a preferable temporary stoma for this group of patients. With the change in unit practice a decision had to be made whether to continue the trial to completion or halt it at the planned analysis. Given the finding of the analysis we felt unjustified in continuing. We are not sure whether continuing the trial would have resulted in any meaningful subgroup analysis, and this comment is mere conjecture.

Only patients requiring antibiotics prescribed specifically for surgical-site infection (SSI) were included in the data, and were prescribed by the treating surgical team (mostly) and by local medical officers (general practitioners). Diagnosis of SSIs was not dependent on prescription of antibiotics, but on application of Centers for Disease Control and Prevention criteria by a trained observer. Only one patient with an SSI, however, had no antibiotics, as spontaneous purulent drainage was felt to be adequate (control arm).

This study did not assess quality of life but did attempt to determine cosmetic outcome, which was felt to be important. The dressings for the purse-string wounds were quite simple and changed only every 2–3 days after discharge from hospital. We did not use packing and patients were told that their wounds would discharge; they were advised to shower and wash the wounds, and to apply a loose absorbent dressing. The deleterious impact of this type of management is minimal; no wound dressing by a community nurse was required, and indeed the mean time to wound healing was quicker in the purse-string group: 20·6 *versus* 24·6 days.

Moreton and colleagues seem to believe that undrained sepsis in 40 per cent of wounds is acceptable; on the contrary, we feel this is undesirable. It increases the risk of general sepsis, as well as long-term outcomes such as herniation, and should be avoided where possible. To that end we recommend that the purse-string technique be applied to all ileostomy closures given the current evidence.

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Hepatic ischaemia–reperfusion injury from bench to bedside (*Br J Surg* 2010; 97: 1461–1475)

Sir

We read with interest the comprehensive review by Bahde and Spiegel. We would like to comment on certain points. Although there is no denying the benefit of preconditioning in experimental studies, clinical studies have not shown any tangible clinical benefit[1].

With better knowledge of hepatic anatomy and newer devices for resection, the need for hilar clamping is limited. For anatomical resections it is generally possible to get control of the portal triad, either extrahepatically or using an intrahepatic glissonian approach. Experience gained with living donor hepatectomies has also shown that anatomical resections can be performed safely without hilar clamping As a result, the number of surgeons clamping hilar structures routinely has decreased[2]. The techniques of preconditioning and intermittent clamping are therefore more for occasional liver surgeons, who might end up doing non-anatomical resections for trauma, etc., rather than experienced hepatopancreatobiliary surgeons. It is important to recognize that no ischaemia–reperfusion (IR) is better than ischaemic preconditioning, which is better than IR without preconditioning.

One situation in which preconditioning may have value is in liver transplantation, where there is no getting away from IR. However, results in cadaveric donors have not shown any definite benefit[3]. For living donor hepatectomies, where simultaneous donor and recipient surgery have minimized cold ischaemia, there might be a benefit of preconditioning. Whether adding another period of warm ischaemia before removal of the partial liver graft will be beneficial or deleterious has yet to be determined. Recent studies have not shown any benefit of preconditioning before living donor hepatectomy[4].

An interesting hypothesis could be remote preconditioning either by clamping the vessels to the remaining liver rather than the graft portion or by limb ischaemia, to see any advantage with reperfusion injury. Similarly, use of chemical preconditioning seems attractive if it can replicate the effect of preconditioning by ultimately enhancing the ability of tissues or organs to withstand reperfusion injury[5].

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Authors' reply: Hepatic ischaemia–reperfusion injury from bench to bedside (*Br J Surg* 2010; 97: 1461–1475)

Sir

We thank Dr Kapoor for his thoughtful observations and comments. He raised very important issues.

The intention of our review was not to encourage surgeons to perform hilar clamping if not needed. Dr Kapoor is right in suggesting that performance of a Pringle manoeuvre in elective hepatectomy is still controversial. Advances in parenchymal transection and the use of precoagulation devices can obviate the need for vascular clamping in cases such as minor liver resections[1]. For major liver resections 10 per cent of responders from the European survey confirmed this idea[2]. In fact, the frequent use of precoagulation correlated with less frequent use of clamping. The survey also revealed that approximately one in five surgeons clamp on a routine basis and clamping appeared to be more frequently applied by more experienced surgeons. The maximally accepted amount of blood loss, the prime indication for clamping, varied greatly and the choice of techniques was highly individualized, indicating the need for uniform guidelines. The prognostic risk of blood transfusions *versus* clamping, for example regarding oncological outcome, has to be determined[3]. Obviously it would be the best solution to perform liver resection without ischaemia but with devices preventing significant blood lost.

The review demonstrates that our current understanding of normothermic hepatic ischaemia–reperfusion (IR) injury gained from experimental data offers the potential for optimization of therapy. This might also play a role in situations such as living donor liver transplantation, where avoidance of the innate immune response may even affect long-term outcome[4]. Ischaemic preconditioning (IP) is one strategy among others to reduce IR injury. Basic research has identified cellular signal transduction pathways and several mediators involved in IP, paving the way for pharmacological preconditioning. The question arises of whether we should keep doing clinical trials with IP in the absence of clinical benefit or target certain specific molecules to improve defence against oxidative stress? This question cannot be answered, because clinical studies using IP are underpowered to prove benefit in terms of clinical outcome

and are not comparable with studies using pharmacological agents owing to their heterogeneity. We agree with Dr Kapoor that further studies are required, especially in face of the increasing percentage of liver resections performed on diseased livers, such as those with steatosis or cirrhosis, or livers damaged by chemotherapy.

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Surgical-site infection (*Br J Surg* 2010; 97: 1601–1602)

Sir

We read with interest the leading article by Dr Leaper. He highlighted this topic with his personal ideas and summarized some current different opinions from three articles published in the same issue of *BJS*. However, some concepts should be discussed.

The Centers for Disease Control and Prevention (CDC) defined four types of infection within this nosocomial infection category called 'surgical-site infection (SSI)': superficial incisional, deep incisional, organ and space infections[1]. Whether or not a SSI develops after a surgical procedure depends on the interaction between the host, the microbes and operation–environment-related factors[2]. Besides the determinants of SSI listed by the author, surgical technique is also very important. Care exercised in tissue handling, removal of devitalized tissue, haemostasis, good drainage of dead space or cavity, and wound closure without tension are paramount.

Compliance is also a requisite in SSI prevention. A survey of almost 590 surgeons in Canada revealed that 63 per cent were not in compliance with recommended guidelines on preoperative bathing, hair removal, antimicrobial prophylaxis or intraoperative skin preparation[3]. The absence of full compliance reflects that infection prevention and its importance is not yet embedded in all routine surgical practice. Of course, key parameters associated with non-compliance should be clearly identified and corrective actions proposed. Education may be one of the cornerstones for improvement of compliance. However, a multidisciplinary approach and ownership from all concerned are required.

Surveillance for SSI is important in both prevention and treatment strategies. Early discovery of SSI means that infection could be managed much earlier, shortening the recovery time, lessening the related complications and lowering the costs. Furthermore, feedback of information to surgeons and other relevant staff has been shown to be an important element in the reduction of SSI occurrence[2].

The reality is that SSIs are the consequence of a multitude of variables, which make it difficult to predict which wounds will become infected. For this reason, patients with risk factors amenable to intervention should be identified as early as possible. Thus, minimization of the risk of wound contamination and support of host defences throughout the continuum of care could be more easily accomplished.

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Author's reply: Surgical-site infection (*Br J Surg* 2010; 97: 1601–1602)

Sir

I am pleased to respond to the comments from Chong-Chi Chiu and colleagues on my leading article. I certainly have no argument with the need for adequate definitions of surgical-site infection (SSI) and classification, although I prefer the use of interval data provided by more precise scoring systems rather than the categorical data from the Centers for Disease Control and Prevention; most certainly so for research purposes.

Their assertion that surgical technique is very important is an old chestnut, often trotted out by surgeons who profess to have a very low SSI rate but have never actually looked. The use of close accurate postdischarge surveillance using a blinded, trained observer is critical for this. We all know of colleagues who are 'fast' surgeons and those who are 'meticulous', but there is no scientific evidence of any difference in their SSI rates. Interestingly, there is plenty of evidence to show that shorter, elective open surgery is associated with lower SSI rates. In the UK we have confidence that a holder of the FRCS and CCT is competent, and I am sure that all consultants in all fields

have SSI rates that reflect compliance with guidelines and care bundles rather than related to their experience or 'skill'. Those in training may seek to emulate this. Training should provide reverent care in handling tissue and avoidance of tension, but show me evidence that good drainage and meticulous haemostasis make a difference.

I agree entirely with compliance with best evidence. In the UK this is offered in guidelines from the National Institute for Health and Clinical Excellence, Scottish Intercollegiate Guidelines Network and High Impact Interventions from the Department of Health. If 'owned' by the surgical tram the results are clear. I also agree about the quality of surveillance. In the UK this is becoming mandatory in many fields of operative surgery, but currently involves only inpatient and readmission data. The value of feedback has been known for two to three decades, but the identification and weighting of risk remains the goal of research for healthcare systems.

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Letter 1: Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine *versus* povidone–iodine in clean-contaminated surgery (*Br J Surg* 2010; 97: 1614–1620)

Sir

We read with interest this review and meta-analysis of topical antiseptic agents for preoperative skin cleansing. Nevertheless, we have concerns with the authors' conclusion. Of the six eligible trials, four evaluated povidone–iodine without alcohol *versus* chlorhexidine–alcohol, in fact one antiseptic agent *versus* two.

Indeed, alcohol is already considered by the Centers for Disease Control and Prevention's current guideline for the prevention of surgical-site infection to be 'the most effective and rapid-acting skin antiseptic'[1]. Likewise, the 2006 Infusion Nursing Society's Standards of Practice state 'Formulations containing a combination of alcohol (ethyl or isopropyl) and either chlorhexidine gluconate or povidone iodine are preferred' for access-site preparation and catheter-site care[2]. Thus in a study performed in adult intensive care units, the use of alcohol-based povidone–iodine was associated with a lower incidence of catheter colonization (13·2 *versus* 35·0 per cent; relative risk 0·38, 95 per cent confidence interval 0·22 to 0·65; $P < 0·001$) and infection (4·7 *versus* 13·7 per cent; relative risk 0·34, 0·13 to 0·91; $P < 0·04$) than aqueous povidone–iodine[3].

So, in future studies, comparing alcoholic povidone–iodine with alcoholic chlorhexidine would be more relevant to reach a definitive conclusion.

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Letter 2: Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine *versus* povidone–iodine in clean-contaminated surgery (*Br J Surg* 2010; 97: 1614–1620)

Sir

We refer to the article by Noorani and colleagues in *BJS* and another by Lee and colleagues[1] in *Infection Control and Hospital Epidemiology*. These are two systematic reviews of what is described as comparisons of 'chlorhexidine *versus* povidone–iodine' for preoperative skin antisepsis. The authors conclude that chlorhexidine is the more effective antiseptic in preventing surgical-site infections (SSIs). However, we believe that the analyses are flawed and this is not a valid conclusion.

In both articles, the effect of preventing SSIs is solely attributed to chlorhexidine. However, the majority of analysed studies used chlorhexidine–alcohol mixtures *versus* aqueous povidone–iodine. Both chlorhexidine and povidone–iodine are available in aqueous and alcoholic formulations. The former have one, the latter two active ingredients. If an agent has two active ingredients, then it is *a priori* not possible to attribute study outcomes to only one, unless there are strong reasons otherwise. Alcohol is clearly a powerful antiseptic on its own, and contributes most to the overall activity in alcoholic chlorhexidine or iodine formulations[2,3].

In our opinion, the articles fail to show clear evidence that the observed effects are solely or even mainly due to chlorhexidine, despite this being the core claim put forward by the authors. At the same time, they ignore the effects the alcohol in the antiseptics is likely to have had. These flaws are very serious, and in our opinion completely invalidate the articles and their conclusions. We are discussing the reasons for this assessment in more detail in a letter in *Infection Control and Hospital Epidemiology*[4].

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Letter 3: Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine *versus* povidone–iodine in clean-contaminated surgery (*Br J Surg* 2010; 97: 1614–1620)

Sir

I would like to congratulate the authors on a well presented paper further reinforcing a simple practice change that will reduce the risk of surgical-site infection. Many hospital trusts are discontinuing their use of povidone–iodine skin preparation in favour of chlorhexidine-based agents in view of this research. I believe there is a further patient safety issue pertaining to this study. The majority of articles analysed used isopropyl alcohol-based chlorhexidine agents. The risk of surgical 'fires' has been well documented[1]. Alcohol-based skin preparations are frequently the cause of surgical burns[2–4]. The benefits of aqueous chlorhexidine preparations have not yet been subjected to rigorous analysis. Do the authors anticipate a more widely adopted practice change if aqueous chlorhexidine solutions are shown to be as effective as the alcohol-based solutions?

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Authors' reply: Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine *versus* povidone–iodine in clean-contaminated surgery (*Br J Surg* 2010; 97: 1614–1620)

Sir

Messrs Maiwald, Nesseler, Owen and colleagues all allude to issues raised by the superiority of alcoholic chlorhexidine over aqueous povidone–iodine in clean-contaminated surgery. Clearly, as Owen and Sheen comment, increased use of alcoholic chlorhexidine provides greater opportunity for unfortunate episodes of conflagration. Due care must be exercised.

Both Maiwald *et al.* and Nesseler and colleagues express concern regarding the potential confounding effect of comparing aqueous povidone–iodine (one antiseptic) with alcoholic chlorhexidine (two antiseptics). In light of this, both groups express doubts regarding our conclusion that alcoholic chlorhexidine is superior to aqueous povidone–iodine. Nesseler and colleagues cite an example in which alcoholic povidone–iodine outperformed the aqueous equivalent. We would strongly dispute the assertion of Maiwald and co-workers that these issues 'completely invalidate' our findings. It is difficult to counter the specific arguments they put forward in a manuscript accepted by another publication, as they have not provided us with the opportunity to read it. Neither group disputes that aqueous povidone–iodine is an inferior antiseptic.

As surgeons, we are concerned to take every possible precaution to minimize morbidity following our technical efforts. Aqueous povidone–iodine is in widespread use for skin preparation before clean-contaminated surgery. Our data clearly demonstrate that this agent is inferior to an alternative. Whether this alternative contains one antiseptic or two is somewhat academic.

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Surgeons and selection of adjuvant therapy for node-negative colonic cancer (*Br J Surg* 2010; 97: 1459–1460)

Sir

High cancer-specific mortality is especially true for stage II colonic cancer. The statement of Horgan and McMillan is therefore absolutely true: it is time for surgeons to focus on the selection of patients with high-risk node-negative colonic cancer for adjuvant therapy. Horgan and McMillan focus on the peritumoral and systemic inflammatory responses as a negative risk factor. We propose another risk factor for disease recurrence in stage II colonic cancer: nodal micrometastases.

Multiple studies have studied the effect of upstaging using sentinel node

mapping added to serial sectioning and detection of micrometastases with immunohistochemistry or reverse transcription–polymerase chain reaction techniques[1,2]. In the recent published study of Bilchik and colleagues[3] a disease recurrence rate of 22 per cent at 4 years was found in node-negative patients upstaged with nodal micrometastases, compared with 6 per cent in true-negative patients. Two conclusions can be drawn from these results. First, nodal micrometastases in sentinel nodes are a high risk factor for disease recurrence in patients with stage II colonic cancer. Whether adjuvant chemotherapy in these patients leads to improved disease-free survival needs to be investigated, but seems plausible. Second, through combined incentives of surgeons and pathologists it is possible to improve nodal staging following resection, thereby providing better estimation of prognosis and possible adjuvant therapy for patients.

The abovementioned aspects stimulated us to launch a randomized phase III clinical trial investigating the influence of micrometastases on prognosis and survival in stage I–II colonic cancer to improve 3-year disease-free survival (EnRoute Study). This multicentre trial has recently started as a feasibility study in the Netherlands and aims to end in 2015. All eligible patients are randomized to adjuvant chemotherapy according to the capecitabine–oxaliplatin (CAPOX/XELOX) treatment scheme. It is through this study that we could respond to the call of Horgan and McMillan: surgeons take the lead in the selection of high-risk node-negative colonic cancer for disease recurrence and mortality. Ultimately these are the patients we operate on with curative intent.

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Authors' reply: Surgeons and selection of adjuvant therapy for node-negative colonic cancer (*Br J Surg* 2010; 97: 1459–1460)

Sir
We read with interest the letter of Lips and colleagues, who echo our call for surgeons to take the lead in the selection of patients with node-negative colonic cancer for adjuvant therapy. In addition to our focus on the peritumoral and systemic inflammatory responses as risk factors, they highlight the importance of identifying nodal micrometastases using immunohistochemical or reverse transcription–polymerase chain reaction techniques. Although we support their work on use of highly sensitive molecular technologies in cancer biomarker research, we wish to urge caution in the use of such techniques in patients who have evidence of an inflammatory response. Specifically, the work of Chechlinska and colleagues[1,2] has shown that many such measurements are confounded by the presence of an inflammatory response. They state 'All potential cancer biomarkers should be validated against their expression in inflammatory conditions as should their independent predictive value. Otherwise we will end up using advanced technologies to assess inflammatory reactions in cancer patients'.

We fully support the application of well validated biomarkers in randomized clinical trials of adjuvant therapy in node-negative colonic cancer.

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Randomized clinical trial of gut-specific nutrients in critically ill surgical patients (*Br J Surg* 2010; 97: 1629–1636)

Sir
We congratulate the authors for undertaking a well designed and executed randomized controlled trial on modulation of gut function in critically ill patients. The results of this study have the potential to have a positive impact on a large group of critically ill patients. The most significant result of this study is perhaps the validation of a quantitative definition of gut function based on intestinal tolerance[1]. The study also lends further evidence to the beneficial effects of glutamine on gut function as reported by earlier studies[2,3].

It is well known that gut dysfunction occurs commonly in critically ill patients. The reduction in gut immunity and increased permeability increase the risk of septic complications and multiorgan failure significantly[4]. Various strategies such as early enteral feeding are currently employed in the endeavour to limit these deleterious effects. Enteral nutrition, however, appears to be successful only in a functioning gut. This study seems to have achieved an

important breakthrough in this regard by demonstrating that gut function can be modulated and early return to full function achieved by gut-specific nutrition (GSN).

Some results of this study, however, need further evaluation. The study seems to be underpowered to evaluate the secondary outcomes such as length of stay in hospital and the intensive care unit (ICU), and mortality. Although a trend towards decreased mortality is evident, it fails to reach significance, and other outcomes such as ICU and hospital stay are very similar in both groups. A larger sample size or different dosing regimen may have perhaps produced significantly different results.

The authors describe a significantly attenuated acute-phase response associated with gut modulation in the GSN group in univariable analysis. According to the results of this study there was no difference in acute-phase markers in the GSN and placebo groups with the respective interventions. If similar changes in acute-phase markers were evident in both groups, this finding appears non-specific to GSN.

It is also surprising to find that, although septic episodes were significantly more common in the placebo group, there was no increase in ICU and hospital stay, as well as readmission rates. The mortality rate did show a non-significant difference. Does this indicate that the modulation of gut function failed to achieve a clinically relevant impact, or is there an alternative explanation?

Furthermore, this study is limited to critically ill surgical patients. A vast majority of ICU admissions are non-surgical and gut failure is evident in these patients for a myriad of reasons including opiates, sedation, lack of mobilization or electrolyte imbalances. A large multicentre study with adequate power for clinical endpoints including all critically ill patients with gut dysfunction is required to validate the results of this study and interpolate the findings to all patients in the ICU.

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Authors' reply: Randomized clinical trial of gut-specific nutrients in critically ill surgical patients (*Br J Surg* 2010; 97: 1629–1636)

Sir

We thank Drs Kanhere for their comments. We share their view that the most significant result from our study is the validation of a quantitative definition of gut function based on enteral tolerance. We recognize that our definition (tolerance of 80 per cent or more of individually calculated nutritional requirements for a minimum continuous period of 48 h) has limitations and is not necessarily applicable to all clinical situations. From a purely theoretical perspective, all other single organs have numerous definitions to differentiate adequate function from failure (for example definitions for renal failure based on serum creatinine levels or glomerular filtration rate or volume of urine excretion per unit mass over time). We envisage that the same should hold true for the gut[1].

Our study was powered only to assess our primary endpoint, which was return of gut function, and specifically to determine whether this could be modulated by the use of gut-specific nutrients. We were, therefore, cautious about drawing firm conclusions about secondary endpoints such as morbidity and mortality. We remain of the view, however, that our hypothesis that gut function will influence morbidity and mortality is supported by the results of this preliminary study; this merits further investigation in larger multicentre studies. To speculate on the mechanism with regards to acute-phase proteins and the inflammatory response is not appropriate at this stage.

We would remind Drs Kanhere that our stated definition of critical illness was the failure of at least one organ system, of which gut function was one. This does have widespread applicability. Our results illustrate an intrinsic weakness of the Acute Physiology and Chronic Health Evaluation II scoring system as a prognostic index because this scoring system, like Sequential Organ Failure Assessment and other scoring systems, do not take any aspect of gut failure into consideration.

We agree that much remains to be understood in this novel area of research.

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