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EDITORIAL

Focus on gastrointestinal system in critically ill patients

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Gastrointestinal or intra-abdominal conditions are a major cause for critical illness. Additionally, critical illness precipitates gastrointestinal injury, mediated by hypoperfusion, hypoxia and systemic inflammation. This editorial reviews the progress made on gastrointestinal issues in critically ill patients as reported in the recent literature in order to focus on the needs for further research in this field (Fig. 1).

A recent observational study by the Abdominal Sepsis Study (AbSeS) group (from European Society of Intensive Care Medicine) included 2621 patients with intra-abdominal infection from 42 countries and reported a mortality rate of 29.1% [1]. The prevalence of antimicrobial resistance was 26.3%; worryingly, it was equally common in community-acquired as in hospital-acquired infection [1].

Beside intra-abdominal infections, one of the important manifestations of gastrointestinal injury during critical illness is stress-related gastrointestinal bleeding (GIB), which is associated with an increased risk of death and length of stay in the intensive care unit (ICU) [2]. Nevertheless, the routine prescription of stress ulcer prophylaxis has been debated. Because new relevant trials including the SUP-ICU trial [3] were recently published, Barbateskovic et al. [4] conducted a systematic review with meta-analysis of randomized clinical trials assessing the effects of proton pump inhibitor (PPI) or histamine-2-receptor antagonists (H2RA) versus placebo or no prophylaxis on mortality, GIB and adverse events. Analyzing 42 trials that included 6899 ICU patients, they found that PPI or H2RA did not improve mortality but reduced GIB by almost 50%. However, the effects on clinically important GIB, serious adverse events, health-related quality of life, myocardial ischemia, pneumonia and *C. difficile* enteritis remained inconclusive.

In order to identify patients at highest risk of GIB, Granholm et al. [5] performed a systematic review and meta-analysis assessing potential predictors of clinically important GIB and overt GIB in adult ICU patients. While confirming the low incidences of clinically important GIB and overt GIB (ranging from 0.6 to 2.8% and 1.3 to 12.8%, respectively), they found that acute kidney injury (AKI), coagulopathy, shock and chronic liver disease were consistently associated with increased risk of GIB. In a specific meta-analysis, Butler et al. [6] reported that systemic corticosteroids might also increase the risk of clinically important GIB slightly, although this effect was unclear given the rarity of bleeding events, infrequent trial reporting and high risk of bias that reduced the overall quality of evidence.

Conversely, there are data suggesting a protective role of enteral nutrition against gastrointestinal tract injury in critically ill patients [5]. Enteral nutrition may, on the one hand, have beneficial effect by limiting bowel villous atrophy. On the other hand, it may have deleterious effects by compromising gut perfusion, especially in case of shock. In an ancillary study of the NUTRIREA-2 trial [7], Piton et al. [8] further investigated this question by comparing the effect of early full enteral nutrition versus early full parenteral nutrition on the bowel mucosa of ventilated adults with shock, using intestinal biomarkers. Early full enteral nutrition compared to early full parenteral nutrition was associated with increased plasma citrulline concentration, a marker for enterocyte mass, suggesting better restoration of enterocyte mass and mucosal trophicity. At the same time, early full enteral nutrition was associated

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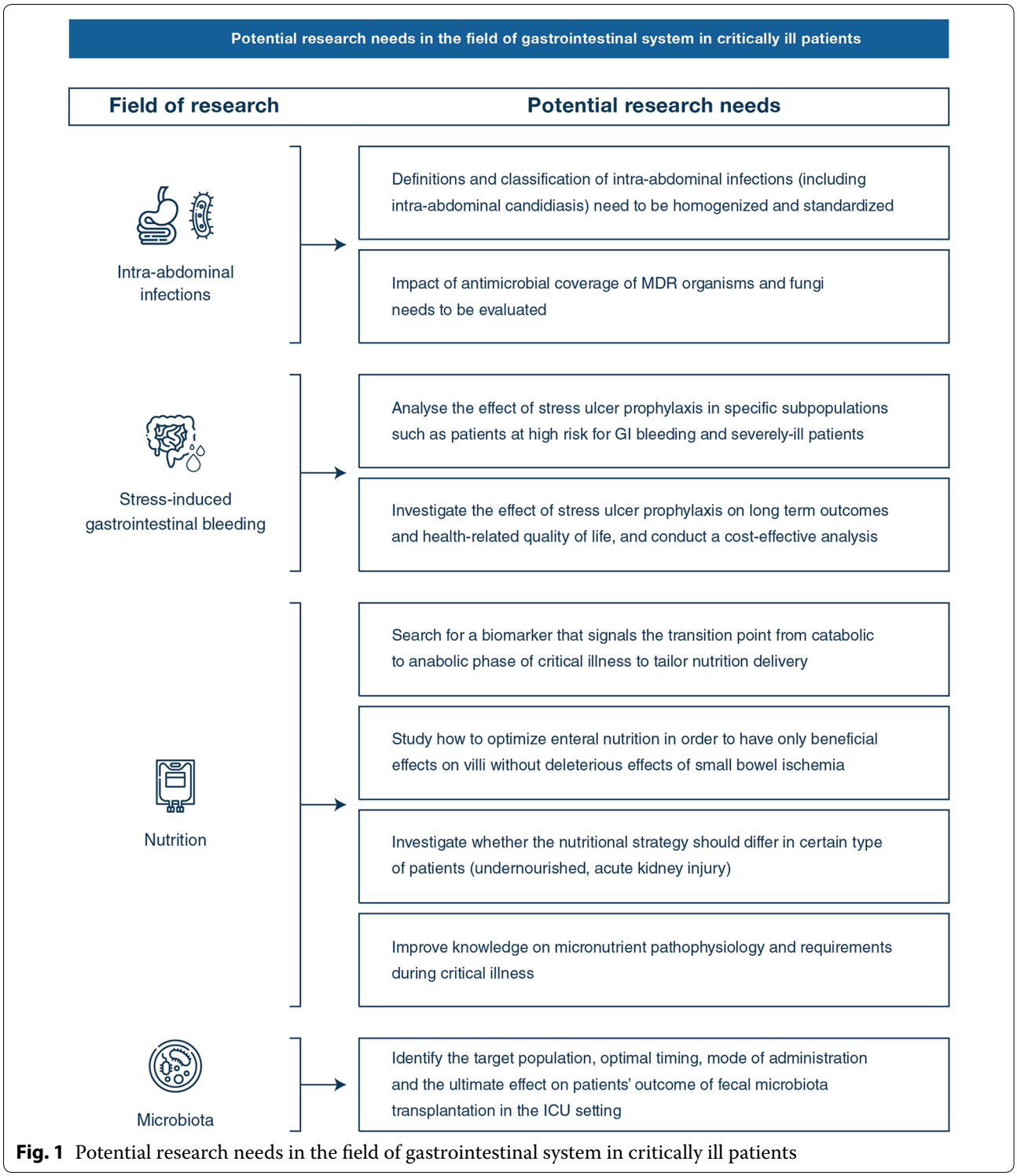

Fig. 1 Potential research needs in the field of gastrointestinal system in critically ill patients

with higher plasma concentrations of the intestinal fatty acid binding protein (I-FABP), a marker of enterocyte damage, raising the question about potential subclinical ischemic injury to the mucosa [9]. These results support the current paradigm of early initiation of enteral nutrition to minimize harm from full starvation, but at the same time advancing enteral nutrition over the first few days of critical illness, reaching full

amounts of energy with the transition into anabolic recovery phase [10]. The amount of micronutrients to deliver during critical illness is still debated; the results of a recent randomized controlled trial showed no benefit of early vitamin D3 supplementation in high-risk patients [11], but the results of several ongoing RCTs should be followed to know whether the provision of dietary reference intakes is sufficient or additional repletion should be considered during critical illness [12]. Furthermore, whether the above principles should apply across all patient types remains to be determined. For instance, high-quality data related to nutrition in patients with AKI in whom baseline deficiency of calories, proteins, vitamins and trace elements may be worsen by renal replacement therapy are lacking [13].

Enteral feeding intolerance (EFI), another manifestation of gastrointestinal injury, is often managed by prokinetics with limited efficacy. The PROMOTE trial compared the novel prokinetic ulimorelin (ghrelin agonist) to metoclopramide for 5 days in 120 critically ill patients with EFI [14]. The efficacy of the two drugs in the treatment of EFI was not different. Notably, only 51 and 55% of patients (ulimorelin and metoclopramide, respectively) achieved feeding success over the 5 treatment days despite using a volume-based protocol together with prokinetics. Given the transient nature of EFI, and the potential side effects of prokinetics, their optimal indications remain to be determined [15].

Gut microbiota changes are recognized to be associated with profound state of immunosuppression and an increased risk of bacterial infections, organ failure and death. Mitigating this dysbiosis may represent a promising approach to improve ICU patient outcome [16]. Fecal microbiota transplantation (FMT) has been shown to be effective for the treatment of severe *C. difficile* infections, paving the way for further evaluation in ICU patients. However, FMT remains understudied in this setting and several practical considerations regarding patient selection, donor screening, route of administration remain to be addressed before the use of FMT in the ICU. FMT safety should also be examined: recent data show a significant risk of bacteraemia associated with the use of probiotic *Lactobacilli* in the ICU and identify cases of transmission of probiotics from capsule to blood in ICU patients [17].

The studies reviewed in this paper further confirm the central role of the GI system in the pathogenesis of critical illness and highlight the evolving knowledge regarding the effects of therapeutic interventions of the GI system on the outcome of critically ill patients. Research on gastrointestinal issues in critically ill patients should continue (Fig. 1).

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Compliance with ethical standards

Conflict of interest
E Weiss reports personal fees from Baxter, MSD France, Biomerieux and Akcea therapeutics and travel reimbursements from MSD France. Y. M. Arabi has no conflict of interest to declare.

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