Assessing gastrointestinal system dysfunction in intensive care

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Purpose of review
To summarize the current knowledge on the assessment of gastrointestinal dysfunction.

Recent findings
Clinical assessment is becoming more structured but remains largely subjective. Some instrumental tools to assess gastrointestinal motility have been developed but not yet widely applied in clinical practice. Imaging techniques offer a good method for static (i.e. nonfunctional) diagnostics but a standardized dynamic assessment at the bedside is currently unavailable. Recent studies on biomarkers have not provided convincing results for accurate evaluation of gastrointestinal function.

Summary
Clinical assessment remains the main tool for assessing gastrointestinal dysfunction. A single sign or symptom does not reflect gastrointestinal dysfunction adequately, and a set of variables might be needed. Studies on tools reflecting gastrointestinal motility and biomarkers for response to enteral nutrients, including absorption, are warranted.

Keywords
critical illness, gastrointestinal diseases/diagnosis, gastrointestinal function tests, multiple organ dysfunction syndrome

INTRODUCTION

The gastrointestinal system has multiple important functions in the human body, with immunological, hormonal and barrier functions reaching far beyond its crucial role in energy homeostasis. However, the definition of a normal gastrointestinal function capturing all its functions is not available, and there is no gold standard for measuring gastrointestinal function. Consequently, normal function is often considered merely as the absence of dysfunction. However, the assessment of gastrointestinal dysfunction is not straightforward and not uniformly performed in critically ill patients, which poses a major obstacle in clinical research.

The lack of a unified definition for gastrointestinal dysfunction significantly hampers clinical practice and research. This ambiguity can lead to inconsistent monitoring and management of gastrointestinal dysfunction in clinical settings, potentially affecting patient outcomes. For instance, the absence of standardized diagnostic criteria may result in delayed recognition and treatment of gastrointestinal complications. In research, the variability in definitions impedes the comparability of study results, making it challenging to draw generalizable conclusions or develop evidence-based guidelines. Several efforts have been made to address this issue [1–3]. A systematic scoping review highlighted the scarcity of standardized diagnostic and therapeutic approaches for gastrointestinal dysfunction in critically ill patients, underscoring the need for consensus on definitions and monitoring techniques [2]. To tackle this task, a core outcome set for daily monitoring of gastrointestinal function in critically ill patients has been developed to provide a framework to guide future research, aiming to enhance comparability across studies and allowing for future definitions of gastrointestinal dysfunction [3]. In this current review, we summarize the available evidence on

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KEY POINTS

- Clinical assessment remains the primary method for evaluating gastrointestinal dysfunction in critically ill patients, but a single sign or symptom does not reflect gastrointestinal dysfunction adequately.
- Therefore, complex clinical assessment, including multiple parameters, is needed, because a gold standard for gastrointestinal dysfunction measurement is lacking.
- Instrumental tools and imaging techniques show promise for assessing gastrointestinal motility and function but are not yet standardized or widely implemented in clinical practice.
- Gastrointestinal dysfunction plays a significant role in multiple organ dysfunction syndrome but is often underrecognized and inadequately assessed.
- Future research should focus on developing standardized clinical assessments, validating instrumental tools, and identifying reliable biomarkers to improve the evaluation of gastrointestinal function in critically ill patients.

the options to assess gastrointestinal function and discuss the role of gastrointestinal dysfunction as a part of multiple organ dysfunction.

ROLE OF GASTROINTESTINAL TRACT IN MULTIPLE ORGAN DYSFUNCTION

Organ dysfunction is a critical concept in intensive care medicine established in the 1990s, characterized by the acute and potentially reversible impairment of organ function [4]. Multiple organ dysfunction is the progressive dysfunction of two or more organ systems following an acute threat to systemic homeostasis. The severity of multiple organ dysfunction correlates strongly with mortality [5].

The pathophysiology of organ dysfunction is complex and multifactorial. Key mechanisms include global perfusion deficits, widespread endothelial damage, mitochondrial dysfunction, intestinal bacterial translocation and dysregulated apoptosis [5]. These processes can lead to a cascade of organ failures, with dysfunction in one system potentially precipitating or exacerbating dysfunction in others [6].

The relationship between gastrointestinal dysfunction and other organ systems in multiorgan failure is complex and bidirectional (Fig. 2) [7,8]. For instance, shock and hypoperfusion can lead to intestinal ischemia, while gut barrier dysfunction can contribute to systemic inflammation and remote organ injury [7]. The focus in critically ill has been on motility (as dysmotility can be assessed during clinical observation), whereas motility is in fact only a prerequisite to perform gastrointestinal functions [9]. Even though dysmotility can also lead to serious consequences, impaired barrier, and immunological function may play a more important role in the pathophysiology of the multiple organ dysfunction syndrome. During critical illness, any of these functions may be impaired, leading to a range of clinical manifestations, from feeding intolerance to severe complications, such as mesenteric ischemia [10▪▪,11]. Although nutrients in the gastrointestinal tract are likely needed to perform gastrointestinal functions adequately, interactions between enteral nutrition and gastrointestinal function in critically ill are unclear, possibly dissipating and dose-dependent, with recent evidence suggesting harm from early full enteral nutrition [10▪▪]. Due to varying definitions and the lack of an objective evaluation system, the development of intervention strategies is limited. So far, no treatment strategies from the various gut hypotheses have demonstrated a way forward. In addition, when considering multiorgan failure, the term gut failure often seems to be missing, making the gut an invisible organ in the context of other vital organs [12].

ASSESSMENT OF GASTROINTESTINAL FUNCTION IN INTENSIVE CARE

Clinical tools

Clinical assessment of gastrointestinal function in critically ill patients remains challenging. Abdominal pain, pathological findings in percussion and palpation, diarrhea, presence and character of bowel sounds, abdominal distension, vomiting and regurgitation and high gastric residual volume (GRV) are some clinical signs and symptoms proposed to assess gastrointestinal dysfunction [13]. However, one symptom alone may not adequately reflect the severity of gastrointestinal dysfunction [9].

Abdominal pain can be evaluated and located, providing valuable diagnostic information [14]. Still, its assessment becomes impossible in unconscious patients, and the incidence and association of abdominal pain with outcomes in critically ill patients remain unknown. Abdominal distension, another common sign, indicates increased abdominal volume. It may have various causes (fluid or air, intraluminal or extraluminal), and its clinical relevance is context-dependent, relying on other clinical findings for accurate interpretation. Moreover, accurate assessment of abdominal distension proves challenging in obese patients [15].

The presence and characteristics of bowel sounds have traditionally been used to indicate disorders, such as ileus or obstruction. There is doubt about its reliability, as no clear correlation has been demonstrated between the return of bowel sounds and restored motility [16]. The lack of uniform definitions for bowel sounds further complicates their interpretation [1,17]. Abdominal palpation can locate pain and masses and detect peritonitis, while percussion may help detect intraluminal or free air. Both techniques may only be suggestive, suffer from subjectivity and prove unreliable in certain common subpopulations in the ICU, such as sedated or postoperative patients [15,18].

Vomiting can be indicative of various gastrointestinal conditions, but regurgitation may go unnoticed in ventilated patients [1]. Evidence suggests that routine GRV monitoring may not improve outcomes and could lead to unnecessary interruptions in enteral feeding [19]. It has been demonstrated that GRV measurements are insufficient to impact morbidity or mortality in mechanically ventilated patients receiving enteral feeding [19]. Although vomiting/regurgitation occurred more often in patients without GRV measurements, enteral feeding intolerance (EFI) was documented more often in patients with GRV measurements simply because a GRV greater than 250 ml was considered EFI [19]. This illustrates the confusion in definitions of EFI and gastrointestinal dysfunction and supports the notion that a single sign or symptom may not represent gastrointestinal dysfunction. Recent data confirms that high GRV levels alone are not associated with patient-relevant outcomes [20] but become important when used as a component of the definition of EFI [21]. Diarrhea can signify intestinal infection, ischemia, or malabsorption. Diarrhea is highly prevalent in ICU patients and requires careful case-by-case evaluation to determine its clinical significance [1,22,23]. Intra-abdominal pressure (IAP) measurement may be another clinical tool that can be used to assess gastrointestinal function indirectly. Bowel distension and/or bowel edema may lead to intra-abdominal hypertension (IAH), associated with impaired outcomes in critically ill patients [24–26]. IAH can lead to hypoperfusion of abdominal organs, trigger fluid therapy and exacerbate gastrointestinal dysfunction. However, routine IAP monitoring is not universally practiced, and gastrointestinal dysfunction may very well be present without elevations of IAP.

A combination of multiple signs and symptoms may be better suited to predict an increase in ICU mortality, an often-used surrogate for gastrointestinal dysfunction [1,11,13]. The recently developed Gastrointestinal Dysfunction Score (GIDS) represents a more comprehensive approach to assessing gastrointestinal function in the ICU, incorporating multiple clinical signs and symptoms into a 0–4-point scale [11]. Variables in the GIDS include vomiting, gastrointestinal paralysis, oral intake, GRV, bowel sounds, abdominal distension, diarrhea, intra-abdominal pressure including abdominal compartment syndrome, mesenteric ischemia, and gastrointestinal bleeding [11]. While promising and increasing the accuracy in mortality prediction when added to the SOFA score [11], the GIDS requires further validation in diverse ICU populations [27].

The recently completed COSMOGI study has identified 13 essential outcomes for daily monitoring of gastrointestinal function in critically ill patients for future research [3]. This outcome set provides a potentially more nuanced approach to gastrointestinal assessment than earlier tools, complemented by specific definitions for each outcome. It may, therefore, aid in better defining and unifying gastrointestinal dysfunction in future research [3,27]. Importantly, the suggested variables for assessment of gastrointestinal dysfunction include both gastrointestinal and abdominal signs and symptoms as well as clinical entities, which are a combination of different signs and symptoms. They also include interventions (i.e. parenteral nutrition or postplyoric feeding) that may be applied due to features of EFI (Fig. 1).

IMAGING AND MEASUREMENT MODALITIES

Advancements in medical technology have led to the development of various experimental and research instruments for more objective monitoring of gastrointestinal function in critically ill patients. Many are still in the research phase and face limitations in routine clinical use.

Nearly three decades ago, it was shown that gastrointestinal tonometry, which estimates gut perfusion by measuring CO_2 diffusion from surrounding tissue into the gastric lumen, may accurately indicate hypoperfusion. However, it is prone to technical and procedural errors and can be influenced by enteral feeding and medication [28], and consequently has not made it to clinical practice.

The 21st century has witnessed the development and utilization of numerous techniques for assessing gastric emptying in patients suffering from acute and chronic gastrointestinal disorders. One group of tools is based on the detection of tracers. These methods involve infusing tracers or markers via a nasogastric tube and detecting their movement

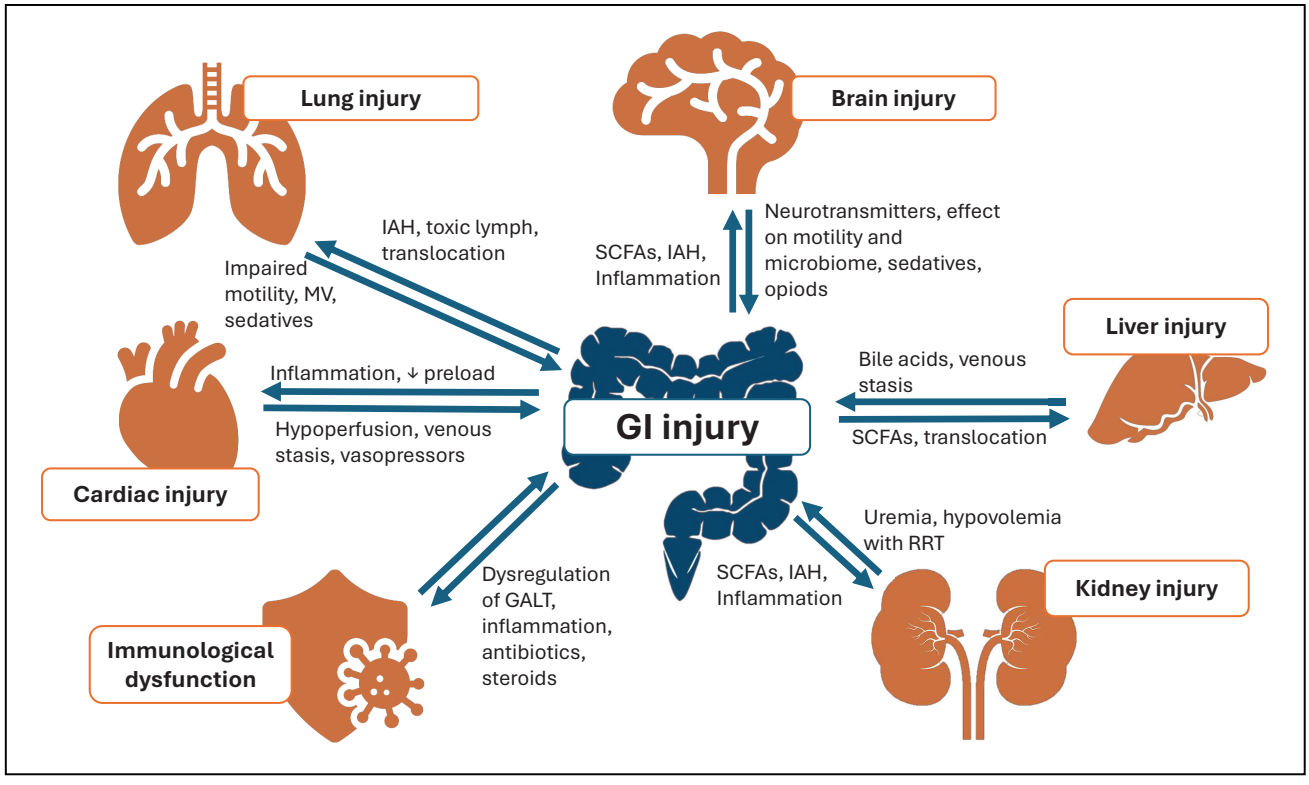

FIGURE 1. Assessment of gastrointestinal dysfunction as part of multiorgan dysfunction. Gastrointestinal injury may impact other organ systems and vice versa. Arrows represent the bidirectional nature of these interactions. When assessing gastrointestinal dysfunction, inter-organ crosstalk should be considered in patients with multiple organ dysfunction.

or absorption through scintigraphy, blood tests or exhaled air analysis. While these techniques may be accurate, they often require special equipment, are time-consuming and expensive, and may involve radioactivity. Moreover, the results depend on gastric emptying and absorption, which can complicate interpretation [29,30]. Scintigraphy is considered the gold standard for assessing gastric emptying, but its time-intensive and labor-intensive nature currently render it impractical for everyday use in the ICU setting [30]. The next generation validated technology that correlates with gastric scintigraphy and radio-opaque markers is the wireless motility capsule (SmartPill), a Food and Drug Administration (FDA)-approved capsule to evaluate gastric transit and clinical disorders, such as gastroparesis, dyspepsia and chronic constipation. Although the technology is generally well tolerated, it poses risks associated with swallowing in dysphagic patients and contraindication in patients with severe gastrointestinal conditions [31]. An innovative approach to detect postoperative ileus involves using an acoustic gastrointestinal surveillance biosensor. This noninvasive method uses a microphone to detect bowel sounds, but its availability is limited, and validation in the ICU is lacking [32,33]. High-resolution manometry (HRM) is another advanced diagnostic tool for assessing esophageal pressure and sphincter function by measuring neuromuscular activity. Although HRM is highly effective, it has limitations in patients with dysphagia and critical illness, as it can be insensitive in assessing broader gastrointestinal dysfunction [34▪]. Specific nasogastric tubes have recently developed to detect gastric motility or gastroesophageal reflux in ICU patients. Still, the high cost and potential safety implications of specific nasogastric catheter use must be considered [35,36]. Radiological imaging, including computed tomography (CT) scan, MRI and abdominal radiography, are routinely employed in ICUs to facilitate diagnosis and guide medical or surgical interventions. These imaging techniques prove particularly valuable in assessing conditions that may necessitate surgical intervention (i.e. intestinal distension, pneumatosis intestinalis, dilated bowel loops, intestinal infarction, bowel wall thickening and perforation). However, the diagnostic process is constrained by the limitations of repeat examinations limiting dynamic assessment, and the potential for missed diagnoses in the early stages of illness

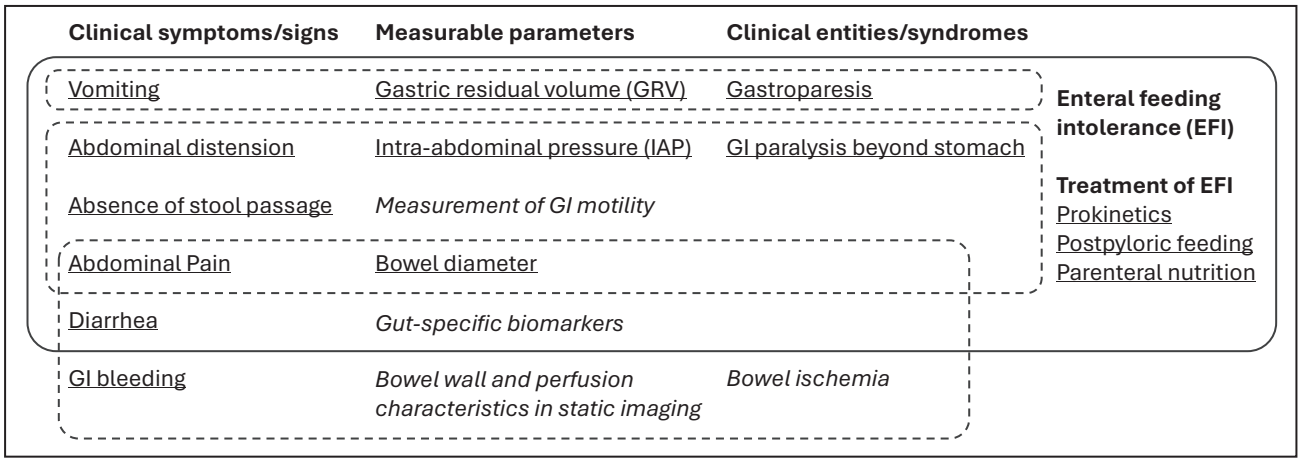

FIGURE 2. Complex assessment of gastrointestinal dysfunction. The possible parameters are grouped as clinical signs and symptoms, measurable parameters, treatment variables of EFI, treatment variables of gastrointestinal dysfunction, and clinical entities. COSMOGI outcomes are underlined (stool passage is replaced by absence of stool and diarrhea). The clinical entities are defined through multiple signs and symptoms as well as measurable parameters as indicated in the figure (i.e. GRV may be part of the gastroparesis assessment, bowel diameter may be part of the assessment for gastrointestinal paralysis). Bowel ischemia as a clinical entity is different from the remaining entities because a diagnosis of ischemia may be confirmed using CT or visual macroscopic inspection (surgery or endoscopy). The list of symptoms is only suggestive and should trigger further diagnostics. In contrast, the remaining clinical entities can be diagnosed using the listed parameters. CT, computed tomography; GRV, gastric residual volume.

progression [37]. A recent novel, noninvasive body gastric mapping device (BSGM) evolved from the traditional electrogastrography uses dense fields of electrodes to assess gastric activity reliably at high spatial resolution. Although, BSGM has been comprehensively validated in chronic gastrointestinal disorders, its application in the acute and critically ill setting has yet to be validated [38,39]. Point-of-care ultrasonography, mainly focused on stomach [40,41,42▪], has gained popularity. However, the evidence for routine use in clinical practice is yet to be established. Its great potential for daily bedside monitoring is counteracted by difficulties developing a useful, standardized approach for assessing the intestines. A recently developed structured gastrointestinal ultrasound (GIUS) protocol considers all these aspects but needs adjustment for feasibility before broader validation in the ICU setting [43].

LABORATORY TOOLS

Various biomarkers have been investigated for their potential to assess gastrointestinal function and EFI in critically ill patients [44]. Potential biomarkers can be categorized into three main groups: enterohormones, markers of enterocyte function, and cytokines/neurotransmitters [45]. They may have the potential to provide objective measures of gastrointestinal function and EFI, which could improve the management of critically ill patients and optimize nutritional support. Enterohormones regulate gastrointestinal motility and appetite, while markers of enterocyte function can indicate intestinal damage or dysfunction [45]. Cytokines and neurotransmitters are involved in inflammatory processes and gut–brain signaling, affecting gastrointestinal function in critical illness [45].

Studies have found that enterohormone concentrations differ between patients who are tolerant and intolerant to gastric enteral nutrition, with intolerant patients demonstrating higher concentrations of total ghrelin and lower concentrations of acyl ghrelin [46]. Cholecystokinin (CCK) is another enterohormone of interest, with increased plasma CCK levels observed in patients tolerant to enteral nutrition, suggesting a potential role in assessing gastrointestinal function [46,47]. Research on other enterohormones, such as motilin and peptide YY (PYY), has not shown significant associations with EFI [48].

Markers of enterocyte function, such as citrulline, I-FABP, I-BABP, zonulin, acetylcholine HBP and GDF15, D-lactate and smooth muscle actin (SMA) have been extensively studied, but most research yielded mixed results [44,45]. There was no significant relationship between citrulline, a nonprotein amino acid produced by enterocytes, and gastrointestinal dysfunction or EFI [49,50]. Decreased concentrations of citrulline and increased concentrations of intestinal fatty acid-binding protein (I-FABP) were observed in

patients with septic shock, also having higher rates of EFI [51▪]. Higher I-FABP concentrations have also been associated with CT signs of bowel hypoperfusion and EFI in patients with severe blunt trauma [52]. At the same time, significant associations between these biomarkers and gastrointestinal dysfunction have been searched but not confirmed [11,53]. Ileal bile acid binding protein (I-BABP) and zonulin have also been investigated, with elevated concentrations of both markers associated with delayed gastric emptying in critically ill patients [29,54]. Higher plasma acetylcholine concentrations have been observed in patients tolerant to enteral nutrition [55] and heparin binding protein (HBP) and growth differentiation factor-15 (GDF15) may also be linked to EFI [56,57]. D-lactate is a potential indicator of intestinal barrier dysfunction and microbial translocation or overgrowth. At the same time, SMA is a smooth muscle protein that may be released during severe intestinal damage. However, both markers are reported to have low specificity and lack diagnostic reliability, which require further evaluation in future studies [58,59].

FUTURE RESEARCH ON ASSESSMENT OF GASTROINTESTINAL FUNCTION

Available evidence on biomarkers potentially reflecting various gastrointestinal functions is somewhat confusing, often showing an association between biomarkers and severity of illness rather than linking biomarkers to gastrointestinal function. This is not surprising, considering the difficulty of measuring gastrointestinal function, and probably indicates that a clinical tool is also needed in studies assessing biomarkers as well as in interventional studies. Two recently completed studies (COSMOGI and GUTPHOS) hopefully bring more clarity and structure to the clinical assessment of gastrointestinal dysfunction [3,27]. As the subjectivity of clinical assessment may only be marginally improved, studies on biomarkers are further warranted. They may possibly benefit from a more structured clinical assessment linking biomarker levels to gastrointestinal signs and symptoms. Next to biomarkers, the development of tools measuring motility and absorption of nutrients is desirable to detect responses to enteral nutrition. The complexity of gastrointestinal dysfunction and its assessment in critical illness and the heterogeneity of patient populations contribute to the challenges of determining the robustness and clinical applicability of any tool for assessing gastrointestinal (dys) function in critical care settings [27]. Gastrointestinal dysfunction as a part of multiple organ dysfunction needs special attention in future mechanistic studies.

CONCLUSION

Despite experimental and research tools offering promising avenues for a more detailed and objective assessment of gastrointestinal function, issues of practicality, cost, and difficulties in validation for routine clinical use in the ICU prevent them from being available during the next years. Clinical assessment of gastrointestinal function is becoming more structured and remains the main approach in clinical practice.

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Conflicts of interest

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