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NEW ANTIBIOTICS FOR ABDOMINAL INFECTIONS

WHAT CAN WE EXPECT?

Recently a number of new antibiotics or combinations for complicated intra-abdominal infections have been introduced. Here we review the currently available data of these new drugs and discuss how they can be used in critically ill patients with complicated intra-abdominal infections.

Complicated intra-abdominal infections (cIAI) remain one of the most challenging infections in the intensive care unit (ICU). Compared to patients with other infections, patients with cIAI typically will develop multiple organ dysfunction syndrome (MODS) more often and have a higher risk of mortality; often they have a protracted stay in the ICU and in the hospital (De Waele et al. 2014). The management of these patients can be challenging. This includes evaluating the need for source control as well as effectively getting the source of infection controlled, but also selecting the appropriate antibiotic in times of changing susceptibility patterns and the rise of antimicrobial resistance (AMR).

The role of source control is more relevant in cIAI than in most other commonly encountered infections in the ICU. At times difficult choices have to be made (Leppäniemi et al. 2015). The role of surgery in this context is changing, new techniques are being introduced, and, increasingly, percutaneous drainage is being used as a primary strategy. Despite the prominent role of source control, administering appropriate antibiotics is equally important. Although there are fewer limitations in correctly diagnosing abdominal infections compared to e.g. respiratory tract infections, both timing and spectrum of empirical antibiotic therapy are critical. Antibiotics should be administered when the diagnosis is made and not postponed until intraoperative cultures are obtained.

Antibiotic resistance is also increasingly described in cIAI. In particular the spread of extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* in community-acquired cIAI is striking, and may limit the use of many currently available antibiotics. This in turn may put an inappropriate strain on the carbapenem antibiotics with the risk of increasing resistance to this class of antibiotics. The need for new antibiotics in this context is urgent.

Options for appropriate empirical therapy are becoming limited in some situations, and every attempt should be made to choose the correct antibiotic for the patient with cIAI. It should also be remembered that cIAI are typically polymicrobial infections with both aerobic and anaerobic bacteria present in most situations, and will typically require antibiotics that cover both Gram-positive and Gram-negative pathogens.

> "new agents should be used only where they have a clearly added value"

Rise of Multidrug Resistance in cIAI

As in other types of infections, AMR is a pressing issue in cIAI. Patients with cIAI may be at increased risk of AMR as they are often exposed to antibiotics for prolonged periods of time, and source control plays a crucial role. Particularly when source control is inadequate or even impossible, the inoculum persists. As bacteria are exposed to antibiotics during that time, AMR is bound to develop. This has been documented in severe abdominal infections including peritonitis and pancreatitis (De Waele 2016; Montravers et al. 2016).

As typically more than one pathogen is involved, the risk of encountering antibiotic resistance is also increased. For the same reason the extensive coverage needed to cover all pathogens (often with multiple antibiotics) may fuel AMR, as bacteria are exposed to more than one antibiotic at the same time. Whereas AMR was only relevant in nosocomial infections until recently, it is now also posing problems in community-acquired disease.

Overall, AMR is a concern mostly with Gram-negative pathogens. ESBL-producing bacteria are a primary worry worldwide (Sartelli et al. 2015), even more so in some areas, e.g. in Asia. Even then important regional differences are present.

The prevalence of ESBL in *E. Coli*, *K. pneumonia*, *K. oxytoca* and *P. Mirabilis* has increased dramatically from 2002 to 2011 in cIAI in Asia and the Middle East, where up to 40% of these pathogens isolated from cIAI produce ESBLs (Morrissey et al. 2013). It is unclear if this trend has changed in more recent years as epidemiological studies on AMR after 2013-2014 are lacking. Regional differences are important, and extrapolating data from other parts of the world to develop local empirical therapy guidelines should be avoided.

Carbapenemase-producing *Klebsiella pneumonia* (KPC) has been posing particular problems in nosocomial infections in some parts of the world. cIAI have not been exempt from KPC involvement, but this appears to be a regional problem mostly at this point.

Although the problem of AMR in cIAI is most relevant for Gram-negative pathogens, trends in Gram-positive infections should not be ignored. Enterococci are considered to be more pathogenic in nosocomial cIAI, and typically are involved in patients who have been exposed to antibiotics that do not cover enterococci, e.g. cephalosporins or fluoroquinolones. Apart from their different appreciation in nosocomial cIAI,

resistance in enterococci is increasing as well; *E. faecium* is typically non-susceptible to penicillin antibiotics, but in *E. faecalis* ampicillin resistance is also rising. Infection with vancomycin-resistant enterococci is also increasingly described.

New Antibiotics for cIAI

Recently a number of new antibiotics or antibiotic combinations have been studied in patients with cIAI. Antibiotics recently introduced or coming soon for the treatment of cIAI include ceftolozane/tazobactam, ceftazidime/avibactam and eravacycline. Although several other new antibiotics may have activity against pathogens typically associated with cIAI, none of them is currently under investigation for this indication, and will not be discussed.

Ceftolozane Plus Tazobactam

Ceftolozane is a new fifth-generation cephalosporin antibiotic that has been marketed in combination with a well-known beta-lactamase inhibitor (BLI), tazobactam, in a fixed 2:1 ratio. It is active against a wide range of Gram-negative bacteria, including *Pseudomonas aeruginosa* and many ESBL-producing *Enterobacteriaceae*. It has been approved by the United States Food and Drug Administration for the treatment of complicated urinary tract infections and cIAI (combined with metronidazole for the latter). Dosing for patients with normal renal function is 1000mg ceftolozane plus 500mg tazobactam TID.

Three clinical trials have been performed in patients with cIAI. In a phase 2 study, 121 patients with cIAI requiring surgery were randomised to receive either meropenem or ceftolozane/tazobactam with metronidazole (Lucasti et al. 2014). Clinical cure rates were 83.6% and 96% for ceftolozane and meropenem respectively, on the basis of which the noninferiority of the drug was concluded. The *Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections (ASPECT-cIAI)* programme, reporting on two identical phase 3 studies with a similar setup to the phase 2 study, and using the same comparator, included 993 patients, 806 of which were analysed in the modified intention to treat (MITT) group (Solomkin et al. 2015). For the primary endpoint clinical cure rates were 83% with ceftolozane/tazobactam plus metronidazole vs. 87.3% with meropenem in the MITT population. In both studies the incidence of adverse effects reported was similar in both groups. Based on these studies, ceftolozane/tazobactam was approved for the indication of cIAI at the end of 2014.

In a recent substudy investigating the outcomes of patients with *Pseudomonas aeruginosa*, the strong in vitro activity of ceftolozane against these pathogens was confirmed, with high clinical cure rates in the subgroup of patients with *Pseudomonas* infections (Miller et al. 2016).

Ceftazidime Plus Avibactam

Avibactam is a novel BLI that restores the activity of beta-lactam antibiotics such as ceftazidime against ESBL-producing pathogens.

In a phase 2 study the combination of ceftazidime/avibactam (2000mg/500mg TID) with metronidazole 500mg TID was compared with meropenem in 204 patients with cIAI (Lucasti et al. 2013). Clinical cure was 91.2% and 93.4% for ceftazidime/avibactam co-administered with metronidazole and meropenem respectively. Adverse events were comparable in both groups.

In two large phase 3 studies with an identical setup 1066 patients with cIAI requiring surgery of percutaneous drainage were randomised to receive ceftazidime/tazobactam plus metronidazole and the combination was found to be noninferior to meropenem (Mazuski et al. 2016). In the microbiologically MITT group, clinical cure at test of cure was statistically not different in the ceftazidime/tazobactam plus metronidazole group (81.6% vs. 85.1% respectively), and at other time points outcome was comparable. Safety evaluation did not demonstrate any differences between the groups.

Eravacycline

Eravacycline is a novel antibiotic in the tetracycline class, structurally comparable with tigecycline. It inhibits bacterial protein synthesis through binding to the 30S ribosomal subunit and has broad-spectrum antimicrobial activity against Gram-positive, Gram-negative and anaerobic bacteria with the exception of *Pseudomonas aeruginosa*, but including MDR pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and some carbapenem-resistant Gram-negative bacteria. In a phase 2 study the efficacy and safety of two dose regimens of eravacycline was compared with ertapenem in adult hospitalised patients with cIAI requiring surgical or percutaneous intervention: 1.5 mg/kg of body weight every 24 hours (q24h), or 1.0 mg/kg every 12 h (q12h) (Mazuski et al. 2016). In the microbiologically evaluable population the clinical cure was 92.9% and 100% in the groups receiving eravacycline at 1.5 and 1.0 mg/kg respectively, and 92.3% in the ertapenem group. Another large phase 3 study comparing eravacycline with ertapenem has been finalised but not yet published (IGNITE 1)—the manufacturer has reported that noninferiority was demonstrated but full analysis is not yet available (Tetraphase Pharmaceuticals 2014).

Caveats for Critical Care

Shortcomings of Recent cIAI Studies From a Critical Care Perspective

Although these antibiotics represent new therapeutic options in the management of cIAI, there are some things to consider from a critical care perspective. This is primarily related to the type of patients in the studies with these new antibiotics, and with the type of patients not included due to an often long list with exclusion criteria. Overall the patients in these studies are mild to moderately ill only, with a high prevalence of infections that are typically not encountered in the ICU, such as appendicitis.

In the studies investigating ceftolozane, it was not reported how many patients were diagnosed with severe sepsis or septic shock, or were admitted to an ICU. In the first study more than half of the patients were treated because of appendicitis, and median Acute Physiology and Chronic Health Evaluation (APACHE)-II score was 6 and 7 respectively (Lucasti et al. 2014). Similarly, in the ASPECT-cIAI programme, APACHE-II scores were 6 and 6.2 in the study groups and degree of organ dysfunction was not reported (Solomkin et al. 2015). Both studies excluded patients with thrombocytopenia or abnormal renal function.

The studies investigating avibactam in combination with metronidazole excluded severely ill patients; exclusion criteria in the phase 2 study included APACHE-II score of 26 or higher, abnormal renal function and fluid-unresponsive septic shock (Lucasti et al. 2013). Only 1 out of 6 patients had an APACHE-II score between 10 and 25, and the appendix and stomach were the most frequent sites of the primary infection. The phase 3 study included mainly patients with low to moderate disease severity as exemplified by the APACHE-II score that was 10 or lower in about 85% of the patients (Mazuski et al. 2016). That study also excluded patients with septic shock or who were receiving haemodialysis. The fact that patients could not be treated with an antifungal agent may have precluded including patients with more severe disease in the study.

One particular finding in the phase 3 study was the worse outcome in patients with moder-

ate renal impairment, defined as a creatinine clearance of 30-50ml/min. This may have been caused by the rapid changes in renal function in the subsequent days when patients still received renal function adjusted doses of the drug, although the effect should be present in both the interventional and comparator group (Mazuski et al. 2016).

The study investigating eravacycline excluded more critically ill patients such as patients with septic shock or an APACHE-II score of 25 or higher. Effectively, APACHE-II score was 6 and 8.2 in the study groups, and appendicitis was the source of infection in more than 50% of the patients. The use of ertapenem as a comparator can also limit the number of critically ill patients included, as this drug is not recommended for the treatment of severe cIAIs (Solomkin et al. 2010).

Implications for Critically Ill Patients With cIAI

So how does this translate to the use of these new agents in the critically ill? Although it is clear that the in vitro activity of these drugs against a wide range of pathogens is similar or better than many of the antibiotics that we are using now, the changes in physiology of the critically ill may be profound and lead to lower concentrations than expected. This phenomenon has been demonstrated for many antibiotics (Roberts et al. 2014) and is now an integral part of most drug development programmes.

In this context it is remarkable that an ongoing study comparing ceftolozane/tazobactam to meropenem for hospital-acquired pneumonia (*Safety and efficacy study of ceftolozane/tazobactam to treat ventilated nosocomial pneumonia* (MK-7625A-008) (ASPECT-NP), NCT02070757) uses a dose that is double what was used in the cIAI study (*clinicaltrials.gov/ct2/show/NCT02070757*). It is unclear if this is solely because of the different infection focus. Future pharmacokinetic studies of these new antibiotics in more severely ill patients should answer these concerns.

The exact place of these new agents in our current armamentarium will need to be discussed primarily considering the local ecology. This is where antibiotic stewardship teams should jointly define the indications as well as consider restriction in the use of these powerful agents. Apart from treating the infections adequately, new agents should be cherished and used only where they have a clearly added value – whether this is in empirical therapy in one country or directed therapy for highly resistant pathogens in another.

Conclusions

Antibiotic therapy of cIAI is becoming increasingly challenging due to the changes in susceptibility of pathogens involved. Although our current armamentarium may be effective in the treatment of many patients, new therapeutic options are highly desirable. The development of ceftolozane/tazobactam, ceftazidime/avibactam and eravacycline offers an opportunity to effectively treat MDR pathogens and avoid more toxic regimens. The exact place of these agents in the treatment of cIAI should be defined by local antibiotic stewardship teams, considering local ecology and other available options.

Conflict of Interest

Jan De Waele declares Consultancy for AtoxBio, Bayer Healthcare, Cubist, Fresenius, Merck. He is Infection section Chair at the European Society of Intensive Care Medicine, President of the Belgian Society of Intensive Care Medicine, Past President of WSACS - the Abdominal Compartment Society and Senior Clinical Investigator at the Flanders Research Foundation. ■

Abbreviations

AMR antimicrobial resistance
APACHE Acute Physiology and Chronic Health Evaluation
ASPECT-cIAI Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections
BLI Beta-lactamase inhibitor
cIAI complicated intra-abdominal infections
ESBL extended spectrum beta-lactamase
ICU intensive care unit
KPC *Klebsiella pneumonia*
MDR multi-drug resistance
MITT modified intention to treat
MODS multiple organ dysfunction syndrome

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IS ENTERAL FEEDING FEASIBLE EARLY AFTER ABDOMINAL CRISIS?

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The enteral route is commonly accepted as the first choice for providing nutrition to patients in the ICU with stable haemodynamics and a functional gastrointestinal (GI) tract. However, there is wide uncertainty regarding safe enteral nutrition in patients with critical pathology in the abdomen. In the current review we address different abdominal conditions in critically ill patients where safety and feasibility of enteral nutrition might be questioned. We discuss respective pathophysiological mechanisms, existing evidence and practical aspects.

Enteral nutrition (EN) prevents loss of physical and immunological barrier function (Kudsk 2002; McClave 2009). Early EN reduces infections and is recommended in critically ill patients with stable haemodynamics and functional gastrointestinal (GI) tract (Taylor et al. 2016).

Feeding in the Early Phase of Critical Illness

Even if feeding is started early, a negative energy balance in the first acute phase of critical illness is generally unavoidable. New insights show that early hypocaloric nutrition may even be preferred (Casaer and Van den Berghe 2014) because of an inflammation-induced endogenous energy production and nutrition-induced inhibition of autophagy. Therefore early EN should be started at a low rate in the acute phase and be slowly increased towards target. This is especially true in patients with, or after, abdominal crisis, with continuing vulnerability of GI tract.

Based on common sense, EN is considered harmful in the case of the clinical syndrome called "acute abdomen", in case of obvious gut ischaemia, mechanical obstruction or perforation, and in cases with no continuity of GI tract. In most other abdominal pathologies initiation of EN remains a matter of "try and see", e.g. starting low dose EN and evaluating feeding tolerance/intolerance.

Feeding intolerance (FI) is not uniformly defined; gastric residual volumes (GRV) have been mainly used for assessment of FI (Reintam Blaser et al. 2014). Some authors suggest abandoning GRV measurements all together (Reignier et al. 2013). We suggest that GRVs may still be useful to avoid gastric overfilling in the initial phase of EN or in the presence of abdominal symptoms (e.g. abdominal distension or pain). Evaluation of gastric filling with ultrasound may offer a good alternative to GRV (Gilja et al. 1999).

Enteral Nutrition in Specific Abdominal Conditions

In critically ill patients with severe abdominal pathology, both abdominal pathology and systemic disease may contribute to GI dysfunction (**Table 1**). GI function will usually recover if haemodynamics and gut perfusion improve, fluid resuscitation-induced gut oedema resolves and analgo-sedation can be reduced. On the contrary, a patient with persisting severe general condition is prone to complications. Thus EN should be initiated at a low rate and slowly increased under careful monitoring of abdominal symptoms to avoid dilatation of the stomach, bowel distension and increasing intra-abdominal pressure (IAP) (**Figure 1**).

Emergency Gastrointestinal Surgery

Direct injury of the GI tract due to trauma or surgery and/or infection/inflammation leads to gut oedema and dysmotility. Denervation, discontinuation of spinal reflexes and resection of enterochromaffin cells producing motilin may add to gut paresis. In emergency GI surgery, gut hypoperfusion due to shock, bowel oedema and intra-abdominal hypertension, exacerbated by inflammation and massive fluid resuscitation, is often evident. Therefore, major factors to consider for recovery after emergency GI surgery (if bowel continuity is restored) are: bowel perfusion, bowel oedema and bowel distension. The intraoperative evaluation of bowel viability is important; therefore good communication with surgeons is crucial. If a stoma is created and bowel cranial to stoma has normal appearance, low dose EN can usually be started within 24 hours. In elective surgery, performed anastomoses will likely heal better

with EN than without (Boelens et al. 2014). The risk of anastomotic leak is much higher if an anastomosis is performed during emergency surgery, but there is no evidence on harmfulness of early EN in this situation. A positive effect of early EN regarding infections after emergent GI surgery has been shown in one randomised controlled study (Singh et al. 1998).

> In most patients EN should be considered early after initial management of abdominal crisis

Damage control surgery enables postponement of restoration of bowel continuity until hypoperfusion, oedema and distension are resolved. Still, trophic EN might already be considered if a diverting stoma is present and the next surgery is not planned within the next 24 hours.

In patients with prolonged abdominal sepsis requiring multiple interventions and clearly not reaching their energy and protein targets with EN, supplemental PN should be considered after a couple of days, while avoiding overfeeding. Supplemental PN should also be considered if such patients have severe diarrhoea with impaired absorption of nutrients.

Open Abdomen

Patients with open abdomen often require multiple surgeries and have increased risk for fistula formation. A few studies have shown that EN is feasible in patients with open abdomen and is associated with a higher rate of abdominal closure and a lower incidence of ventilator-associated pneumonia (Collier 2007; Byrnes et al. 2010; Dissanaike 2008).

EN should be applied early, as soon as bowel continuity is confirmed or restored and haemodynamic and tissue perfusion goals can be reached with or without vasopressors/inotropes. Continuing need for fluid resuscitation may refer to unsolved abdominal pathology, whereas losses due to the open abdomen need to be taken into account.

Abdominal Aortic Surgery

Rupture of the abdominal aorta and associated surgery carry a risk of massive bleeding and transfusion, retroperitoneal haematoma formation and impaired gut perfusion, which might be an argument for delaying EN in these patients. The major adverse event after abdominal aortic surgery is colonic ischaemia (CI), which occurs in about 2% of patients after elective surgery for aneurysm, and 10% in case of rupture (Björck et al. 1996; Van Damme et al. 2000), somewhat less in endovascular repair (Becquemin et al. 2008). Presumed causes of CI are ligation or obstruction of supply arteries (inferior mesenteric artery, hypogastric arteries, meandering mesenteric arteries), non-occlusive ischaemia due to shock or vasopressor drugs, and (micro) embolisation (Steele 2007).

Length of operation, aneurysm rupture and renal insufficiency are independent risk factors of CI (Becquemin et al. 2008). Surgical details (reimplantation of inferior mesenteric artery, intraoperative assessment of blood flow by Doppler flowmetry, large bowel viability, etc.) should be carefully recognised. The main clinical symptoms of CI are early diarrhoea, haematoschisis (Björck et al. 1996) and ileus (Valentine et al. 1998). Colonoscopy remains the method of choice to detect ischaemic lesions of colonic mucosa, but its routine application is not supported (Steele 2007). Whether and how the endoscopic findings can guide EN is not clear. Circulating biochemical markers such as intestinal fatty acid-binding protein may facilitate the recognition of CI (Vermeulen Windsant et al. 2012), but whether this information can be used for feeding decisions remains unknown.

Taking the relatively low incidence of CI, it is not rational to delay EN in all patients routinely for several days after abdominal aortic surgery. Instead, EN should be initiated with low dose under careful monitoring of abdominal symptoms, IAP and signs of CI, and increased gradually (van Zanten 2013). In overt bowel ischaemia, EN should be withheld.

Abdominal Trauma

Abdominal trauma is a complex injury, where a multidisciplinary approach has made non-operative management increasingly feasible and effective (Prachalias and Kontis 2014). Early EN may be well integrated in this approach. However, obstacles such as GI tract discontinuity, compromised gut perfusion and/or abdominal compartment syndrome may necessitate delay of EN. At the same time, some older RCTs using needle catheter jejunostomy have shown benefit of early EN over early PN (Kudsk 1992) and over delayed EN (Moore 1986) regarding infectious complications. We suggest starting EN early after abdominal trauma if continuity of GI tract is

Table 1. Main Pathophysiological Mechanisms Contributing to GI Dysfunction and Possibly Conflicting With EN In Different Clinical Conditions

Pathophysiological mechanisms		Condition/diagnosis
Local/ gastrointestinal	1. direct injury in GI tract 2. inflammation/infection 3. bowel distension 4. ischaemia 5. dysmotility 6. gut oedema 7. reduction of bowel length	GI perforation GI surgery GI bleeding Bowel ischaemia Fistula Colitis Ileus
Abdominal/ peritoneal/ retroperitoneal	1. inflammation/infection 2. intra-abdominal hypertension 3. intra-abdominal bleeding	Abdominal trauma Abdominal surgery Abdominal bleeding Retroperitoneal bleeding Peritonitis Pancreatitis
Systemic	1. hypoperfusion 2. tissue oedema 3. splanchnic vasoconstriction 4. inflammation/infection 5. dysmotility caused by drugs or electrolyte disturbances	Shock Capillary leak syndrome Massive fluid resuscitation Vasoconstrictors Drugs causing hypomotility: e.g. vasoactives, opiates, sedatives Drugs causing hypermotility (diarrhoea): e.g. antibiotics Electrolyte disturbances

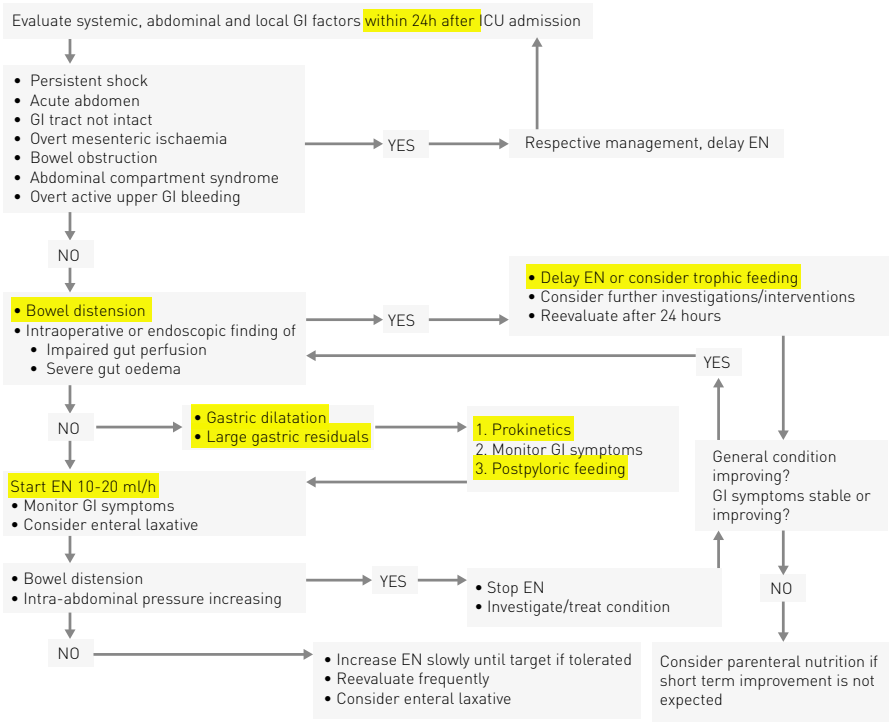

Figure 1. Algorithm for Using EN Early after Abdominal Crisis

confirmed/restored, and abdominal compartment syndrome and bowel ischaemia excluded.

Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS), defined as IAP above 20 mmHg along with new or worsening organ failure, is an immediately life-threatening condition, where prompt measures to reduce IAP are needed. These measures include decompression of GI tract and avoidance of adding any volume into the abdomen (Kirkpatrick et al. 2013), thereby excluding EN. Moreover, splanchnic perfusion is severely jeopardised during ACS.

EN should be considered at elevated IAPs between 12 and 20 mmHg without ACS, but high incidence of feeding intolerance has been described (Reintam et al 2008). Further, EN itself may cause an increase in IAP. We suggest incorporating IAP measurements into standard monitoring of critically ill patients with abdominal pathologies in the initial phase of EN, and cessation of feeding to be considered if worsening of clinical status is possibly attributed to increasing IAP.

Severe GI Bleeding

Patients admitted to the ICU due to acute GI bleeding require immediate diagnostics and intervention to localise and stop bleeding. EN might be considered when the bleeding has been stopped endoscopically or surgically. The main rationale to withhold EN after stopping active bleeding is disturbed visibility if a new endoscopy is needed; therefore delaying enteral intake for at least 48 hours in case of high risk of rebleeding has been suggested (Hébuterne and Vanbiervliet 2011). Such a time frame is not well justified nor supported by the evidence. We suggest that when upper GI bleeding has been stopped and there are no signs of rebleeding, low dose EN can be started within 48 hours. In case of lower GI bleeding EN could be started immediately.

Bowel Ischaemia

EN increases gut perfusion (Matheson 2000), but only if the vasculature is intact and the systemic haemodynamics sufficient. There is broad consensus to withhold EN in patients with suspected small bowel ischaemia. This condition requires optimisation of the circulation and, if symptoms of ischaemia persist, a surgical or radiological intervention. In addition, continuous thoracic epidural anaesthesia may increase splanchnic blood flow by blocking afferent sympathic reflexes (Holte 2000). Local mucosal ischaemia of the colon has a tendency to heal when the general condition of the patient improves. Therefore EN should be considered in patients with colonic mucosal ischaemia without bowel distension. Bowel distension may possibly be aggravated by EN and lead to further impairment of bowel wall perfusion. We suggest that EN should not be started if transmural bowel ischaemia is confirmed or suspected or signs of local mucosal ischaemia are seen in severely distended bowel.

Bowel Obstruction

Bowel obstruction leads to obstructive ileus, with initial hypermotility (be warned: presence of bowel sounds is misleading) to force bowel contents through the obstruction and subsequent bowel distension above the obstruction. Bowel obstruction requires a surgical or endoscopic intervention to restore passage of bowel contents or to create a proximal stoma. EN should be withheld in case of obstructive symptoms, but can be carefully initiated as soon as passage is restored or a proximal stoma has been created. It may take a couple of days before bowel distension and paresis are resolved and EN can be increased.

Bowel Paralysis

EN itself promotes motility and has beneficial effects regarding the physical and immunological gut barrier, whereas prolonged enteral fasting will aggravate dysmotility and should be avoided. Since gastroparesis is often more pronounced than small intestinal paralysis, the use of prokinetics and postpyloric feeding should be considered early in case of gastric intolerance to EN. However, paralytic ileus is often encountered in patients with peritonitis. Inflammation-induced dysmotility is mediated by cytokines and nitric oxide produced by locally activated macrophages in the muscular layer, and by neuronal pathways (Schmidt et al. 2012). Non-abdominal sepsis may also be associated with bowel paresis, due to the release of nitric oxide, which causes bowel relaxation, oxidative stress and the systemic release of tumour necrosis factor (TNF), which inhibits the central vagal pathways (Emch et al. 2000). Furthermore, many conditions and therapies in critically ill patients (e.g. hyperglycaemia, hypokalaemia, acidosis, use of dopamine, opioids, clonidine and dexmedetomidine) may contribute to bowel paralysis.

In rare cases, isolated large bowel distension mainly in the caecum region occurs,

called Ogilvie's syndrome seu colonic pseudo-obstruction. This condition carries high risk of bowel ischaemia and perforation due to distension, and should be promptly recognised and managed (Oudemans-van Straaten 2011; De Giorgio and Knowles 2009) with intravenous neostigmine (van der Spoel et al. 2001; Valle and Godoy 2014), endoscopic decompression or temporary coecostomy. Early start of lactulose or polyethylene glycol (van der Spoel et al. 2007) and neostigmine, if defaecation does not occur, may help to prevent Ogilvie's syndrome. In less severe cases of bowel paralysis, there are no confirmed contraindications to start a trial of low dose EN under careful monitoring of symptoms and promotion of defaecation with laxatives and neostigmine.

Acute Colitis with Toxic Megacolon

Acute colitis as a cause of diarrhoea in intensive care is a rare condition that is mostly caused by a *Clostridium difficile* infection. Sometimes severe enterocolitis is caused by chemotherapy for haematological disorders. In most severe cases toxic megacolon—a severe and life-threatening condition associated with systemic toxicity—may develop (Oudemans-van Straaten 2011). Colitis requires specific therapy, including antibiotics, discontinuation of motility impairing drugs, replacement of intravenous fluids, electrolytes, trace elements and vitamins (Dickinson 2014; Oudemans-van Straaten 2011). In rare cases of toxic megacolon, total colectomy becomes necessary for the patient's survival. In most patients with colitis, there is no contraindication for EN, because the small intestine is intact. However, EN should probably not be applied to patients with toxic megacolon.

Conclusions

In most patients EN should be considered early after initial management of abdominal crisis, when continuity of GI tract is confirmed or restored, and bowel ischaemia and abdominal compartment syndrome are excluded. However, EN should be started at a slow rate under careful monitoring of GI symptoms and IAP. ■

Conflict of interest

Annika Reintam Blaser declares that she has no conflict of interest. Heleen M. Oudemans-van Straaten declares that she has no conflict of interest. Joel Starkopf declares that he has no conflict of interest.

Abbreviations

ACS abdominal compartment syndrome
CI colonic ischaemia
EN enteral nutrition
FI feeding intolerance
GRV gastric residual volume
IAP intra-abdominal pressure
TNF tumour necrosis factor

For full references, please email editorial@icu management.org, visit icu-management.org or use the article QR code.