**Table. Study proposals for voting 2.** Please find all abbreviations at the end of the document.

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| STUDY PROJECTS ranked 1-20 after the Voting round number 1 | | | | | | | |
| Study acronym | **Research questions/aims** | **Study design** | **Subjects** | | **Details/Intervention** | **Outcome variables** | **Comments /**  **problems / open questions** |
| 1: Bio-  markers for GI dysfunction | Validate biomarkers for absorption of nutrients and GI dysfunction | Prospective observational multicenter | Ventilated adult ICU patients with tube feeding expected to stay for at least 3 days | | BOMB calorimetry of feces (24-h fecal coll.), Increase in plasma AA, D lactate, Fecal fat/fatty acids, stool details (Bristol scale, volume, pH). Absorption (3-OMG). Citrulline, I-FABP. Lactulose/ rhamnose or cellobiose/rhamnose gut permeability test | COS #  Associations between biomarkers and clinically relevant outcomes, or scores (e.g. SOFA) | Gold standards for absorption of specific nutrients? Stool specific analyses for malabsorption of different macronutrients to be considered/specified.  Potentially additional biomarkers based on iSOFA results |
| 2: Gut barrier and EN | To study whether early EN is able to preserve intestinal wall integrity | RCT  Early EN vs early PN (isocaloric and in both groups slow progression to target) | Ventilated ICU patients on vasopressor support, after stabilisation of shock | | Early EN vs early PN  Measurement of I-FABP; I-BABP; zonulin-1, citrullin, lactulose/ rhamnose or cellobiose/ rhamnose), duodenal biopsies if feasible. Indirect calorimetry | Inflammatory and gut permeability markers, Endotoxin, bacterial DNA, peptidoglycans in blood. Monocyte activation. CD-4 T cell reactivity. Infections. NOMI. 90d outcome.  Hypermetabolic response (IC) | Timing of measurements to be defined |
| 3: Biomarkers of intestinal ischemia and barrier function in ICU | Validate biomarkers in predicting mesenteric ischemia in ICU patients.  Barrier function: characterize epithelial first and second line defense in critically ill patients with intestinal ischemia | Observational large scale cohort study.  Subgroups: 1) abdominal surgery  2) medical ICU pt (with shock) | Consecutive adult MV ICU pt with increased risk of intestinal ischemia | | I-FABP, α-GST, SMA, citrulline, D-lactate, sCD14, Claudin 3, RT PCR Bacteroides and Entero-coccus sp. Stool analysis (mucins, AMPs, IgA, eosinophil cationic protein, calprotectin). Analysis of intest. fluid (endosc). | Predictive value of biomarkers to diagnose mesenteric ischemia – confirmed by endoscopy or surgery. Link with short and long term intestinal, vital and functional outcome (including Sepsis, LOS ICU and hospital, 28 & 90 days mortality). Association between clinical symptoms and biomarkers. | Systematic review needed to define study group (risk pt).  All patients with suspected ischemia (e.g. GI bleeding) need endoscopy if no surgery.  Endoscopy or surgery needed for final diagnosis of mesenteric ischemia. |
| 4: Diarrhea prevention | Does routine use of fiber feeds reduce diarrhea? | RCT | Critically ill patients in need of EN | | Fiber feeds versus non-fiber feeds | Bristol stool chart  GI symptoms \* | Standard protocol for diarrhea management is advisable.  Study EN solution to be discussed (mixed fibers vs. only soluble fibers) |
| Acronym | **Questions/aims** | **Study design** | **Subjects** | | **Details/Intervention** | **Outcome variables** | **Comments** |
| 5: Diarrhea management | Does reduction or discontinuation of EN reduce diarrhea? | RCT (3-armed study) | Patients with severe diarrhea during EN | | 1. Continuation of EN  2. Reduction of EN by 50%  3. Trophic EN + supplemental PN (after 3-7 days) | Bristol stool scale  GI symptoms \*  LOS  infections | Severe diarrhoea = requiring interventions (fluid, electrolyte replacement).  Use of laxatives needs to be standardized. |
| 6: Prophylaxis vs Treatment of upper GI intolerance | Is the prophylactic use of prokinetics superior to therapeutic use? | Multicenter RCT | Adult ICU pt. at high risk of gastroparesis | | Two study arms, same drugs (erythromycin, metoclopramide, alizapride, ..) and dosages, different timing (routine administration or only in confirmed gastroparesis) | COS #  Pneumonia incidence  Long-term outcomes  Adverse effects (prolonged QT, extrapyramidal side effects, colonisation with multi-resistant microbes) | Patients at risk may include patients receiving high doses of opioids, patients having undergone GI surgery, and patients with peritonitis, sepsis, diabetes or recovering from shock |
| 7: US-Gastric 1 | Is US a reliable technique for routine bedside assessment of gastric emptying in critically ill | Multicenter observational | Ventilated adult ICU patients with tube feeding | | Repeated US assess-ments against labeled carbon absorption and exhalation (and GRV) | Correlation of US-assessed changes in gastric volume and labeled carbon exhalation and GRV |  |
| 8: Indication of postpyloric feeding | Is postpyloric feeding superior to PN in case of gastroparesis? | Multicenter RCT | Adult ICU patients with gastroparesis (e.g. GRV>500ml with prokinetics) | | Postpyloric feeding versus PN | Infections  Gastrointestinal complications (including non-occlusive bowel ischemia)  Mortality  Meeting nutritional target |  |
| 9: Pancreatic Insufficiency in ICU | What is the real incidence and prevalence of exocrine pancreatic enzyme deficiency in ICU patients? | Prospective observational | Adult ICU patients receiving EN | | None | GI symptoms \*  Success of EN  Fecal fat  Elastase-1 stool  Serum trypsinogen  BOMB calorimetry | Additional option to study the correlation with pancreatic endocrine function (C-peptide). Consider assessment of small bowel fluid in patients undergoing endocsopy |
| 10: AGI prospective | Does subjectively given AGI score (AGI I-IV) predict the outcome? | Prospective observational | Consecutive ICU patients being mechanically ventilated for non-elective reason (planned MV after elective surgery excluded) | | AGI score documented daily. Decisions for diagnostics or treatment taken based on daily assessed GI symptoms \* documented daily. | GI symptoms \*, pneumonia, COS#,  ICU outcome, 90-day outcome, long-term patient-centered outcome, NOBN, GI anastomosis leakage (if relevant) | No standard definition of gastric FI (a part of AGI score).  Preferably adoption of a similar feeding protocol (& suggestions for prokinetics) in all centers. |
| Acronym | **Questions/aims** | **Study design** | **Subjects** | | **Details/Intervention** | **Outcome variables** | **Comments** |
| 11: AGIbiome (+Abxbiome) | Identification of intestinal microbiome signatures and correlation with AGI and SOFA score | Prospective, observational | >200 ICU patients with EN and/or PN | | Microbiome (multiple body site) sampling  Effects of different antibiotics / feeding routes | Variability and specificity of dysbiosis patterns according to different AGI grades  Intra- and interindividual microbial changes | Large sample size required  Adjustment for different (antimicrobial) treatment  Standardized sampling and analysis to be established |
| 12: GI diagnosis | 1. Is motility, distension and bowel wall thickness as assessed by US associated with GI symptoms \* and outcome?  2. Can clinical assessment and abdominal US predict adverse outcomes (e.g. perforation) | Prospective observational | 1. Adult ICU patients  2. Undergoing planned abdominal CT or laparotomy/ scopy | | 1. Clinical examination with vs. without ultrasound.  GRV and IAP measured  2. computed tomography and/or surgical findings. US performed before CT/surgery | 1. GI symptoms \*, feeding intolerance, success of EN, ICU and hospital outcome  2. Verified clinical outcome:  1) Gut distension (stomach/ small/large bowel)  2) Perforation  3) Peritonitis  4) Gut ischemia | Clinical and radiological assessors need to be blinded for radiological and clinical results respectively. Ideally they are not part of the treating team. Potentially, this study may help to define and grade FI. |
| 13: US-Bowel 1 | Can US be used for assessment of  a) bowel peristalsis (and EN tolerance)?  b) bowel distension and bowel wall thickness? | Proof-of- concept  Observational study | a) Adult ICU patients in need of tube feeding expected to stay for at least 3 days  b) with indication for abdominal CT | | US daily  Abdominal ultrasound. Observer blinded to CT-scan results  Measurement of bowel motility (e.g. gastro-graphin X-ray and /or high-resolution manometry large bowel) | Success of EN, GI symptoms \*  Correlation of US and clinical symptoms with CT scan results (Comparison of small and large bowel diameter and wall thickness US vs. CT and X-ray) | Potential difficulties to correlate US location with CT-scan.  Radiologist blinded for the other investigation. |
| 14: IAH-GI + NOMI-AGI | 1) Does protocolised monitoring of IAP and management of IAH improve outcome?  2) Is increased IAP associated with GI dysmotility? | 1) RCT  2) observational substudy | MV patients at risk of IAH. | | Intervention: Monitoring and management of IAP based on the protocol (bundle of preventive measures). Control: standard care.  US in intervention group | Mesenteric ischemia  Incidence of infections / sepsis  Mortality 90d, LOS, GI symptoms\*  Obervational substudy:  Correlation between IAP and GI motility as assessed by US |  |
| 15: PPI and dysbiosis | Does usage of PPI versus no PPI alters the intestinal microbiome? | RCT | Mech. ventilated ICU patients in need of EN and without an absolute indication for PPI | | Faecal microbiome  Clostridium difficile infection | Faecal microbiome pattern  Incidence of Clostridium difficile colitis | Large sample size required if also powered for clinical endpoints |
| Acronym | **Questions/aims** | **Study design** | **Subjects** | | **Details/Intervention** | **Outcome variables** | **Comments** |
| 16: Prophylaxis vs Treatment of lower GI intolerance | Does the prophylactic use of motility agents (prokinetics and laxative drugs) reduce time to defecation, improve feeding tolerance and GI dysfunction based on AGI grading? | Multicenter RCT | Adult consecutive ICU patients with with expected stay of >3d? | | Two study arms, same drugs (e.g. Macrogol, Laxatives) and dosages, different timing (routine administration or only in confirmed constipation/ bowel paralysis) | AGI dynamics  COS (clinical outcomes)  Infections  Diarrhoea  Mesenteric ischemia | Study duration to be defined |
| 17: Fluids 2 | Are bowel distension and wall thickness and dysmotility related to vasopressor dose and fluid balance? | Observational study | ICU patients scheduled for abdominal CT scan | | Vasopressor dose and  (cumulative) fluid balance | Association between small and large bowel diameter/wall thickness (US/CT) and vasopressor dose/cumulative fluid balance | Vasopressor dose difficult to quantify in patients receiving different vasopressors. A priori agreement on the definition of vasopressor dose and (cumulative) fluid balance |
| 18: BA-MA | To validate bile acid signaling molecules as biomarkers for malabsorption | Prospective, multicenter observational study | MV ICU pt expected stay for >=3 days | | Measurement of biomarkers (serum BA, FXR, FGF-19). 3-OMG. Cholestasis-parameters,  BOMB-calorimetry | Association between BAs (and regulators/ligands) and malabsorption. Associations between clinical symptoms and bile acid metabolites | Timing of measurements to be defined.  Definition/reference standard for malabsorbtion of different macronutrients needed. |
| 19: GI and IAP | Which GI symptoms \* should trigger IAP measurements?  Which IAP values should trigger specific monitoring of GI? | Post-hoc analysis of combined databases (prospective observational) | Patients in performed studies IROI, iSOFA)? | | identification and merging of existing databases (iSOFA, IROI, others?) | Association of GI symptoms with IAH, mesenteric ischemia and mortality |  |
| 20: Opioid-antagonists for bowel paralysis | Do opioid antagonists reduce time to defecation and GI symptoms?  (Validate opioid antagonists for constipation in ICU)  Potential substudy: study the impact on intestinal absorption | Multicenter RCT | Adult ICU patients with opioid requirement above a minimal dosage | Methylnaltrexone vs Placebo.  Other opioid antagonists. | | Time to first defecation  COS #  Diarrhoea  GI symptoms \*  (Absorption)  Infections |  |

**Abbreviations**

*α-GST – α-glutathione S-tranferase*

*AA – amino acids*

*AGI – acute gastrointestinal injury*

*BA – bile acids*

*CH - carbohydrate*

*COS – core outcome set for studies on GI (dys)function*

*CRP – C-reactive protein*

*CT – computed tomography*

*EN – enteral nutrition*

*FGF-19 - Fibroblast Growth Factor 19*

*FI – feeding intolerance*

*FXR – Farnesoid X receptor*

*GI – gastrointestinal*

*GRV – gastric residual volume*

*IAH – intra-abdominal hypertension*

*IAP – intra-abdominal pressure*

*IC – indirect calorimetry*

*ICU – intensive care unit*

*I-FABP – intestinal fatty acid binding protein*

*IL - interleukin*

*LOS – length of stay*

*MV – mechanical ventilation*

*NOMI – non-occlusive mesenteric ischemia*

*PN – parenteral nutrition*

*PPI – proton pump inhibitors*

*RCT – randomized controlled trial*

*RT PCR – real time polymerase chain reaction*

*SMA – smooth muscle actin*

*SOFA – sequential organ failure assessment*

*TNF – tumor necrosis factor*

*US – ultrasound*

*3-OMG - 3-O-methylglucose*

*\* GI symptoms include vomiting/regurgitation, abdominal distension, GI bleeding, diarrohea, bowel paralysis,. Expanded (if performed/possible to assess): nausea, abdominal pain, absence of bowel sounds, large GRV (>500 ml/6h), bowel dilatation (radiological), bowel wall thickening/bowel edema (radiological) 1,2*

*# Core outcome set (COS) to be identified in consensus process*

1. Reintam Blaser A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, Braun JP, Poeze M, Spies C. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 2012 Mar;38(3):384-94. doi:10.1007/s00134-011-2459-y
2. Reintam Blaser A, Starkopf J, Moonen PJ, Malbrain MLNG, Oudemans-van Straaten HM. Perioperative gastrointestinal problems in the ICU. Anaesthesiol Intensive Ther. 2018;50(1):59-71. doi: 10.5603/AIT.a2017.0064