Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Role of endoscopy in hepatology

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ARTICLE INFO

Article history:
Received 20 November 2023
Accepted 27 November 2023
Available online xxx

Keywords:
Endo-hepatology
ERCP
Cirrhosis
Portal hypertension
Cholangioscopy
Cirrhosis gastro-esophageal varices
Endoscopic ultrasound

ABSTRACT

The growing and evolving field of EUS and advanced hepatobiliary endoscopy has amplified traditional upper gastrointestinal endoscopy and unveiled novel options for remaining unsolved hepatobiliary issues, both diagnostically and therapeutically. This conceptually appealing and fascinating integration of endoscopy within the practice of hepatology is referred to as 'endo-hepatology'. Endo-hepatology focuses on the one hand on disorders of the liver parenchyma and liver vasculature and of the hepatobiliary tract on the other hand. Applications hanging under the umbrella of endohepatology involve amongst others EUS-guided liver biopsy, EUS-guided portal pressure measurement, EUS-guided portal venous blood sampling, EUS-guided coil & glue embolization of gastric varices and spontaneous portosystemic shunts as well as ERCP in the challenging context of (decompensated cirrhosis) and intraductal cholangioscopy for primary sclerosing cholangitis. Although endoscopic proficiency however does not necessarily equal in an actual straightforward end-solution for currently persisting (complex) hepatobiliary situations. Therefore, endohepatology continues to generate high-quality data to validate and standardize procedures against currently considered (best available) "golden standards" while continuing to search and trying to provide novel minimally invasive solutions for persisting hepatological stalemate situations. In the current review, we aim to critically appraise the status and potential future directions of endo-hepatology.
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1. Endo–hepatologfy: where hepatology meets endoscopy!

The overall burden of liver disease is on the rise, causing over 2 million deaths annually, accounting for 1 out of every 25 deaths worldwide and making liver disease the 11th leading cause of mortality [1–3]. Never has the global call for awareness, recognition and management of liver diseases been so loud as in recent years and even with a challenge to make a paradigm shift from tackling liver disease to protecting liver health [3–5]. As a result, hepatologists are striving to enhance means of detection and intervention for liver disease. Endoscopy has always formed a backbone in diagnosis and management of hepatobiliary disorders and their complications. So, it is not surprising that with evolving aspirations of the liver community, the number of endoscopic procedures relevant to patients with liver disease have significantly increased and diversified in terms of indications and applications over the last decade. The growing interest in endoscopic ultrasound (EUS) and advanced endoscopy in gastroenterology has largely fueled and cross-contamined the 'endoscopic liver rush' [6–9]. "Endo-hepatology" is the modern, comprehensive term used to designate the integration of "advanced endoscopy" within the practice of hepatology [7–10]. Fundamentally, endo-hepatology is based on two pillars: the first one addresses disorders of the hepatobiliary tract which are captured via endoscopic retrograde cholangiopancreatography (ERCP), EUS and advanced intrabiliary imaging via cholangioscopy, while the other focuses primarily on disorders of the liver parenchyma and hepatic vasculature which are mainly mastered via EUS. Applications under the umbrella of endo-hepatology include, amongst others, ERCP in cirrhosis, PSC and for posttransplant-complications, EUS-guided liver biopsy, EUS-guided portal pressure gradient measurement as well as EUS-guided coil and glue embolization of gastric varices.

In addition to its conceptually attractive technical and innovative characteristics, "endo-hepatology" is also an appealing practical option for daily practice as many of these interventions can be offered as a "one-stop-clinic" concept where all comprehensive endoscopic diagnostic and/or therapeutic testing is performed in a

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https://doi.org/10.1016/j.dld.2023.11.032
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Please cite this article as: W. Laleman, K.-H. Peiffer, M. Tischendorf et al., Role of endoscopy in hepatology, Digestive and Liver Disease, https://doi.org/10.1016/j.dld.2023.11.032

single procedure and outpatient visit [7–9]. In the following paragraphs, we aim to review the status and potential future directions of endo-hepatology.

2. Endoscopic focus on the hepatobiliary tract

The prospect of visualisation and intervention in the biliary tree has intrigued endoscopists for decades [11,12]. ERCP, since its introduction in 1968 by Dr William S. McCune (an obstetrician by the way), has become a pivotal endoscopic intervention for managing hepatobiliary and pancreatic diseases. Although initially merely introduced for diagnostic purposes, the first therapeutic ERCP, an endoscopic sphincterotomy, was independently performed and reported in 1974 by Kawai et al. [13], Classen and Demling [14] and Sohma et al. [15]. Ever since, endoscopes, accessories and specific skillsets have undergone tremendous leaps forward and was further revolutionized by the addition of EUS. Nowadays ERCP and EUS are undeniably intertwined as part of the integrated approach to biliopancreatic disorders, both diagnostically and therapeutically, and are therefore often referred to as EUSRCP [8,9,11,16]. Meanwhile, a myriad of internal biliary drainage techniques facilitated by EUS-assisted biliary access have expanded our options, in addition to percutaneous approaches, with similar or even improved efficacy, safety and tolerance, which are extensively discussed elsewhere [16]. For hepatologists, biliary interventions in patients with cirrhosis and for post-transplant biliary complications as well as diagnostic and endo-therapeutic challenges in primary sclerosing cholangitis (PSC) form the most substantial interface between hepatology and endoscopy [8-10,17-19].

2.1. ERCP in cirrhosis

In daily clinical practice, patients with cirrhosis may occasionally require advanced procedures such as ERCP. In these situations, clinicians need to balance meticulously risks and benefits of such procedures as they potentially could trigger acute decompensation, acute-on-chronic liver failure (ACLF) or death [20].

2.1.1. Cirrhosis: a risk factor for gallstones

Cirrhosis poses a risk factor for gallstone development as it doubles its prevalence in comparison with the general population (26.4% vs 13.4%) [21]. The increased risk relates to *altered bile composition* during cirrhogenesis via reduced bile acid synthesis, diminished cholesterol secretion and increased hydrolysis of conjugated bilirubin leading to increased pigment lithogenesis, *enhanced crystal nucleation* leading to increased cholesterol lithogenesis, *gallbladder wall thickening and hypomotility* [21]. Moreover, the risk increases with age, severity of liver disease and – strangely enough – male gender. If we review trends of ERCP utilization and outcomes in decompensated cirrhosis, a recent American study, using the National Inpatient Sample database, showed a significant increase in ERCP utilization (+218% from 2000 to 2013) in patients with decompensated cirrhosis, mainly for common bile duct stones or complications hereof which considering the previous is not surprising [22]. Of additional interest, the study also noted a nearly complete elimination of ERCP as a diagnostic procedure and a decrease in overall in-hospital mortality among patients with decompensated cirrhosis undergoing ERCP (from 13.9% in 2000 to 9.8% in 2013) [22]. Factors affecting mortality include older age, the presence of sepsis, hepatic encephalopathy and comorbidities which clearly impact on an already fragile patient population.

2.1.2. ERCP in cirrhosis: 'risky business' or 'just do it'?

A multicenter, retrospective, matched-cohort study, including 441 ERCPs performed in 158 patients with cirrhosis, highlighted that complications, such as cholangitis, post-sphincterotomy bleeding and post-ERCP-pancreatitis, developed significantly more frequently compared to patients without cirrhosis (overall 17 vs. 10%; cholangitis 6 vs. 2%; post-sphincterotomy bleeding 9 vs. 3%) [23]. More dramatically, post-ERCP adverse can trigger ACLF in cirrhotic patients. Overall, the rate of post-ERCP ACLF development is 11% within the first month with a 3-times higher risk for patients with a MELD of $\geq$ 15 [23]. Even though most of the ACLF episodes are mild (grade 1, 55%), the overall 30-day mortality amounts as high as 44% [23]. This is not surprising since the PREDICT study showed that bacterial infections (cholangitis) and GI bleedings (post sphincterotomy bleedings) are 2 of the main precipitating events for ACLF [24]. Of note, some cirrhotic patients undergoing ERCP developed ACLF without first getting typical post-ERCP complications suggesting that the invasive nature of the procedure itself can trigger an episode of ACLF, probably by causing subclinical bacterial translocation from the bile microbiome [25]. Overall, the rate of post-ERCP ACLF development is 11% within the first month with a 3-times higher risk for patients with a MELD of $\geq$ 15 [23]. Even though most of the ACLF episodes are mild (grade 1, 55%), the overall 30-day mortality amounts as high as 44% [23].

What does this imply for the endoscopist considering an ERCP in a cirrhotic patient? First, when the indication is strong, for instance after confirmation of gallstones via MRCP or EUS pre-ERCP, the benefit of ERCP always outweighs the risk. Secondly, these patients are managed by a multidisciplinary inpatient cirrhosis care team with dedicated liver ICU and transplant facilities. A general overview of pre- and periprocedural preventive practices are summarized in Table 1 [26–31]. Antibiotic prophylaxis merits some more clarification. Bacterial infections are diagnosed in 40% of in-hospital cirrhotic patients and lead to a minimal four-fold increase in mortality. Moreover, sepsis and bacterial infection are recognized as distinct precipitants of ACLF and therefore contribute to the high mortality. Considering the high sepsis rate of 10.5% after GI endoscopy in decompensated cirrhotic patients waiting for liver transplantation, one could argue to consider antibiotic prophylaxis as this was shown to reduce the risk by 92% in a recent single-center series [23,30]. In terms of procedural technical considerations, endoscopic sphincterotomy should be executed cautiously given the almost 3-times higher risk of post-sphincterotomy bleeding in comparison to the general population [23]. Alternatively, sphincteroplasty via transpapillary large balloon dilatation can be preferred as it reduces the risk by a factor 2 [32]. Endoscopists should remain vigilant about periampullary or intraductal varices, as these may lead to severe and substantial bleedings, typically necessitating a covered transpapillary metallic stent for immediate hemostasis [33].

2.2. ERCP in PSC

Endoscopic interventions in PSC are performed for both diagnostic and therapeutic purposes. In case of cholestatic symptoms (new onset jaundice, cholangitis, hepatogenic pruritus), worsening liver tests or an increase in CA19.9 levels, diagnostic assessment should primarily be performed by use of non-invasive imaging via MRCP [34]. In case of detection of a new or worsening biliary stricture(s) or enhancing mass lesion, endoscopic appraisal via ERCP should be considered. To replace confusing terms such as "high grade" or "dominant" strictures, recent consensus introduced the term "relevant strictures" to denote a high-grade biliary stricture (defined as $a > 75\%$ reduction of duct diameter) on imaging in the common bile duct or hepatic ducts *with* functional impairment such as signs or symptoms of obstructive cholestasis and/or bacterial cholangitis [34,35]. The prevalence of high-grade strictures amounts to 50% in PSC patients and always harbors the intrinsic risk of a cholangiocarcinoma [36–39]. Indeed,

Table 1
General overview of pre- and periprocedural preventive practicesb before ERCP in patients with cirrhosis.

Extensive informed consent (risk benefit)
Routine INR, platelet, kidney function (baseline)
Correction of coagulation factors and thrombocytes:
• Correction of a prolonged INR with FFP, prothrombin complex concentrate or tranexaminic acid is not recommended before the procedure
• Usof a TPO-R agonist or routine infusion of platelet concentrate
◦ should not routinely be performed when platelet count is $> 50 \times 10^9$/L.
◦ may be considered on a case-by-case basis when the platelet count is between 20 and 50×10^9/L,
◦ should be considered when platelet count is $< 20 \times 10^9$/L
Consider traditional **ERCP prophylactic measures** (hyperhydration, rectal indomethacin, prophylactic pancreatic stenting) *on a case-by-case basis*
Consider non-opioid **pain killers** (paracetamol max 2–3 g/d)
Sedation
• avoid benzodiazepines & narcotic (fentanyl) sedation
• Options for sedation:
• Propofol: sedative of choice
• general anaesthesia, physician-driven or *monitored anaesthesia care sedation*
Antibiotic prophylaxis: no formal recommendation (see text)

cholangiocarcinoma is one of the main life-threatening complications of PSC if one considers a 20%-lifetime risk with half of the diagnoses being made within the first year after diagnosis of PSC. It can appear at any stage of the disease, independent of the presence of cirrhosis [37–39]. Diagnosis is always challenging as the clinical spectrum largely overlaps with relevant fibroinflammatory strictures and non-invasive cross-sectional imaging lacks sensitivity and specificity to confidently rule in or out tumor. From that perspective, every relevant or high-grade stricture should be considered malignant, unless proven otherwise. If one honors such a dogma, this implies tissue sampling or direct in-situ evaluation. In the following paragraph, we will discuss current and potential future endoscopic means to optimize tissue evaluation. Traditional ERCP techniques involve tissue sampling via brushing cytology and/or fluoroscopy-guided intraductal biopsies but lack satisfactory sensitivity (27–44%) and accuracy (39–54%) [12,40–44]. Adding fluorescence in situ hybridization (FISH) to detect polysomy to the cytopathological evaluation of the traditionally obtained tissue only marginally improved sensitivity to 51% [45]. As a result, other ERCP-based modalities have been explored. Much was expected of single-operator cholangioscopy as it allows direct visualization and visually targeted biopsies [46,47]. Expectations were however quickly toned down for visual assessment of high-grade strictures after a study by the European Cholangioscopy Group which revealed low sensitivity (72.7–74%) and specificity (46.9–62.5%) for mere visual appraisal of high-grade strictures, both blinded and unblinded to clinical context [48]. When comparing ERCP with brushing cytology or FISH, confocal laser endomicroscopy and single-operator cholangioscopy with targeted biopsies in meta-analysis, single-operator cholangioscopy with targeted biopsies appeared to be the most accurate ERCP-based modality for diagnosing cholangiocarcinoma with a sensitivity of 65% and accuracy of 96% [42]. Refining visually targeted tissue sampling therefore may be the most important contribution of cholangioscopy in stricture evaluation in PSC for now and a platform to be further exploited. Complementing FISH to pathological evaluation of visually obtained biopsies increases sensitivity by 10–15% but remains unsatisfactory and was even questioned in the specific context of PSC [49,50]. Of interest, implementation of next-generation sequencing mutation analysis on biliary brush cytology was reported to detect oncogenic mutations with increased sensitivity (75%) and specificity (85%) and might represent a valuable future accessory but requires further validation [51]. New imaging technologies directed at evaluating biliary strictures in vivo, such as optical coherence tomography, intraductal ultrasound-Mini probes or probe-based confocal laser endomicroscopy, were shown to have high sensitivity but have not progressed due to associated costs, lack of validation or technical anatomical limitations [52–54]. A growing field which is shortly expected to impact further on optimized performance is the integration of *artificial intelligence* [55,56]. Some of the most advanced attempts within endo-hepatology involve characterization of indefinite biliary strictures [57] and focal liver lesions [58] as well as enabling fluoroscopy to minimise radiation exposure during fluoroscopy-guided endoscopic procedures [59].

In terms of intervention, endotherapy should be considered for relevant strictures, i.e., high-grade strictures regarded as the cause of complications such as bacterial cholangitis, evolving cholestasis with/without icteric decompensation and refractory hepatogenic pruritus and/or suspected cholangiocarcinoma. It is important to realize that ERCP in PSC is associated with higher risks, reported in up to 18%, such as perforation, cholangitis, and pancreatitis, which are highest after first ERCP and sphincterotomy [60]. Stringent preventive measures such as hyperhydration and prophylactic antibiotics must be implemented. Regarding stricture management, the choice between balloon dilatation vs short-term stenting was left to the endoscopist's discretion in the EASL-ESGE guidelines of 2017 [44]. A recent randomized trial demonstrated no superiority of short-term stent placement vs mere balloon dilatation with regard to recurrence-free rate but reported increased risk of serious adverse events such as pancreatitis and bacterial cholangitis in the stent group [61]. Therefore, if stents are applied for example because of contrast retention, they should be removed within 2–4 weeks after placement. Patients with severe acute cholangitis and high-grade bile duct strictures are at high risk of mortality and require urgent biliary decompression in addition to conventional medical therapy. From the above, there's no one-size-fits-all approach in PSC endotherapy, and decisions should be made in collaboration with tertiary care centers considering the broader therapeutic perspective including liver transplantation.

2.3. ERCP in post-transplant biliary complications

Biliary complications, most often strictures, are frequently encountered after liver transplantation. These strictures are classified as anastomotic (AS) or non-anastomotic (NAS). Intervention for these strictures is nowadays almost exclusively managed via ERCP with balloon dilatation and progressive stenting managed via stent exchange programs with success rates for AS up to 94% and NAS up to 50% [62,63]. For exhaustive review, the reader is referred elsewhere [64–66].

2.4. Duodenoscope-related infections: single-use endoscopes for an increasingly surfacing threat?

An unfortunate escalating threat over the last years for patients undergoing ERCP, especially for cirrhotic, PSC and transplant-

patients, are duodenoscope-related infections with emerging multi-drug resistant bacteria despite all efforts to optimize disinfection protocols [67]. A recent systematic review revealed a contamination rate of 15% despite reprocessed patient-ready duodenoscopes [68]. Single-use duodenoscopes could represent a potential alternative avenue to circumvent the problem of reprocessing and thus risk of exogenous patient-to-patient transmission. These devices are currently first-generation designs but were found to be safe, accommodating and adequately performing over a broad range of ERCP procedures [67,69]. Nevertheless, further technical optimization, cost-effectiveness and ecological sustainability remains to be pursued [67,70].

3. Endoscopic focus on liver parenchyma and vasculature

In addition to endoscopic applications for hepatobiliary disorders, endohepatology also addresses disorders related to the liver parenchyma and vasculature. One of the most traditional endoscopic procedures in this context involves screening and treatment for gastro-oesophageal varices and related bleeding whereas the recent introduction of EUS has opened a whole new world of possibilities for liver-related issues. The reason for this latter is five-fold. Firstly, EUS has evolved from a mere diagnostic to a mature therapeutic modality. Secondly, it is increasingly applied within gastroenterology and has therefore become more and more integrated, and thus accessible, within everyday GI practice. Thirdly, there is a flourishing sprawl of techniques and device platforms which knows an inimitable expansion in terms of applicability. Thirdly, there is an expansive growth in techniques and device platforms, significantly broadening its range of applications. Fourthly, the evolving liver disease landscape presents both unresolved needs and novel challenges. Fifthly, the endohepatology concept is a conceptually and practically attractive option as extensive comprehensive diagnostic testing can be combined with endoscopic intervention in a single outpatient visit. Finally, pursuance of assessment and treatment of liver disease and portal hypertension is assimilated by the liver/gastrointestinal specialist him/herself [7–9].

3.1. Conventional endoscopy for gastro-oesophageal varices

Until recently, upper endoscopy was systematically advocated in patients with newly diagnosed cirrhosis and for surveillance thereafter in case of absence or presence of merely low risk varices (Fig. 1, left panel). This dogma was fueled by the morbidity and mortality associated with gastro-oesopheal variceal hemorrhage which still amounts to 10–20% within 6 weeks after the index bleeding [71–75]. The emergence of serum fibrosis markers and liver stiffness measurement (LSM) via vibration controlled transient elastography as non-invasive tools to assess liver fibrosis and cirrhosis were instrumental in challenging the considered irrefutable dogma of systematic endoscopic screening. The BAVENO VI consensus conference was the first to propose a non-invasive two-step strategy, referred to as the “BAVENO VI criteria” to make endoscopic screening conditional. Patients with newly diagnosed compensated advanced chronic liver disease (cACLD), the term now commonly used to capture patients with chronic liver disease at risk of developing clinically significant portal hypertension (CSPH) and defined as an LSM $>$ 10 kPa, can safely avoid screening endoscopy if they comply with a LSM $<$20 kPa combined with a platelet count $>150 \times 10^9$/L. In this scenario, 14% endoscopies can be spared at the cost of missing varices needing treatment (VNT) in 3% [76,77]. This algorithm has meanwhile globally been validated and endorsed across different etiologies [78]. Conversely, attempts at expanding these criteria were shown to undermine its negative predictive value [77,78]. Decompensated and recompensated patients, which per definition encompass CSPH, are beyond the scope of this algorithm and still require endoscopic screening [73]. The implementation of spleen stiffness might probably enhance the existing algorithm, although this remains to be further explored. Inspired by the PREDESCI study, the BAVENO VII consensus meeting aspired to thrust the BAVENO VI concept to the next level by taking on the broader concept of ‘prevention of decompensation’ and initiation of non-selective beta-blockers in patients at risk of decompensation, and thus beyond mere prevention of GOV bleeding [73,79]. Although the “rule of five” for LSM is proposed as the tool to stratify the risk of liver related events and amongst others to rule in (LSM $>$ 25 kPa) and rule out (LSM $\langle$ 15 kPa and platelet count $\rangle$ 150 $\times$ 10^9/L) CSPH in patients with viral hepatitis, alcoholic and non-obese steatotic liver disease, it still needs further refinement given that fact 40–50% of patients are left in a diagnostic grey zone [80,81]. Moreover, broad dissemination, acceptance and large-scale practical implementation of this novel concept remains far from daily clinical reality according to a recent survey [82]. The current BAVENO VI-VII algorithm is graphically summarized in Fig. 1 (right upper panel).

The suspicion of acute variceal bleeding implies the immediate rollout of an algorithm that includes safeguarding vital parameters, initiation of fluid resuscitation, prophylactic antibiotics, and vasoactive drugs, after which endoscopy to obtain hemostasis should be pursued as soon as possible after initial stabilization but within a 12-hour window after index bleeding. The early integration of transjugular intrahepatic portosystemic shunt (TIPS), either as rescue or pre-emptive, should also be considered. An up-to-date algorithm is depicted in Fig. 1 (lower right panel) and discussed in detail elsewhere [75,83].

3.2. EUS-guided applications

3.2.1. EUS-guided elastography

Chronic liver diseases are silent killers and cover a spectrum of minimal to advanced fibrosis and finally cirrhosis. Risk stratification is therefore of the utmost importance not only to inform the patient but also guide intervention, follow up, prevention of complications and prognostication. For a long time, (repeated) liver biopsies were one of the main trades of the hepatologist. This is now gradually taken over by transabdominal elastography which is truly becoming the “virtual” biopsy. Vibration-controlled transient elastography (VCTE) has taken an indispensable and instrumental position herein given its potential to quantify liver stiffness and correlate this measurement to the stage of liver disease but also to rule out/in CSPH [84].). However, these transabdominal elastography devices may be less accurate in certain conditions such as ascites, thick subcutaneous fat, narrow intercostal spaces, and hepatic atrophy. Recently, quantitative EUS-shear wave elastography (EUS-SWE) has also surfaced in clinical hepatological practice [85,86]. In 2023, the first published prospective tandem study comparing EUS-SWE with VCTE in 42 consecutive patients, with liver biopsy as gold standard reference, showed that EUS-SWE was feasible in all patients whereas VCTE was unreliable in 8 patients [86]. In the patients with paired data, AUROCs for advanced fibrosis and cirrhosis were equivalent for VCTE and right- and left-lobe EUS-SWE [86]. This first experience potentially sets the stage for extrapolation of the dogmatical BAVENO “rule of 5″, provided it gets validated [73]. It is unlikely that EUS will be performed exclusively for the purpose of SWE given the less invasive and costly transabdominal elastography applications Instead EUS-SWE should/could be considered as an adjunctive decision-making tool in more complex cases where an endoscopic multiparamet-

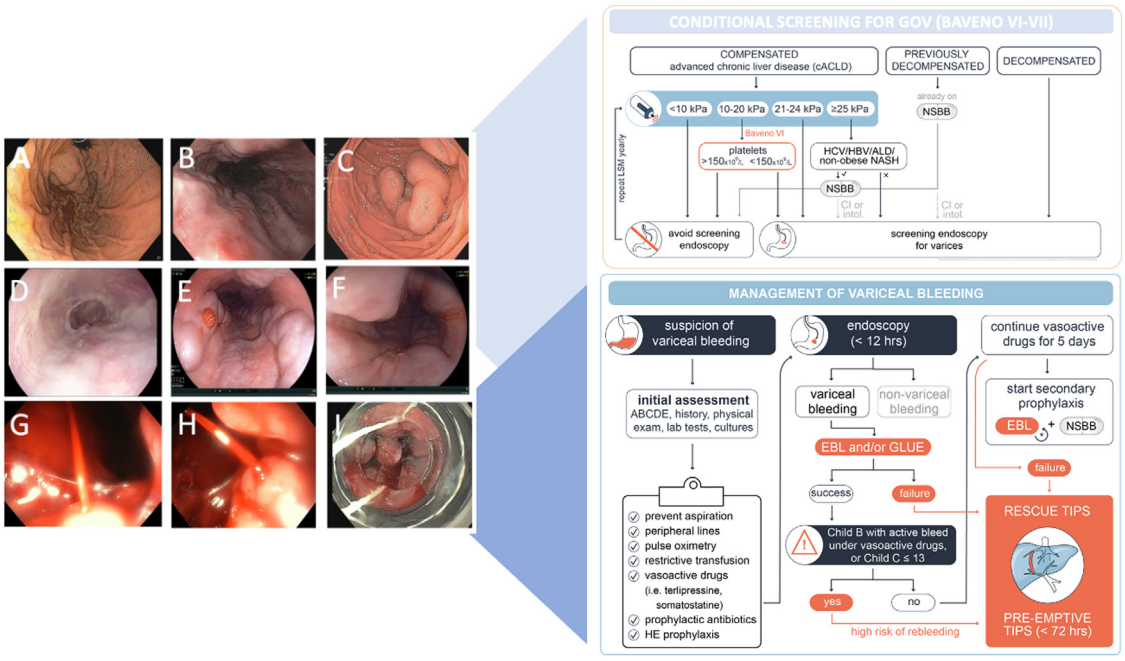

Fig. 1. Endoscopic view of various upper gastrointestinal varices (A. fundic varices (IGV1), B. oesofageal varices grade 2 with red spots, C. Ectopic duodenal, D–F. oesofageal varices grade 1 (D), grade 2 (E) and grade 3 (F), G–H. spurting oesofageal variceal bleeding, I. Endoscopic band ligation of oesofageal varices with haemostasis) combined with an updated algorithm for screening of varices (upper right panel) and management of acute upper gastrointestinal variceal bleeding (lower right panel).
Abbreviations: IGV-1: intragastric varices type 1, NSBB: non-selective beta blockers; CI: contraindications; intol: intolerance; EBL: endoscopic band ligation; TIPS; transjugular intrahepatic portosystemic shunt.

ric approach, including GOV screening, EUS-guided liver biopsy and portal pressure measurement, might be necessary.

3.2.2. EUS-guided liver biopsy (EUS-LB)

Despite the coup of elastography, there always will be a need for liver tissue. The staging of fibrosis may largely be taken over via an elastographic "virtual biopsy", but a histological identification upon of an unclear clinical diagnosis and - probably more relevant in due time – is the necessity for additional high-throughput omics [87]. This holds true for metabolic dysfunction associated steatotic liver disease (MASLD). A recent single center analysis of trends in liver biopsy practice revealed a non-surprising shift of indication toward MASLD and at the same time a notably (and counterintuitively) increased liver biopsy volume, with EUS guidance (80%) as the most common approach for liver biopsy [88]. Comparative studies have demonstrated that both endoscopic and non-endoscopic approaches (percutaneous, transjugular, CT-guided) are similar in terms of diagnostic yield (95% for EUS-LB), accuracy (94% for EUS-LB), and adverse events (9.7% of for EUS-LB of which 8.8 related to self-limiting abdominal pain) [88–92]. Yet in comparison to other means, EUS-LB offers the advantage of a lower perceived apprehension by the patient (facilitated by the standard use of sedation, lower post-procedural discomfort, and reduced recovery time). Additionally, EUS-LB enables bilobar sampling (minimizing sampling error), real-time ultrasound and doppler monitoring and elastography as well as the option to combine it with evaluation of biliopancreatic tract, measurement of portal pressure and/or eradication of GOV in the same procedure which would make it cost-effective [7-9,93]. This approach might prove particularly useful in morbidly obese and uncooperative patients or in case of intercurrent cystic or vascular lesions. The current technical state of the art realisation of an EUS-LB involves the use of a 19 G needle (preferably Franseen type), implementation of the "wet heparinised" suction technique, a minimum of 3 actuations when moving the needle to-and-fro intrahepatically and specific tissue handling via a tissue sieve or cassette before transferring it into fixation solution

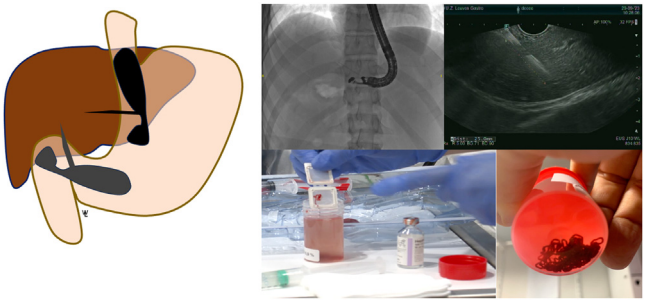

Fig. 2. Bilobar EUS-guided liver biopsy (cartoon left-side): Fluoroscopic image of EUS-guided intrahepatic entry of the FNA-needle (upper left panel), sonographic image of the biopsy needle trajectory over 25 mm (upper right panel), capturing the liver core directly on a tissue cassette and transferring into the recipient (lower left panel) and the overall amount of tissue obtained at EUS-LB (lower right panel).

[7-9,93-96]. A schematic illustration and stepwise representation are summarized in Fig. 2.

3.2.3. EUS-guided portal pressure gradient measurement (EUS-PPG) (Fig. 3)

CPSH, defined as a hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, is established as the main driver in the development of GOV and other PHT-related decompensations. Therefore, it is decisive in terms of prognosis and thus prompts diagnosis, intensified management, and follow-up.

Identifying, and thus measuring CSPH, has traditionally been performed by HVPG which reflects an indirect portal pressure measurement via transvenous hepatic vein catheterization. Although HVPG is the considered gold standard technique, it has several downsides. First, it concerns an interventional radiological skill set which requires radiation and contrast and is usually limited to dedicated liver centers. Secondly, HVPG only captures disorders with sinusoidal portal hypertension and thus overlooks

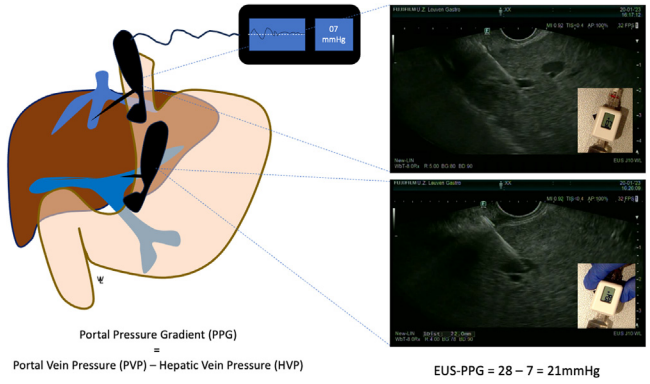

Fig. 3. EUS-portal pressure gradient measurement procedure with first puncture of the middle hepatic vein (ultrasound image upper right panel) and thereafter portal vein (ultrasound image lower right panel).

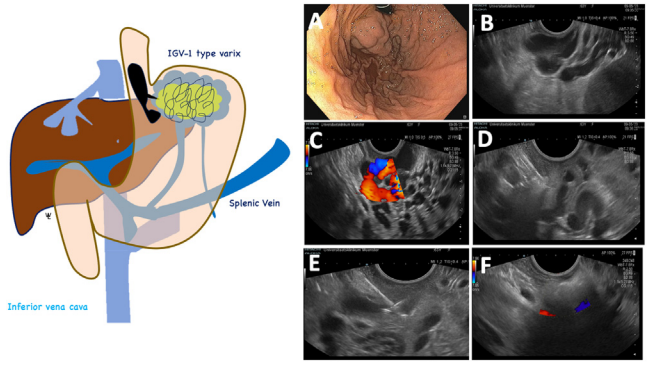

Fig. 4. Exemplary EUS coiling and glue of fundal gastric varices (cartoon left -side) with step-by-step approach: identifying gastric varix on endoscopic retrovision (A), endosonographic correlate of the gastric varix (B), with Doppler (C), inserting a coil (arrow) into the varix under EUS-guidance (D), injecting glue after coil insertion (E), and confirming obliteration via doppler (F).

causes of presinusoidal origin such as patients with portosinusoidal vascular disorder (PSVD) who display non-cirrhotic portal hypertension [97,98]. Moreover, in MASLD, one of the currently leading global causes of chronic liver disease, the discriminatory accuracy of HVPG has been challenged [99]. Thirdly, excessive veno-ovenous shunting, reported up to 36.5% of patients with cirrhosis [100], may lead to a false negative read out of the wedge pressure. Following further on the path of non-invasive testing, BAVENO VII has suggested that an LSM > 25 kPa in patients with virus- and/or alcohol-related compensated advanced chronic liver disease (cA-

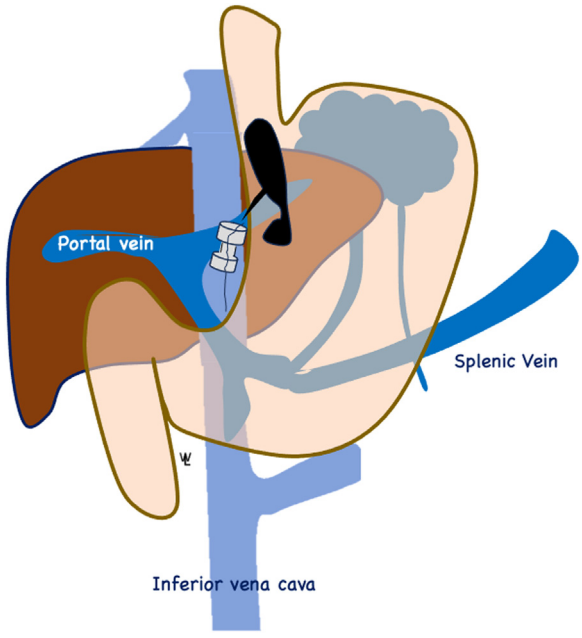

Fig. 6. EUS-guided intrahepatic portosystemic shunt (EUS-IPSS). EUS-guided transgastric creation of an iatrogenic shunt between the portal vein and inferior vena cava using a lumen-apposing metal stent in experimental animal models.

CLD, LSM ≥10 kPa) and non-obese (BMI <30 kg/m^2) MASH-related cACLD is sufficient to rule in CSPH (specificity and positive predictive value >90%) whereas an LSM ≤15 kPa plus platelet count ≥150 × 10^9/L rules out CSPH (sensitivity and negative predictive value >90%). Nevertheless, 45.7% of an Austrian cohort of patients with evidence of cACLD and simultaneous HVPG measurement were unclassifiable according to the earlier mentioned BAVENO VII criteria [101]. Taken together, all these elements clearly indicate an unmet need for alternatives to assess CSPH. EUS-guided portal pressure gradient (EUS-PPG) measurement may represent such a viable alternative given the fact that EUS is highly integrated within most GI practices, it overcomes most of the shortcomings of HVPG given its direct portal pressure assessment and involves a skillset that is basic competency for an endosonographer [7-10,102].

The technique involves directly measuring intravascular pressure by taking advantage of the proximity of the portal and hepatic vein to the tip of the EUS-scope in the stomach guiding a transgastric transhepatic puncture in real-time with an FNA-needle

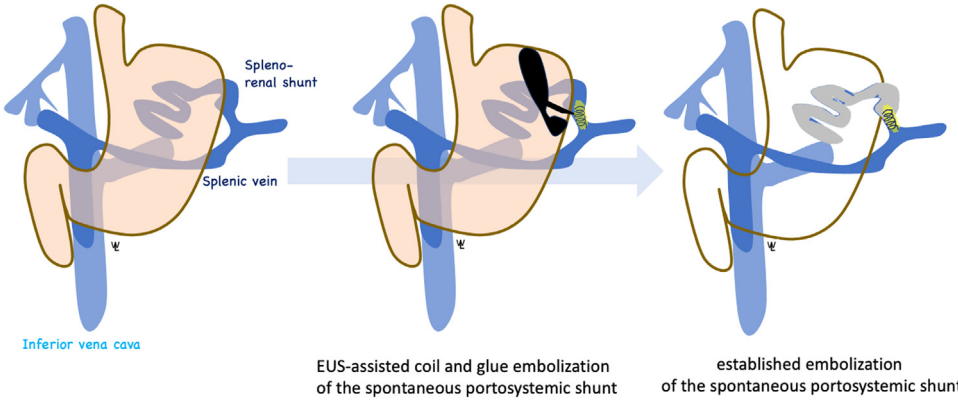

Fig. 5. EUS-guided transgastric portosystemic shunt obliteration. Schematic representation of splenorenal shunt (left panel), identification of the splenorenal shunt via EUS and application of combined coil & glue embolization (middle panel), established embolization of the spontaneous portosystemic shunt (left panel).

connected to a manometer. The gradient represents the subtraction of the portal vein pressure by the hepatic venous pressure. The feasibility of EUS-guided portal vein catheterization by using a 22-gauge FNA needle was studied and reported for the first time in 2004 in 7 normal and 14 portal hypertensive pigs [103]. An improved platform, using a 25 G needle, confirmed to correlate with HVPG in a porcine model in 2016 [104] and was shown feasible and safe in a consecutive human pilot [105] followed by real-life cohorts [106–108] after which it was FDA-approved. Except for one series in 12 patients with Budd-Chiari or sinusoidal obstruction syndrome, there are no reports of paired simultaneous correlation of EUS-PPG to HVPG [109]. Currently in Europe, the ENCOUNTER-study (NCT 04987034) is ongoing and studies the correlation of simultaneously performed HVPG with EUS-PPG in real-time in patients with cirrhosis. If EUS-PPG is confirmed to provide an accurate read-out of portal pressure, further standardization of EUS-PPG protocols will be required, one of them being sedation given the proven impact of moderate to deep sedation on HVPG measurements [110]. Low-dose midazolam (0.02 mg/kg) or fentanyl (1.0mcg/kg) could be considered given data that these approaches do not interfere with PPG [111,112].

3.2.4. EUS-guided treatment of gastric varices (Fig. 4)

Bleeding gastric varices remain one of the most dreadful complications of portal hypertension and an endoscopic stalemate [113,114]. The conventional first-line endoscopic treatment for fundal and isolated gastric varices involves direct, albeit untargeted, endoscopic injection of cyanoacrylate, a tissue adhesive ("glue"). This technique was described by Soehendra in the 80′s and that time was perceived as a revolution [115]. Forty years later, this technique is still widely applied and considered the (best available) golden standard with hemostasis rates between 58 and 100%, rebleeding rates between 0 and 40% at the price of an embolic risk of 4% reported in initial cohorts [116,117]. These technical drawbacks have remained unchanged over time and relate in essence to the mutual reinforcing combination of an untargeted (some would call it "blind") nature of the conventional endoscopic approach on the one hand and the underappreciated complexity of the vascular anatomy of the culprit gastric varix [118]. Indeed, gastric varices consist of a large submucosal component with different feeding and draining vessels characterized in detail in different afferent and efferent venous in- and outflow types described by Kiyosue et al. [119]. As a result, and not surprisingly, there are reports showing that up to 60% of the conventionally injected glue was located para-variceal [120], incomplete obliteration (or residual patency after initial treatment) expedited rebleeding [121] and higher amounts of glue aliquots (> 4.3 mL range 2,5–8 mL) [122] are required which in turn increase the embolic risk typical of this intervention. An EUS-guided approach overcomes all these issues as EUS not only allows precise targeting of the vessels responsible for feeding the gastric varix but also directly monitors, via Doppler, the effect of therapy on variceal flow in real time, as well as the theoretical risk of embolization [118,123]. In addition to EUS-guidance, the combined application of vascular platinum coils (preferably with synthetic strands), which serve as a scaffold, with glue upgraded our game against gastric varices [118]. Binmoeller et al. [123] were the first to report on this combined EUS-guided approach initially as a rescue strategy and later as a worthy, and even superior, alternative. Meanwhile, several series, and even meta-analysis, have supported the durable effects of EUS-guided coil and glue in acute hemostasis or secondary prophylaxis [124–127]. EUS-guided therapy combining coil and glue demonstrated higher clinical efficacy for treatment of gastric varices in terms of obliteration (86% vs 62% for conventional endoscopy), recurrence (5% vs 18%) and long-term bleeding (9% vs 17%) and proved equal regarding acute hemostasis and prevention of early rebleeding [125–127]. A recent single-center observational study [128] also substantiated the beneficial effects of EUS-guided coil and glue injection in primary prophylaxis for high-risk gastric varices, defined as those with a size >10 mm or with presence of cherry red spot. Technical success was achieved in 100% ($n = 80$), 96.7% had EUS confirmation of variceal obliteration of which 67.7% was obtained with 1 treatment session. Although these data are encouraging and promising, they require further validation and are not (yet) the primary strategy of care considering the BAVENO VII [73] and thus for now can only be considered on a case-by-case basis (f.e. splanchnic vein thrombosis) as also suggested by the most recent ESGE guideline [83]. Additionally, endoscopists should also realize that varices are a symptom of a larger entity, being portal hypertension, and balance an endoscopic approach versus other potentially more performant alternatives such as TIPS, balloon-occluded or coil-assisted retrograde transvenous obliteration (BRTO or CARTO) or shunt surgery and even liver transplantation [73,118].

3.2.5. EUS-guided transgastric portosystemic shunt obliteration (Fig. 5)

Spontaneous portosystemic shunts (SPSS) are an often-neglected cause of chronic protracted or recurrent hepatic encephalopathy associated with cirrhosis [129,130]. In a multicenter European cohort study, we substantiated the effectiveness and safety of embolization of these shunts via interventional radiology, provided there is sufficient functional liver reserve [131]. Rathi et al. [132] extended the concept of EUS-guided embolization of gastric varices for the first time to transmural EUS-guided embolization of portosystemic shunts for the treatment of refractory hepatic encephalopathy. EUS-guided transgastric shunt obliteration was performed by injecting coils and glue directly into the SPSS. In a single center cohort of 7 patients, with splenorenal shunt as culprit SPSS, complete occlusion was obtained in 6/7 (86%) with a correlating adequate clinical success in 5/7 (71%) in on average 27 min, without any procedure-related complications. EUS-guided SPSS obliteration could be an additional interesting utensil in the toolbox of SPSS embolization although it needs further validation.

3.2.6. EUS-guided intrahepatic portosystemic shunt (EUS-IPSS) (Fig. 6)

Decompression of the portal vein by placement of a TIPS via interventional radiology is frequently used to treat portal hypertensive complications in selected patients. The effectiveness of TIPS is well established for acute variceal bleeding [133–135], recurrent ascites [136] and even for prevention of further decompensation [137]. Also in this context, it has been shown feasible via EUS to establish a transgastric intrahepatic portosystemic shunt (IPSS) procedure using the left hepatic and portal vein with a functional operational bypass in a large animal model [138,139]. The recent availability of lumen-apposing metal stents, used for drainage of peripancreatic fluid collections, was shown to 'simplify' an IPSS procedure [139]. Although feasible and operational, it is important to underscore that IPSS is purely experimental and is unlikely to replace conventional TIPS. However, it underscores the unbridled urge of EUS for expansion.

3.2.7. EUS-guided portal venous blood sampling

The gut-liver axis is rapidly gaining interest as a source of novel pathophysiological insights and identification of potentially relevant pathways that could lead to diagnostic biomarkers and therapeutic targets [140,141]. Indeed, the liver-gut axis is THE interphase where interaction between gut microbiota and the liver occur in its most pure form and most tangible via the portal vascular territory, which currently is only accessible via a TIPS approach or surgery. EUS, via transgastric transhepatic puncture of the left portal vein

or main trunk, could offer a less invasive, safe, and reproducible window to the gut-liver axis and solve a long-lasting impediment to this clinically remaining blind spot [142].

4. Conclusion: future evolution & remaining hurdles

The growing and evolving field of EUS and advanced hepatobiliary endoscopy has amplified the traditional endoscopic armamentarium and unveiled novel options for remaining stalemate hepatobiliary conditions, both diagnostically and therapeutically. This conceptually appealing and fascinating integration of endoscopy within the practice of hepatology is referred to as 'endohepatology' with EUS-LB, EUS-PPG and EUS coil and glue embolization as most renowned applications. Although this aspiring endoscopic concept seems in clear opposition to the more contemplative hepatological trend to shift towards surrogate non-invasive testing and for some even proclaimed as a stalemate between interventionalists versus non-interventionalists, the clinical reality is quite the opposite since both paradigms are to be considered complementary and could even transcend the sum of their distinct components to stratify risk and individualize hepatological care.

Nevertheless, some gaps remain to be bridged. First, while some of these interventions are already in the process of being certified and may offer a conceptually attractive (one-stop) solution to aid liver specialists in managing patients with complex chronic liver disease, others remain to be explored, may prove only useful for highly selected/exceptional cases or may not be sustainable at all given safer, more efficient and/or cost-effective alternatives. Secondly, endoscopists should keep in mind that "being endoscopically feasible" does not equal actual definitive treatment of a complication (such as bleeding gastric varices) as this latter might represent only a piece of much larger puzzle (like that of portal hypertension and/or cirrhosis). Management of these patients should therefore incorporate a multidisciplinary approach to consider the best possible option, which does not necessarily extend to endocopical intervention, but might also involve pharmacological (i.e., nonselective beta-blockers), radiological (including transjugular intrahepatic portosystemic shunt and balloon-occluded retrograde transvenous obliteration) or surgical intervention (e.g., shunt surgery or liver transplantation). Thirdly, achieving competency in endo-hepatology is still in search of definition and consensus defined and in search of consensus. Ideally, the future liver-driven physician is trained as a hybrid hepatologist-endoscopist or alternatively unites with therapeutic endoscopists, provided these latter are acquainted with the "hepatological" mindset. At present, there are no specific established societal recommendations yet on how to achieve competence in endo-hepatology.

Nonetheless, from the above it is clear that endo-hepatology is here to stay and will continue to evolve in attempt at providing novel minimally invasive solutions for persisting hepatological stalemate situations.

The 'endoscopic liver rush' therefore untiringly thunders on ….

Author contributions

The manuscript was drafted by WL in collaboration with all co-authors. All authors read and approved the final manuscript.

Conflict of interest

WL has received consultancy and speaker fees from Cook Medical and Boston-Scientific. MP has received consultancy and speaker fees from Gore.

Funding

JT was supported by the German Research Foundation (DFG) project ID 403224013 – SFB 1382 (A09), by the German Federal Ministry of Education and Research (BMBF) for the DEEP-HCC project and by the Hessian Ministry of Higher Education, Research and the Arts (HMWK) for the ENABLE and ACLF-I cluster projects. The MICROB-PREDICT (project ID 825694), DECISION (project ID 847949), GALAXY (project ID 668031), LIVERHOPE (project ID 731875), and IHMCSA (project ID 964590) projects have received funding from the European Union's Horizon 2020 research and innovation program. The program of Endohepatology in the Department of Medicine B was funded by the Stiftung für Universitätsmedizin Münster. WL received funding from the MICROB-PREDICT (project ID 825694), is co-holder of the Boston-Scientific Chair in interventional echo endoscopy and consultant for the LIVERHOPE (project ID 731875). MP is funded by the Ernst-und-Berta Grimmke Foundation (No. 5/19) and BONFOR research program of the University of Bonn (grant ID 2020-2A-07 and 2021-2A-07) and by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy – EXC2151 – 390873048.

KP is funded by the Deutsche Forschungsgemeinschaft (DFG, PE 2403/2-4) and the LOEWE program of the "Hessische Ministerium für Wissenschaft und Kunst" (ACLF-I: project P7 and DRUID: project D2).

The manuscript reflects only the authors' views, and the European Commission is not responsible for any use that may be made of the information it contains. The funders had no influence on study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgement

The authors thank Dr. Emma Vanderschueren for helpful assistance with the figures.

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