Volume 11.1 August 2023

EMJ Hepatology

Review of EASL Congress 2023

Interviews

Nancy Reau, Irene Bargellini, and Marina Berenguer discuss their career pathways and explore topics from imaging to transplantation

Infographic

Exploring biomarkers for liver disease: biopsy versus emerging methods, gaps in research, and future directions

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Give every little star the chance to thrive

Bylvay▼(odevixibat), the first and only licensed treatment for all types of PFIC[1]

Progressive Familial Intrahepatic Cholestasis (PFIC) is a progressively worsening group of rare, genetic cholestatic disorders with elevated serum bile acid (SBA) levels, debilitating pruritus and ultimately liver failure[2,3]

Outcomes are often devastating with many children requiring a lifesaving liver transplant by 5 years of age[4]

Rare genetic defects leading to dysfunction in bile acid transport are mostly present in childhood, but advances in genetic testing increasingly indicate links to adult onset PFIC[3,5]

Evolving spectrum of known and potential PFIC gene defects[6,7]

	PFIC 1	PFIC 2	PFIC 3	PFIC 4	PFIC 5	PFIC 6	PFIC 7	PFIC 8-12
Affected Protein	FIC 1	BSEP	MDR3	TJP2	FXR	MYO5B	USP53	Ongoing research continues to highlight links to new genes e.g. KIF12, ZFYVE19, SEMA7A, SLC51A, VPS33B
Affected Gene	*ATP8B1*	*ABCB11*	*ABCB4*	*TJP2*	*NR1H4*	*MYO5B*	*USP53*	

In a recent study, ~ 1 in 4 patients with adult-onset cholestatic liver disease had a PFIC related genotype[8]

Children with PFIC experience a complex array of physical and psychosocial complications that diminish their childhoods and hold back their health, development and wellbeing[9]

*Sensorineural deafness is an extrahepatic effect in patients with PFIC.

Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older[1]

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1. Bylvay summary of product characteristics. **2.** Gunaydin M, *et al.* Hepat Med. 2018;10:95–104. **3.** Bedoyan S, *et al.* Expert Opinion on Pharmacotherapy, DOI: 10.1080/14656566.2022.21400403. **4.** van Wessel DBE, *et al.* Hepatol. 2021;74(2):892–906. **5.** Henkel SAF, *et al.* World J Hepatol. 2019;11(5):450–463. **6.** Goldberg A, Mack CL. Clin Liver Dis (Hoboken). 2020;15(3):105-9 **7.** OMNIM.org. Phenotypic Series - PS211600. Available at https://www.omim.org/phenotypicSeries/PS211600. Last accessed November 2022. **8.** Nagayam J, *et al.* Hepatol Commun. 2022;6:2654–64. **9.** Baker A, *et al.* Clinics and Research in Hepatology and Gastroenterology (2019) 43, 20—36 **10.** Srivastava A. J Clin Exp Hepatol. 2014;4(1):25–36. **11.** Albireo press release. Available at https://ir.albireopharma.com/node/13771/pdf. Last accessed November 2022. **12.** Mighiu C, *et al.* Orphanet Journal of Rare Diseases. 2022;17:32. **13.** Clemson C, *et al.* Presentation at AASLD: The Liver Meeting 2022, American Association for the Study of Liver Diseases; November 4–8, 2022; Washington, DC, USA. **14.** NICE (National Institute for clinical excellence) technology appraisal: Odevixibat for treating progressive familial intrahepatic cholesta. Available at www.nice.org.uk/guidance/hst17. Last accessed November 2022. **15.** Thompson RJ, *et al.* Lancet Gastroenterol Hepatol 2022; 7: 830–42. **16.** Karpen S, *et al.* Hepatology International (2020) 14:677–689. **17.** Clemson C, *et al.* Native liver survival in odevixibat serum bile acid responders: data from the PEDFIC studies in patients with progressive familial intrahepatic cholestasis. Presented at AASLD: American Association for the Study of Liver Diseases; November 4–8, 2022; Washington, DC, USA. **18.** Sturm E, *et al.* Outcomes with Odevixibat in patients with progressive familial intrahepatic cholestasis by level of pruritus reduction: pooled analysis from the PEDFIC trials. Poster presented at the 2022 NASPGHAN/CPNP/APGNN Annual Meeting, October 12–15, 2022; Orlando, FL, USA. **19.** Thompson RJ, *et al.* Poster presented at AASLD: The Liver Meeting 2022, American Association for the Study of Liver Diseases; November 4–8, 2022; Washington, DC, USA. **20.** Gupte, *et al.* 2022 EASL International Liver Congress, June 22–28, 2022; London, UK.

Bylvay is the first non-surgical treatment for all PFIC types[1]

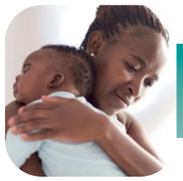
Bylvay is a novel, reversible, potent, selective ileal bile acid transporter (IBAT) inhibitor[1]

Bylvay helps preserve native liver, address the underlying cause of cholestasis and potentially negates the need for surgical biliary diversion[3,13-15]

Lowering sBA levels is associated with less liver injury and higher native liver survival[16]

Protect their livers

- Bylvay had a significant, clinically meaningful effect on sBA reduction vs placebo at 24 weeks and sustained over 96 weeks[†1,17]
- In a post-hoc analysis, all Bylvay responders remained transplant-free over 3 years (p=0.005 vs non-responders)[17]



Provide symptom-relief

- Bylvay delivered a clinically meaningful improvement in pruritus vs placebo at 24 weeks[‡1]
- 68% of children had clinically meaningful reductions in itch at 72 weeks[18]

Preserve their futures

- Sustained gains in growth with height and weight across 96 weeks[19]
- Pruritus responders and their families benefitted from improved sleeping patterns with less disruption[20]

Find out more about how Bylvay can help children and adults with PFIC to thrive at Bylvay.eu

[†]PEDFIC 1, Primary Endpoint: Proportion of patients with at least a 70% reduction in fasting sBA levels from baseline to the end of treatment or who achieved a level ≤70 mcmol/L at week 24.

[‡]Proportion of positive pruritus assessments at the patient level over the 24-week treatment period, based on an observer-reported outcome (ObsRO) instrument. Patients' pruritus was recorded by an observer twice daily (morning and evening). Efficacy was assessed using an ObsRO scale from 0–4, with 0 being no itching. An ObsRO score change of -1 point from baseline could be considered clinically meaningful.

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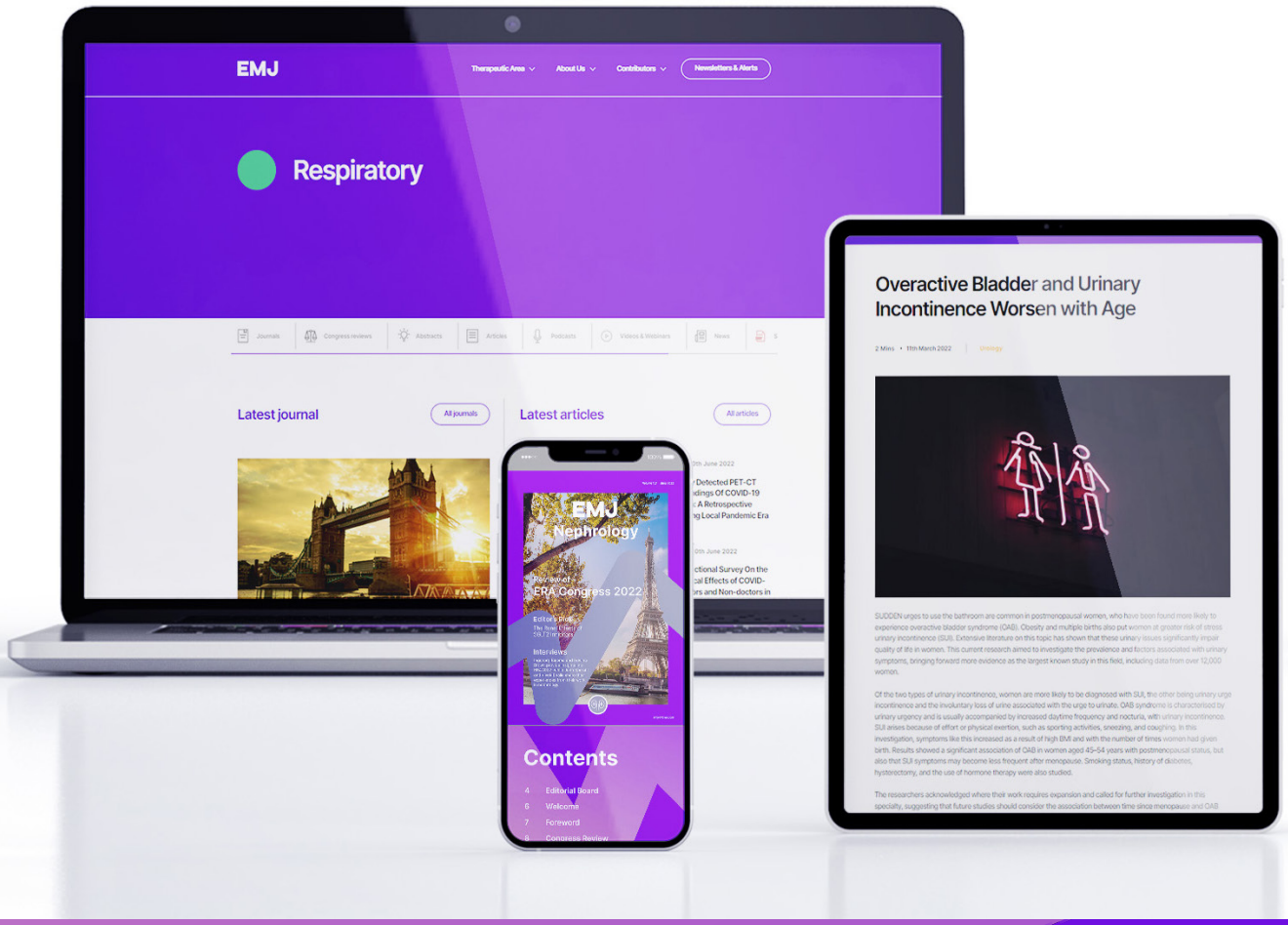

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Welcome to the 2023 issue of *EMJ Hepatology*! In this issue, we have covered key topics discussed at this year's European Association for the Study of the Liver (EASL) Congress, which took place in Vienna, Austria. The congress was a hive of discussions, with hepatitis and non-alcoholic steatohepatitis being areas of important developments.

A personal highlight from the event was taking part in a press round-table, where a number of experts discussed the current status and future of artificial intelligence in hepatology with members of the press. Raising public awareness on liver health has become a key priority, and the association engaged with the local community by visiting schools to talk about this, and also offered free liver scans in the vicinity of the congress.

We have handpicked the abstracts presented and summarised them here, showing the overarching themes across the congress. We are proud to also feature interviews with three key experts, who talk to us about their career paths and their areas of interest.

I am sure many of you will find our infographic highly engaging, as it explores the current topic of liver biomarkers, offering an overview of imaging in non-alcoholic steatohepatitis and non-alcoholic fatty liver disease, and highlighting gaps in research.

I would like to take this opportunity to thank our Editorial Board, contributors, interviewees, and peer reviewers for bringing this content together. The EMJ team is already looking forward to next year's issue, and is welcoming your manuscript submissions in relevant topics.

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Foreword

Dear Colleagues,

I am pleased to present the latest issue of *EMJ Hepatology*, which features highlights from the European Association for the Study of Liver's (EASL) annual meeting, the International Liver Congress (ILC) 2023, and several fascinating articles from experts in the field.

EMJ had the privilege of speaking to Nancy Reau, Department of Internal Medicine, Division of Digestive Diseases and Nutrition, Rush Medical College, Chicago, Illinois, USA, about her career, and the fields she feels need further study. Marina Berenguer, University of Medicine; and Hepatology and Liver Transplantation Unit, Servicio de Medicina Digestivo, Hospital Universitari i Politècnic La Fe, both in Valencia, Spain, also discussed her career, as well as the challenges that EASL face in achieving their goals. Plus, Irene Bargellini, Diagnostic and Interventional Radiology Department, Candiolo Cancer Institute, Turin, Italy, provided her insights on liver cancer imaging as an interventional radiologist.

Inside this issue, discover highlights from the EASL Congress 2023, covering the potential of faecal microbiota transplantation in treating advanced liver disease; an update from the MAESTRO-NASH trial; how sensitivity to combination therapy can be predicted by deep learning in patients with hepatocellular carcinoma; and much more! We further include a feature on viral hepatitis from a session at this congress.

Also included is an infographic that discusses biomarkers for liver disease. It provides information on what is currently used to determine liver function, comparing these techniques with newer biomarkers, which show promise in assessing hepatic steatosis, inflammation, and fibrosis. Detailing the gaps in the research, and where more research is needed, this infographic is definitely worth a look.

Finally, I would like to thank everyone who contributed to this issue of *EMJ Hepatology*, from the authors and the interviewees to the Editorial Board. Thank you for helping to create yet another insightful and intuitive journal that delves into the field of hepatology.

Ken Simpson

Senior Lecturer in Hepatology, University of Edinburgh; Honorary Consultant Physician, Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh, Edinburgh, UK

EASL 2023

Review of the European Association for Study of the Liver (EASL) Congress 2023

Location:	Vienna, Austria
Date:	21st–24th June 2023
Citation:	EMJ Hepatol. 2023;11[1]:12-20. DOI/10.33590/emjhepatol/10307349. https://doi.org/10.33590/emjhepatol/10307349.

STRIVING to become the 'home of hepatology', the annual European Association for Study of the Liver (EASL) Congress took place in Vienna, Austria, between the 21st–24th June 2023. This meeting facilitated the exchange of scientific knowledge, promoted research of the liver, and provided education to participants as EASL continues to tackle liver disease.

Austria's capital and most populous city is one ingrained with a rich history in music, where residents Mozart and Beethoven made their name. During this event, Vienna hosted an orchestra of 6,000 delegates from 108 countries interested in advancing care for the liver.

Thomas Berg, EASL Secretary General, acted as conductor for the opening ceremony by welcoming all of the delegates, and updating attendees on where EASL is in its 4-year strategy; this aims to keep the organisation focused throughout changes in leadership, uniting hepatology, and increasing its member base.

Berg introduced Maggie Bassendine, University of Newcastle, UK, who was recognised as EASL Congress Honorary President for this event. Bassendine reflected on the growth of EASL, from its founding in 1966 when it was made up of just 70 hepatologists, to today. Bassendine acknowledged some of the major scientific events on this journey, including the discovery of hepatitis C and the human genome project, and described the EASL as a "trailblazer" for gender equality with its balance in presenters.

Aleksander Krag, EASL Vice-Secretary General, spoke during this ceremony about EASL's interaction with global societies, such as World Health Organization (WHO) Europe, and their collaborations to advance liver health. Krag spotlighted events like World Liver Day in April 2023, where organisations came together. Later in the Congress, Krag succeeded Berg as Secretary General, with Debbie Shawcross, King's College London, UK, stepping in as Vice-Secretary.

Gathering clinicians, researchers, nurses, and other healthcare professionals with an interest in liver disease, EASL 2023 offered the chance to engage with several types of interactive sessions. These came in the form of symposia, abstract presentations, ePosters, workshops, and even the chance to have your liver scanned via ultrasound. "We are very proud of having something for everybody," was the way Saskia van Mil, EASL Scientific Committee, described the diversity and spread of the scientific programme on offer. EASL also made a real effort

"During this event, Vienna hosted an orchestra of 6,000 delegates from 108 countries interested in advancing care for the liver."

as an association to interact with the people and the city of Vienna, providing school clinics and education to the locals. This is an avenue they hope to continue in future congresses, starting with the 2024 meeting which will be held in Milan, Italy, next summer.

> **"We are very proud of having something for everybody."**

Eric Trépo, EASL Young Investigator Task Force Governing Board Representative, was on hand to deliver the Emerging Leader Awards, dedicated annually to vibrant fellows under the age of 40, with outstanding contributions to liver research. These were awarded to David Pinato, Imperial College London, UK; and Lung Yi Mak, University of Hong Kong, Hong Kong. The Nurses and AHPs Rising Star Award was delivered by Patrizia Künzler-Heule, Chair of EASL Nurses and AHPs Task Force, to Marta Carol Perdiguer, University of Barcelona, Spain. EASL Recognition Awards were also given to Julia Wendon, King's College London, UK; George Papatheodoridis, University of Athens, Greece; and Antonio Bertoletti, Duke-NUS Medical School, Singapore, for their major scientific contributions to the field.

Quoting Abraham Lincoln, Thomas Berg looked ahead as they thanked their support group for their guidance during their time leading the association. Berg encouraged participation and growth for EASL and the wider field of hepatology, stating: "The best way to predict the future is to create it."

> **"The best way to predict the future is to create it."**

This edition of *EMJ Hepatology* contains the scientific highlights from EASL 2023, summarising the press releases shared and abstracts from presenters at congress, and covering branches of hepatology from hepatocellular carcinoma to cirrhosis.

Liver Disease: A Potential Use for Faecal Microbiota Transplant

THE ANNOUNCEMENT of a pioneering clinical trial to assess whether faecal microbiota transplant (FMT) could be used to not only treat advanced liver disease, but also combat antimicrobial resistance, was made at EASL 2023.

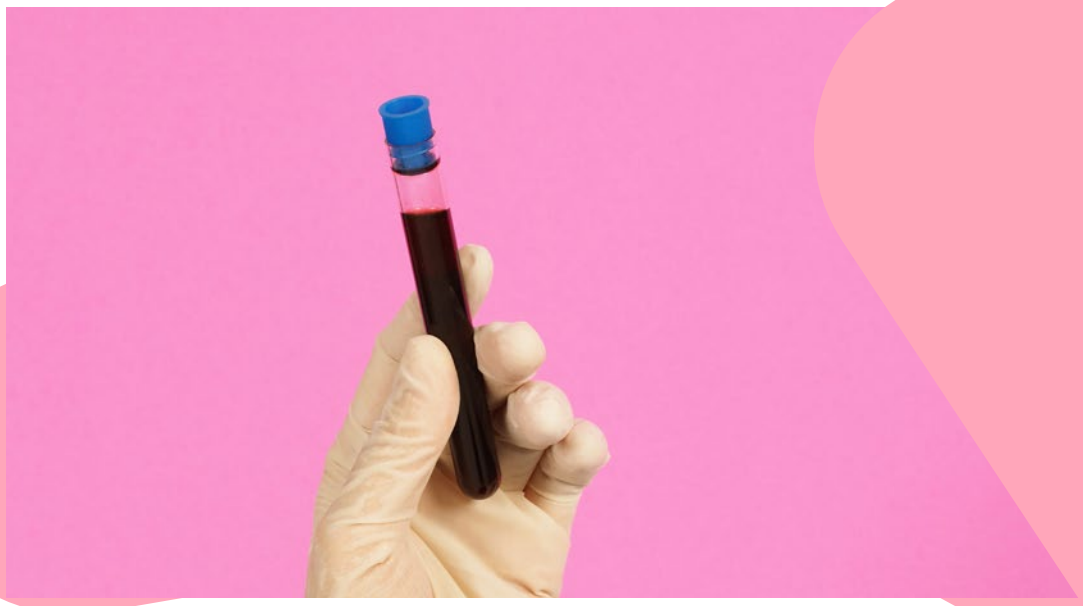
Researchers from King's College London, UK, plan to build on their FMT research initially conducted in the National Institute for Health and Care Research (NIHR)-funded PROFIT trial. This was a European safety and feasibility trial conducted in 32 patients with liver disease, which showed that endoscopically-delivered FMT was safe and well-tolerated. The team also found that endoscopically-administered FMT modified patient gut microbiota, and enhanced intestinal barrier function, antimicrobial mucosal immunity, and metabolism of ammonia. These results are of interest, given the susceptibility of patients with liver cirrhosis to infections, and concerns with antimicrobial resistance.

Patients with cirrhosis are at high-risk for antimicrobial resistant infections due to a disproportionate exposure to antibiotics, with one-quarter of patients receiving long-term antibiotic treatment. For many patients with cirrhosis, liver transplant is the only definitive treatment option available; however, transplant cannot be performed in the setting of an antimicrobial-resistant infection. Therefore, infections in this patient cohort can be severe and fatal. This spotlights the need to identify strategies to overcome the risk of such infections, and reduce antibiotic use in this cohort to help improve patient outcomes and incidence of antimicrobial resistance.

The announced PROMISE trial, funded by a NIHR and Medical Research Council (MRC) partnership, is the next stage in this research. It aims to recruit 300 patients diagnosed with liver cirrhosis from 16 sites across the UK, to evaluate whether oral FMT capsules containing freeze-dried stool from healthy volunteers reduce the likelihood of getting an infection. Enrolled participants will be randomised to receive either oral FMT capsules or placebo every 3 months for 2 years.

Debbie Shawcross, King's College London, and chief investigator for the PROMISE trial, discussed how results from the PROFIT trial are encouraging, and that the PROMISE trial may offer new hope for patients with cirrhosis.

"These results are of interest, given the susceptibility of patients with liver cirrhosis to infections."



Long-Term Efficacy of Tenofovir Alafenamide in Patients with Chronic Hepatitis B

RESEARCH presented at the EASL 2023 explored the long-term efficacy of tenofovir alafenamide (TAF) in patients with hepatitis B e antigen (HBeAg)-positive and -negative chronic hepatitis B (HBV). In data from two similarly designed double-blind, randomised, Phase III studies on patients with HBeAg-positive and -negative chronic HBV, TAF demonstrated non-inferior efficacy compared to tenofovir disoproxil fumarate (TDF). The final 8-year results from the trial were shared at EASL 2023.

> **"The final 8-year results from the trial were shared at EASL 2023."**

The studies measured efficacy through the missing equals excluded approach of the full analysis set, and included serial assessments for viral suppression (HBV DNA <9 IU/mL), alanine transaminase normalisation by 2018 American Association for the Study of Liver Diseases (AASLD) criteria, serologic responses, and fibrosis change by serum FibroTest (BioPredictive, Paris, France). The researchers additionally carried out resistance analyses, including deep sequencing of HBV pol/reverse transcriptase, both at baseline and annually for individuals with virologic breakthrough/blip; persistent viraemia, or treatment discontinuation with viraemia; as well as phenotyping qualifying samples.

The researchers found that of the 1,298 randomised and treated patients, 1,157 (89%; 775 TAF; 382 TDF) entered the open label (OL) phase, including 180 and 202 TDF-treated patients who began OL TAF at Week 96 (TDF-OL TAF 6-year) or Week 144 (TDF-OL TAF 5-year), based on timing of a protocol amendment. Overall, 974 (95%) of the participants completed the OL study treatment. The most common reasons for discontinuation were the withdrawal of consent, loss of follow-up, or investigator discretion. Similar rates of virologic suppression and alanine transaminase normalisation were achieved and maintained in all treatment groups. Additionally, sequencing and phenotype analyses over 6 years showed no resistance to TAF.

In conclusion, 8-year treatment with TAF, or up to 6 years after switch from TDF, virologic suppression rates remained high across all treatment groups, with 33% achieving HBeAg/hepatitis B e antibody seroconversion.

Vibration-Controlled Transient Elastography Scoring in At-Risk Patients with NASH

THE TARGET population for Phase IIb and III clinical trials in non-alcoholic steatohepatitis (NASH) is patients with NASH with fibrosis (F) 2–3. Due to high rates of screening failure during biopsies, which lead to slower enrolment and drug development, non-invasive tests have undergone development to reduce screening failure rates. Research aiming to assess composite scores related to vibration-controlled transient elastography through comparison to traditional methods was presented by Mazen Noureddin, Houston Methodist Hospital, Texas, USA, at EASL 2023.

The researchers used screening data from six ongoing biopsy-proved therapeutic NASH trials, which included over 5,000 patients. In the study, liver data was read centrally, and the diagnostic accuracy of FibroScan-AST score (FAST) and liver stiffness measurements (LSM) were assessed using vibration-controlled transient elastography. The cut-offs of 0.5 (FAST) and 8.2 kPa (LSM) were used to identify patients with F3. Similarly, the diagnostic accuracy of Agile 3+ (Echosens, Verona, Italy) and LSM were also assessed, with cut-offs of 0.6 (Agile 3+) and 9.7 kPa (LSM). Patients with F4 were excluded from the study.

A total of 1,048 patients with an average age of 54.7 years were included, of whom 61% were female. The data showed a fibrosis prevalence of 92 (9%) for F0, 231 (22%) for F1, 290 (28%) for F2, and 435 (42%) for F3 across participants. FAST showed better specificity (51.7 versus 8.4), negative predictive value (58.2 versus 48.6), positive predictive value (71.7 versus 62.2), positive likelihood ratio (1.59 versus 1.03), negative likelihood ratio (0.45 versus 0.66), and the correct classification (0.67 versus 0.61) compared with LSM in patients with NASH F2–3. Agile3+ showed better specificity (62.0 versus 35.7), positive predictive value (51.6 versus 43.5), positive likelihood ratio (1.78 versus 1.29), negative likelihood ratio (0.52 versus 0.48) and the correct classification (0.64 versus 0.53) compared with traditional LSM in patients with NASH F3.

Overall, the study concluded that FAST and Agile3+ performed more effective screening tests than traditional methods of liver stiffness in patients with NASH F2–F3 and NASH F3. The researchers recommend using these scoring systems as screening criteria in Phase IIb/III NASH clinical trials.

"The researchers used screening data from six ongoing biopsy-proved therapeutic NASH trials, which included over 5,000 patients."

Bulevirtide Safe in Treatment of Chronic Hepatitis D

BULEVIRTIDE (BLV) is safe and well-tolerated as monotherapy in the treatment of chronic hepatitis D, according to data presented at EASL 2023. BLV, a first-in-class entry inhibitor for chronic hepatitis D, was first conditionally approved for use in the European Union (EU) in July 2020.

MYR301, a Phase III randomised study, showed that BLV 2 mg or 10 mg subcutaneously was safe and well-tolerated, and superior to no-active hepatitis D virus (HDV) treatment based on combined viral and biochemical response, with similar efficacy for both doses at Week 48. Results at Week 96 were presented at the Congress.

Researchers randomised and stratified 150 patients with CDH into three arms based on the presence or absence of compensated cirrhosis. Arm A included no active anti-HDV treatment for 48 weeks, followed by 10 mg/day BLV for 96 weeks (n=51); arm B immediate treatment with 2 mg/day BLV for 144 weeks (n=49); and arm C immediate treatment with 10 mg/day BLV for 144 weeks. Follow-up continued up to 96 weeks after end of treatment (Week 240). Endpoints included combined response, defined as a HDV RNA decrease of ≥2 $\log_{10}$ IU/mL from baseline and ALT normalisation or undetectable HDV RNA; viral response, defined by HDV RNA decrease by ≥2$\log_{10}$ IU/mL from baseline or undetectable HDV RNA; change in liver stiffness by transient elastography and $\log_{10}$ change in HDV RNA; and alanine transaminase normalisation.

At baseline, 47% of participants had compensated cirrhosis, mean HDV RNA was 5.05 $\log_{10}$ IU/mL, mean ALT 110.9 U/L, mean liver stiffness 15 kPa, and 61% were on concomitant nucleos(t)ide analogues therapy. Of the 150 participants, 95% completed all 96 weeks of treatment. Results showed that efficacy responses had improved compared to Week 58. Arms B and C had similar combined responses and biochemical responses at Week 96.

> **"Results showed that efficacy responses had improved compared to Week 58."**

There were no serious adverse events, deaths, or drug discontinuations; however, researchers noted an increase in bile acids without an association to pruritus or other symptoms, as well as a higher proportion of injection site reactions in those who received 10 mg/day.

The team concluded that BLV is safe and well-tolerated through Week 96 in this population, and that biochemical and virological responses were higher with long-term therapy.

Potential to Safely Treat Patients with Liver Fibrosis

RESMETIROM appears to be safe and well-tolerated by patients with liver fibrosis and non-alcoholic steatohepatitis (NASH), according to the preliminary results of the MAESTRO-NASH trial, presented at EASL 2023. This Phase III registrational double blind, placebo-controlled trial is ongoing, and studies the effect of once daily 80 or 100 mg resmetirom compared with placebo in patients with liver fibrosis and NASH.

A total of 966 patients with liver fibrosis and NASH enrolled in the study from approximately 200 sites around the world. Two central pathologists used glass slides as a primary analysis to read liver biopsies; the results were then combined using a statistical algorithm to generate a single treatment effect. If the two readers disagreed, digitalised images were sent to a supportive consensus group. Unfortunately, 11 patients were excluded after Week 60 due to COVID-19 at the site.

The endpoints of the 52-week study were ≥1 stage reduction in fibrosis, with no worsening of Non-Alcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS), or resolution of NASH, with no worsening of fibrosis. NASH resolution meant scores of 0 for ballooning and 0 for inflammation, as well as at least a 2-point reduction in NAS. Another key endpoint was a reduction of low-density lipoprotein cholesterol.

All endpoints were met with both doses, with similar results being obtained by the central pathologists. Other liver biopsy endpoints, including fibrosis reduction and NASH resolution, were met. A reduction was also seen in alanine transaminase, aspartate transaminase, and γ-glutamyltransferase levels. Both doses had similar numbers of serious adverse events, and saw an increase of diarrhoea and nausea at the start of therapy.

While ongoing, the preliminary results of this study support resmetirom as a potential treatment for patients with liver fibrosis and NASH. It has been well-tolerated in both treatment groups. ●

"966 patients with liver fibrosis and NASH enrolled in the study from approximately 200 sites around the world."

Sensitivity to Combination Therapy Predicted by Deep Learning

RESEARCHERS have discovered that deep learning can predict the sensitivity of patients to atezolizumab-bevacizumab, the standard first-line treatment for hepatocellular carcinoma (HCC). Despite being the standard of care for this disease, objective responses to treatment with atezolizumab-bevacizumab are observed in just a minority of patients.

Predictive biomarker development is crucial in improving outcomes for patients diagnosed with HCC. Previously, progress has been made in developing the *ABRS* gene signature to improve standard of care; however, it is very challenging to implement molecular profiling techniques into clinical practice, due to the expertise required in bioinformatics and molecular biology.

Lead study author Julien Calderado, Laboratoire d'Informatique Paris Descartes (LIPADE), Université Paris Cité, France, and colleagues aimed to develop a regression-based deep learning model, which had the ability to estimate *ABRS* expression value using histological digital slides of HCC disease. They then wanted to determine if this particular model could predict progression-free survival (PFS) in patients with HCC who have received treatment.

Their model, ABRS-P, was trained to use the Cancer Genome Atlas (TCGA), which was created to accelerate clinical understanding of the molecular basis of cancer. Specific image features were extracted from slides, and were incorporated, along with their *ABRS* gene signature expression as a label, into the model. This model was externally validated using two independent sets of data: a resection series from Henri Mondor University Hospital, University of Paris, France (n=225), and a biopsy series from Henri Mondor University Hospital and Avicenne University Hospital, Paris, France (n=157). This dataset had a significant difference compared to 3'RNA sequencing used in gene profiling technology.

> **"Their model, ABRS-P, was trained to use the Cancer Genome Atlas (TCGA)."**

Researchers then tested a series of 122 biopsy samples taken from patients with HCC who were treated with atezolizumab-bevacizumab, against a control group treated with other systemic therapies (n=44). Spatial transcriptomics were performed on HCC samples. The mean Pearson correlation coefficient of ABRS-P was 0.62 (0.46–0.72). Patients with ABRS-P tumours showed prolonged PFS (p=0.0014) once atezolizumab-bevacizumab treatment was initiated. Researchers observed no impact on ABRS-P prediction on PFS in the patient cohort treated with other therapies.

To conclude, this study has shown that artificial intelligence, when applied to digital slides of HCC, can predict PFS in patients treated with atezolizumab-bevacizumab. It is hoped that fast and inexpensive biomarkers of sensitivity to specific therapies can be developed, which can be easily implemented in clinical settings, for a variety of diseases. ●

Effects of Naltrexone on Achieving Abstinence and Reducing Alcohol Craving in Patients with Cirrhosis

PRESENTED at EASL 2023, Manasa Alla, Institute of Liver and Biliary Sciences, New Delhi, India, emphasised the importance of establishing safety and efficacy profile of naltrexone in patients with alcohol-related liver disease.

Alla and colleagues performed a single-centre, double-blind, placebo-controlled, randomised trial between April 2020–July 2022 in patients (n=147) with compensated cirrhosis with alcohol use disorder (AUD). As per inclusion and exclusion criteria of the study, 100 patients with compensated cirrhosis fulfilling the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for AUD were enrolled and randomised between naltrexone or placebo, given for 12 weeks. The primary outcome was the proportion of patients achieving and maintaining alcohol abstinence at 12 weeks, while the secondary outcomes included the proportion of patients maintaining abstinence at 6 months and 12 months; adverse effects; lapses; and relapses at 3, 6, and 12 months. Both groups were offered behavioural therapy and counselling.

Both groups had comparable baseline demographics, clinical characteristics, alcohol use disorders identification test (AUDIT), and obsessive-compulsive drinking scale (OCDS) scores. At 12 weeks, a significantly higher proportion of patients achieved abstinence with naltrexone compared to the placebo group (64% versus 22%; p<0.001). Likewise, the maintenance of abstinence after 6-months of follow-up was higher with naltrexone (22% versus 8%; p=0.09).

At 12 weeks, the naltrexone group had a significantly lower number of relapses (28% versus 54%; p=0.01), while the placebo group had higher rates of relapses (28% versus 12%; p=0.07). Naltrexone demonstrated significantly lower mean craving scores at 12 weeks, as indicated by the OCDS-O score (6.63±1.16 versus 9.29±1.78; p<0.01) and the OCDS-C score (6.3±1.23 versus 9.02±1.86; p<0.01). Both groups demonstrated comparable adverse events, and no patients required discontinuation of the drug.

The authors concluded that naltrexone can be safely administered for AUD in patients with compensated cirrhosis, and it demonstrated efficacy in achieving abstinence, as well as reducing craving scores at the 3-month mark.

"At 12 weeks, a significantly higher proportion of patients achieved abstinence with naltrexone compared to the placebo group."

The Spectrum of Viruses Causing Hepatitis

Authors: Evan Kimber, EMJ, London, UK

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VIRAL hepatitis presents one of the most diverse challenges currently perplexing experts within the field of hepatology. An insightful session at the European Association for Study of the Liver (EASL) Congress 2023 collated vital new information in this area for clinicians to take away and incorporate into their practice. Presenting at this meeting, held in Vienna, Austria, between the 21st–24th June, Tassos Grammatikopoulos, King's College Hospital NHS Trust, London, UK, gave an update on the interaction of adenoviruses with hepatitis. Meanwhile Gonzalo Crespo, University of Barcelona, Spain, spoke about post-liver transplant viruses.

ADENOVIRUSES CAUSING HEPATITIS

Grammatikopoulos began by discussing viruses causing acute severe hepatitis in paediatric populations, and presented data that crossed over with the COVID-19 pandemic. Looking back to 2014, Grammatikopoulos referenced the low figure of 33% for unexplained cases of hepatitis in the UK and Ireland, and that 1 in 39 children presented with non-A or B hepatitis-related acute liver failure that required a transplant, before comparing these with far higher figures from 2022. Grammatikopoulos also presented retrospective data from between 2017–2021 and 2021–2022, as well as data from 2022.

In 2022, paediatric hepatologists saw the annual number of patients they would usually treat with acute liver failure who needed transplant within the first trimester rise to a significantly higher incidence than expected. "Hepatitis in itself really evolved hand-in-hand with the cases of adenovirus that were identified in the general population, [and] in children's faecal material," was the description Grammatikopoulos gave, reflecting on this association during the pandemic. Moving on to outline virology and liver histology, Grammatikopoulos described that close to 70% of their study cohort presented with adenovirus, stressing the variable degree of fibrosis uncovered in these patients, along with the difficulty clinicians experience calculating this because of extensive hepatocellular necrosis.

Grammatikopoulos acknowledged that a higher incidence of human adenovirus led to a stronger association with paediatric acute liver failure in the 2022 epidemic. Interestingly, this relationship was found not to be a novel phenomenon, and up to 75% of a similar cohort experienced positivity for adenoviraemia but did not experience as much liver failure between the years 2017–2019. Jaundice was highlighted as a key feature for identifying hepatitis, showing agreement in European and American branches of study.

Finishing with treatment options for clinicians to consider in their practice, Grammatikopoulos focused on the use of ribavirin, ganciclovir, Ig, and cidofovir, which they flagged as the medicine of choice. Despite receiving a high dose of cidofovir 5 mg/kg, intervention in the discussed cohort failed to halt the clinical progression of disease, which was not changed in about 70% of patients, who consequently required a transplant. What is clear from this is that adenoviraemia remains a complex issue that is linked with liver disease, there is a significant but not clearly defined crossover with COVID-19, and further research is needed

"A higher incidence of human adenovirus led to a stronger association with paediatric acute liver failure."

to guide advances in practice, and build on the currently limited treatment options.

POST-LIVER TRANSPLANT VIRUSES

Recognising that times have changed, and that significant advances have been made in the field, Crespo chose to focus much of their talk on hepatitis E, cytomegalovirus, herpes, and torque teno virus instead of hepatitis B, C, and D, which might have dominated a presentation of this nature previously.

After liver transplant, hepatitis E virus remains a common cause of acute hepatitis in endemic countries, such as Mexico, as well as much of Asia and Africa. Crespo provided data from a study from Southern France, showing that this infection may evolve into chronic hepatitis, and stating that this is often due to a third genotype of zoonotic infection and ingestion of undercooked meat.

Discussing the prevalence of IgG and IgM in recipients of transplant, Crespo acknowledged that using serology to define hepatitis E infection is not as accurate as researchers would like, and they briefly spoke about the challenges associated with this in patients who are immunocompromised. Crespo explained the importance of using hepatitis E virus RNA molecular testing as the standard of care in defining recipients who are suitable for liver transplant to overcome this. Clinicians observing this presentation would note the following key actions after diagnosing hepatitis E virus infection: a decrease in immunosuppression, and then a 3-month wait to see if the infection evolves to a chronic state, and intervening with ribavirin treatment, which has an admirable 80% success profile. Crespo mentioned the vaccine for hepatitis E virus, which is currently approved for use in China, stating that it may be useful, but requires further confirmation and study in other areas.

Moving on to discuss the characteristically latent herpesvirus, Crespo clarified the recent confusion and disagreement among experts when classifying the subgroup cytomegalovirus, defining this as any detectable viraemia, regardless of symptoms. Answering one of the key questions clinicians are faced with in their treatment of cytomegalovirus, Crespo discussed the pros and cons of prophylactic and pre-emptive approaches. For patients of high-risk liver transplant, 3 months of prophylaxis with (val)ganciclovir is recommended. Meanwhile, in low- and mid-risk cases, a pre-emptive approach should be employed, using weekly or bi-weekly cytomegalovirus PCR to monitor viral load, and beginning treatment when this reaches a predetermined threshold. In the patients who experience side effects, are refractory to these drugs, or present with resistant disease, alternative interventions are recommended. This should involve a higher dose of ganciclovir for the latter two. Alternatively, foscarnet and maribavir provide good treatment options to clear cytomegalovirus viraemia.

Bringing their presentation to a close, Crespo spoke about torque teno virus from transfusion transmission, highlighting that this reflects immune status after liver transplant. More research is needed in this field to investigate if this may be used as a biomarker to guide immunosuppression, an integral part of dealing with all the discussed branches of hepatitis in this section of the session.

"After liver transplant, hepatitis E virus remains a common cause of acute hepatitis in endemic countries."

CONCLUDING REMARKS

This symposium was governed by chairs Jane Hartley, University of Birmingham, UK, and Ralf Bartenschlager, Heidelberg University, Germany, who reflected on the information provided by both speakers. Hartley described it as “very, very informative.” Both presentations furthered understanding, and gave a new perspective on different aspects of hepatitis, helping to shape the practice of onlooking clinicians, and guide next steps for researchers. ●

Management of Cholestatic Pruritus in Primary Biliary Cholangitis: Ileal Bile Acid Transporter Inhibition and Holistic Care

These industry-sponsored symposia took place on Friday 23rd June as part of the 2023 European Association for the Study of the Liver (EASL) Congress held in Vienna, Austria

Chairpeople:	David Jones[1,2]
Speakers:	Robert Mitchell-Thain,[3] Cynthia Levy,[4] Kris Kowdley,[5] Kathryn Houghton,[1] Alan Bonder[6]

1. Newcastle University, UK
2. Newcastle Hospitals NHS Foundation Trust, UK
3. The PBC Foundation, Edinburgh, UK
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5. Elson S. Floyd College of Medicine, Washington State University, Pullman, USA
6. Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

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Meeting Summary

Symptoms of the progressive cholestatic liver disease primary biliary cholangitis (PBC) include pruritus and fatigue. Pruritus can persist chronically in at least one-third of people with PBC and can range from mild to severe, with fluctuations over time, including on a daily basis. Proposed causative factors for PBC-associated pruritus include bile acids, lysophosphatidic acid (LPA), and endogenous opioids, with proposed symptom mechanisms linked to increases of these substances, or associated pathways. All offer potential routes for drug treatment to help alleviate pruritus in some patients. PBC-associated pruritus can have a significantly detrimental effect on a person's quality of life (QoL) due to a sometimes constant feeling of 'bugs crawling' on their skin, and the need to 'tear my skin off'. Pruritus may lead to secondary skin lesions, embarrassment, and social isolation. Pruritus is associated with sleep deprivation and subsequent daytime tiredness and fatigue, as well as depression, and sometimes in the worst cases, leading to suicide. Treatments for PBC-associated pruritus include bile acid sequestrants, rifampicin, opioid antagonists, sertraline, and gabapentin, as well as topical moisturisers, behavioural changes, and ultraviolet light therapy. Though not currently approved for such, ileal bile acid transporter (IBAT) inhibitors are undergoing clinical trials, as success in alleviating pruritus is shown in similar conditions. In patients where PBC-associated pruritus is very severe, liver transplantation is a consideration. At the 2023 European Association for the Study of the Liver (EASL) Congress, leading experts in the field of PBC, including clinician-researchers, a nurse specialist, and a representative from the PBC Foundation, highlighted the importance of discussing, assessing, and treating pruritus in people with PBC, using a holistic approach to understanding and caring for this QoL-affecting symptom.

Introduction

Symptoms of PBC, a chronic, progressive, immune-mediated, cholestatic liver disease arise due to gradual destruction of intrahepatic bile ducts.[1] PBC predominantly occurs in middle age, although it can affect people of all ages, and is up to nine times more common in females compared to males.[2]

Cholestatic pruritus as a symptom of PBC can occur in up to 81% of patients,[3] and may persist chronically in at least 35%.[4] However, pruritus occurrence shows both inter- and intra-individual variation, with severity fluctuating and not necessarily related to PBC stage or activity.[5] For many, pruritus primarily arises in the limbs, especially the soles of the feet and palms of the hands.[6] Typically, pruritus occurs more often and is more intense in the evening,[6,7] and it may be exacerbated by contact with some fabrics, especially wool; by heat; during pregnancy; during the premenstrual period; and when taking hormone replacement therapy.[5,7,8] There is no primary rash associated with cholestatic pruritus;[5] however, even though for many scratching does not relieve the itch sensation, patients may persist with scratching to the point of creating secondary skin lesions.[6,8]

Over two symposia, the experience and treatment of pruritus in people with PBC were discussed by leading experts in the field. They included the clinician-researchers David Jones, Newcastle University, and Newcastle Hospitals NHS Foundation Trust, UK; Cynthia Levy, Division of Digestive Health and Liver Diseases, Schiff Center for Liver Diseases, University of Miami, Florida, USA; Kris Kowdley, Elson S. Floyd College of Medicine, Washington State University, Pullman, USA; Alan Bonder, Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; Kathryn Houghton, a hepatology research nurse and autoimmune specialist nurse; and Robert Mitchell-Thain, CEO of the PBC Foundation, Edinburgh, UK.

Potential Causative Factors for Cholestatic Pruritus

Cholestatic pruritus occurs when itch receptors in the skin are activated internally and the itch signal is transmitted to the thalamus, where it triggers the itch sensation (Figure 1).[9] Several causative factors for the triggers of this sensation in PBC are postulated. As PBC is a disease of the bile ducts, pruritus may occur due to accumulation of bile acids in the blood and skin. Indeed, ingestion of bile acids can induce pruritus in healthy volunteers, or worsen it in patients who are cholestatic, and cholestatic pruritus can be reduced through bile acid sequestrants. However, pruritus occurrence and extent do not necessarily correlate with bile acid levels, and bile acid sequestrants do not reduce this symptom in all patients.[7,10-14]

Another potential cause of cholestatic pruritus is LPA, as activity of autotaxin, the enzyme that hydrolyses LPA from its precursor molecule, correlates with PBC-associated pruritus intensity, and injection of LPA into mice leads to dose-related pruritus. There may also be a role for endogenous opioids, as these are increased in many patients with PBC pruritus, and this symptom can be lessened by opiate antagonists.[7]

The Patient Experience of Primary Biliary Cholangitis-Associated Pruritus

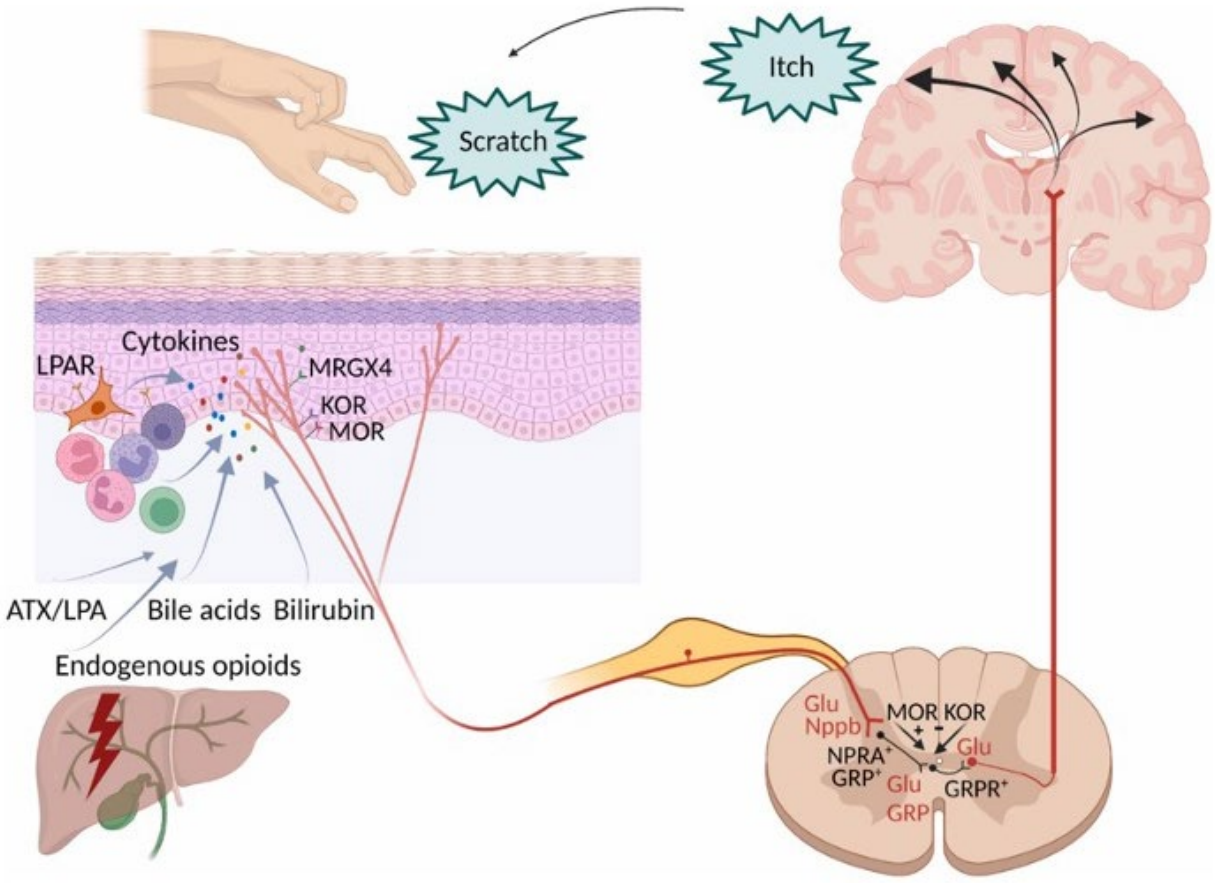
"PBC-associated pruritus," Jones said, "is a real problem in a significant group of people but is one that we are perhaps not taking as seriously as we should do, and the people who lose out with that are the patients." In fact, said Mitchell-Thain, the PBC Foundation has talked to patients "that have been treated for tactile hallucinations or as self-harmers, because of what's happening inside their own body."

"Itch is indiscriminate," highlighted Mitchell-Thain, when discussing an analysis of a PBC Foundation survey including 498 respondents that showed that itch occurred in both males and females, in participants of any age (31–70 years), and regardless of how many years they had been diagnosed with PBC.[15] "Itch is more than just itch, though," they said, "itch is days and days of torture, thousands of thousands of ants and spiders crawling under your hands, your ears, absolutely everywhere." In confirmation of this, a survey of 201 patients with PBC-related pruritus found that 35% agreed that it was akin to 'bugs crawling', 29% responded that the symptom was 'deep and relentless', and 18% said it made them want to 'tear my skin off'.[5] As such, Mitchell-Thain asked of healthcare professionals that "when a patient talks to you about their itch, hear them, see them, treat them."

"Severe itch," said Jones, "has a really dramatic effect on people." Using a measure of health utility that assesses QoL,[16] a study of 147 people with PBC found that baseline health utility value in participants with severe pruritus[17] was similar to patients with severe Parkinson's disease,[18] with both being around 0.5 on a scale of 0–1.[17,18]

Several studies have found pruritus affects people in several domains, including sleep, mood, and fatigue. For example, in a study of 211 people with PBC, those with pruritus scored significantly worse ($p<0.0001$) than those with no or mild pruritus on several PBC-40 measures (described below) domains, including fatigue and cognitive, emotional, and social areas.[19] With the latter in mind, other studies investigating PBC-associated pruritus have illustrated how it can lead a patient to socially isolate, as they feel self-conscious about scratching, which can impact QoL.[20,21]

Figure 1: Mechanism of cholestatic pruritus.[9]



Adapted from Düll MM, Kremer AE.[9]

ATX: autotaxin; Glu: glutamate; GRP: gastrin-releasing peptide; GRPR+: gastrin-releasing peptide receptor; KOR: k-opioid receptor; LPAR: lysophosphatidic acid receptor; LPA: lysophosphatidic acid; MOR: m-opioid receptor; MRGX4: MAS-related G protein-couple receptor, member X4; Nppb: neuropeptide natriuretic polypeptide b; NPRA: natriuretic polypeptide receptor.

Sleep deprivation in people with PBC-associated pruritus, reported Mitchell-Thain is "a form of torture that can profoundly affect you physically, emotionally, and psychologically." In a survey by the PBC Foundation, including 395 patients with PBC, 58% reported itch occurring daily, and 72% said they had sleep disturbances.[22] Another survey, based on data from the GLIMMER study of an IBAT inhibitor, found that all participants with PBC (n=147) had at least mild sleep interference, with 66% of 35 patients with severe pruritus and 8% of 76 patients with moderate pruritus reporting severe sleep interference.[23]

Fatigue can also be a symptom of PBC, with 86% of 227 respondents to a PBC Foundation survey reporting this symptom.[24] However, Houghton suggested a patient may not know fatigue is related to the pruritus they are experiencing. Bonder reported findings from their autoimmune clinic and registry, where patient demographics, medical, and PBC diagnosis data are captured alongside results of patient QoL surveys. In an analysis of survey data including 118 patients with autoimmune hepatitis (AIH), 31.4% of whom also had PBC, lower scores on fatigue, systemic symptoms, and emotional domains were associated with significant QoL impairment.[25] Another analysis showed that poor treatment adherence was more common in patients with AIH and PBC, compared with those with AIH alone, and was significantly associated with

lower health-related QoL, which was related to fatigue and systemic symptoms.[26]

In the PBC Foundation survey discussed above, 31% of 227 people with PBC reported mental health issues.[24] Another survey found that 43% of 35 patients with severe pruritus, 11% of 76 patients with moderate pruritus, and 20% of 35 patients with mild pruritus reported moderate or severe depression.[23] This was considered as very important by Jones, who recounted how they "knew people who find life intolerable because of their itch, and there have, sadly, been people who have taken their own lives because of it."

Assessing and Tracking Primary Biliary Cholangitis-Associated Pruritus

Despite the above figures, in an analysis of 8,461 UK hospital-based patients with PBC, 38% did not undergo any assessment of pruritus.[27] In another study, 70% of 149 patients said their physician did not evaluate itch.[5] Similarly, in the PBC Foundation patient survey of 227 patients, only 60% reported being asked about their symptoms by a clinician in the previous 12 months.[24]

As PBC-related pruritus is not associated with liver disease severity, occurrence may be perceived by physicians as well-controlled when looking at lab values, even if symptoms interfere with a person's QoL.[28] As such, the speakers discussed various ways a person's experience of pruritus could be measured. This is vital as, according to Houghton: "The patient's view of the itch is very subjective, so it is important that you get their view, and not your view, of what you think their itch is." Indeed, one study showed a mismatch between physician and patient ratings of pruritus occurrence and severity, with concordance rates for mild or moderate pruritus being lower than for severe or very severe pruritus.[29]

Most simply, Levy discussed how in the clinic, just asking the patient whether they are experiencing pruritus, and whether it is interfering with their QoL, may be enough to gauge if the symptom needs addressing. However, to record the occurrence and level of pruritus, Kowdley suggested: "Itch severity measurements can provide objectivity and a true assessment of a patient's health and QoL." They further discussed how, "while the patient is in the waiting room, we give them a visual analogue scale of 0–10, where all they have to do is draw a line as to where their itch is, because how they report the itch when you ask them can be very different to how they record it on a form."

For this, a numeric rating scale is available, where 0 is no itch and 10 is the worst itch imaginable.[30] Itch can also be evaluated using a Patient Global Impression of Severity scale, ranging from Absent to Very Severe.[30,31] Levy also recalled how utilising a 0–10 numeric rating scale at each consult can help with comparing pruritus levels over time, and gauge the impact of a treatment, with a 3–4 point reduction being, in their opinion, very clinically relevant.

To investigate how PBC symptoms affect a person, the disease-specific PBC-40 QoL measure contains 40 PBC-related questions, including how often itching disturbs a person's sleep, whether scratching the itch makes the skin raw, and how often a person is embarrassed because of scratching. Frequency (in the past 4 weeks) is scored from 0 (no itch/does not apply) and 1 (never), to 4 (most of the time) and 5 (always).[32,33] The pruritus-specific 5-D itch score can also be used to assess this symptom more thoroughly.[34]

According to Kowdley, "if you have something the patient can do between visits, especially that can track sleep, we might be able to do even better." In fact, the PBC Foundation has an app that patients can use to track their symptoms daily over time. The app can graph the data, and a patient can show this to their clinical team, and use it for self-care.[35]

Measuring symptoms using such tools, suggested Jones, "gives you something to talk about, and it also validates the patient's experience." Above all, agreed Kowdley, you need to provide hope, and the patient needs to feel they are believed, and that their concerns about the impact of pruritus on their daily life are taken seriously.

Management of Cholestatic Pruritus in Primary Biliary Cholangitis

The above findings regarding cholestatic pruritus, according to Jones, prompt the question of whether enough priority is being given to managing PBC symptoms and their impact on patients. Indeed, in a study including 211 patients with PBC-associated pruritus, 33% did not receive any treatment for this symptom.[3] In one of the PBC Foundation surveys, when discussing itch with their clinician, only 45% of 227 respondents said they were prescribed treatments, and 32% were given information about remedies to try. Still, only 6% were informed of helpful lifestyle changes, and 9% reported the symptom of itch was dismissed as something else, or that they were not believed or taken seriously. Of the 32% of the 227 patients who said they did not raise the issue of itch during their appointments, 35% said they did not think anything could be done to help it, and 12% said there was not enough time in their appointment.[24]

Findings such as these, said Jones, raise the need for a patient-centric approach, where symptoms are readily assessed and managed in addition to starting disease-modifying therapy. "I do not think it is a stretch," Jones discussed, "to imagine that if we can stop people suffering from severe itch in PBC, that we can improve their health utility and QoL substantially."

While the guideline-recommended first-line treatment for PBC, ursodeoxycholic acid, aids some PBC symptoms, it is not shown to improve pruritus.[7,36] EASL, the American Association for the Study of Liver Diseases (AASLD), and The British Society of Gastroenterology (BSG) suggest treatment pathways for cholestatic pruritus in PBC. However, these also may not be effective for all patients, and not all have undergone formal clinical testing for PBC. First-line medications are the bile acid sequestrants cholestyramine, colestipol, and colesevelam. For refractory pruritus, rifampicin is the second line treatment, followed by oral opioid antagonists, such as naltrexone and nalmefene, and then the selective serotonin uptake inhibitor sertraline and the anticonvulsant gabapentin.[7,13,14]

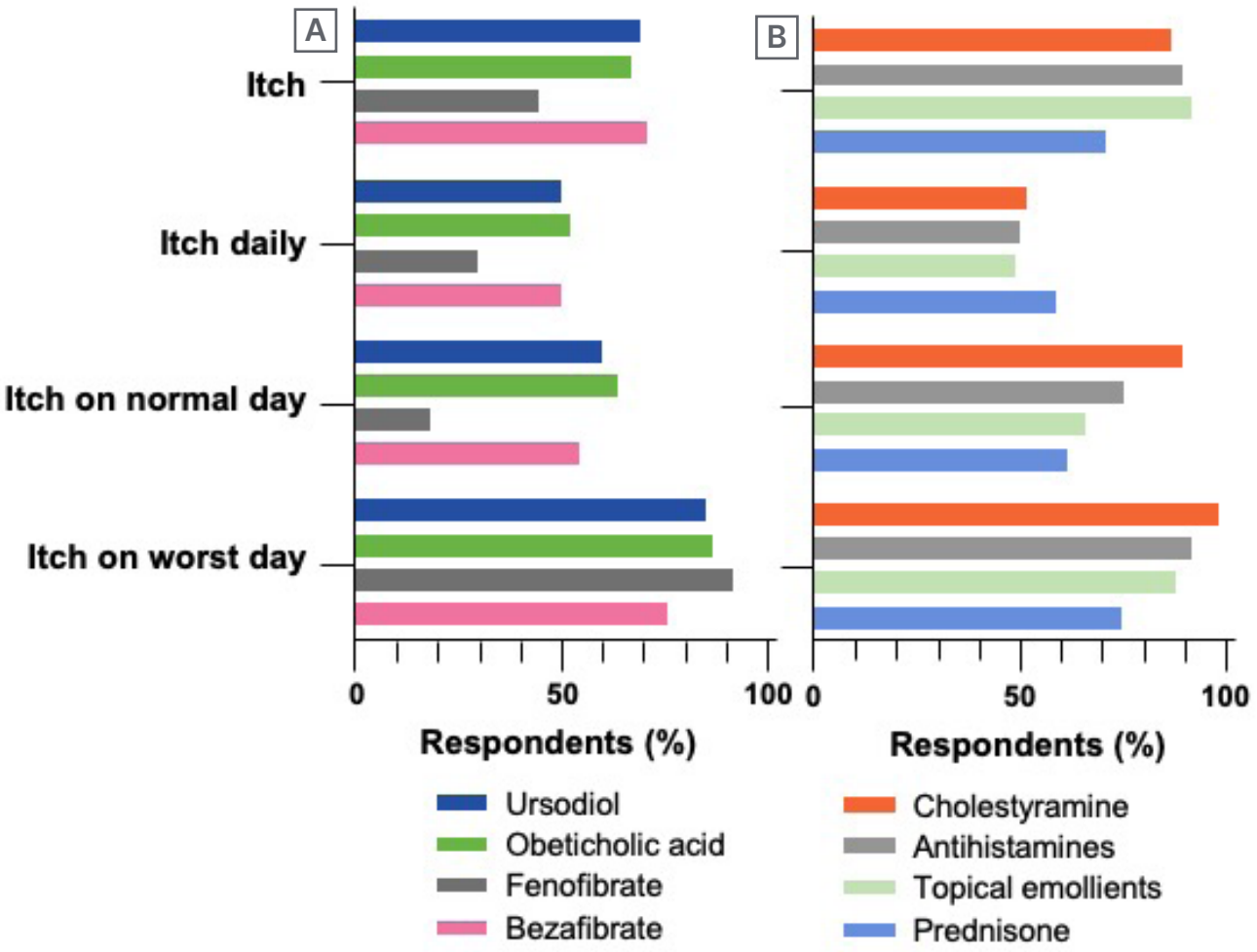
If the patient does not respond to these, there may be clinical trials they can be entered into.[7,13,14] In a recent PBC Foundation patient survey (n=227), just over two-thirds of respondents said they would consider participating in a clinical trial; however, only 15% reported they had had a conversation with their clinician about such participation.[24] If pruritus is severe, liver transplantation can be considered.[7,13,14] While the latter is rare, of note, Mitchell-Thain was speaking at the symposia on behalf of Mo Christie, the Head of Patient Services at the PBC Foundation, and a person with PBC, who agreed to their story being shared. They had been scheduled to appear at this symposium, but were unable to, as they had recently undergone surgery following a liver transplant, due to untreatable pruritus.

Other recommendations, that may mitigate itch but not provide a cure, include training that can help stop the itch-scratch-itch cycle and being taught relaxation techniques. Potential pruritus-relieving treatments include moisturisers and emollients (not water-based); topical agents, such as menthol and camphor; applying moist, cooling skin wraps; and bathing with tepid water. Pruritogenic medications, such as narcotics, should be avoided. Behavioural measures include being in a cool, but not dry, environment; keeping nails short; and avoiding tight or sticky clothing.[13,37] Another therapy is controlled ultraviolet exposure,[13,37] with Houghton discussing how they have had success in some patients when they combine medication with light therapy under a dermatologist's guidance.

Of note from PBC Foundation data, people with cholestatic pruritus may be prescribed treatments that are not recommended, such as, in a survey of 395 patients, antihistamines, which were prescribed to approximately 30% of respondents.[22] A PBC Foundation analysis of their mobile app data (n=498) showed that many patients still experienced pruritus, despite being prescribed a treatment for PBC (Figure 2A), or a treatment for pruritus (Figure 2B).[15]

Although not presently indicated for PBC-associated pruritus, Levy discussed the use of IBAT inhibitors, as such treatments have had success in pruritus treatment in the paediatric conditions of progressive familial intrahepatic cholestasis and Alagille syndrome. Two IBAT inhibitors are currently under investigation in adults with PBC (Table 1).[38,39]

Figure 2: Current therapies for primary biliary cholangitis, or pruritus reported on the PBC Foundation mobile app by patients with primary biliary cholangitis (n=498).



A) Primary biliary cholangitis; **B)** pruritus.

Itch: itch occurring on any day; itch daily: itch occurring at least once/day; itch on normal day: itch level moderate-to-severe on a typically day; itch on worst day: itch level moderate-to-severe on worse day.

IBAT inhibitors work by decreasing the amount of bile acid re-uptake in the terminal ileum, which occurs as part of enterohepatic circulation following excretion of bile acids into the bile duct, then the duodenum. As the use of IBAT inhibitors increases faecal excretion of bile acids,[50] this may lead to some gastrointestinal adverse effects. In Phase II trials of maralixibat for patients with PBC or primary sclerosing cholangitis, approximately 81% of participants experienced treatment-emergent gastrointestinal adverse events.[51,52] In linerixibat clinical trials in people with PBC and pruritus (n=147), diarrhoea and abdominal pain led to drug discontinuation in a dose-dependent manner of 14% of the participants who received the active drug (n=111).[46]

Holistic Care for People with Primary Biliary Cholangitis-Associated Pruritus

"Empowering patients to know what they're dealing with, and what they're expecting from their disease, is so important," stressed Bonder, who reiterated: "We need to take a holistic view in PBC; we need to treat not only the disease but

Table 1: Ileal bile acid transporter inhibitors approved and under investigation for the treatment of cholestatic pruritus.

IBAT inhibitor	Status
Odevixibat	**Approved** for patients with PFIC aged ≥6 months by the EMA[40] and aged ≥3 months by the FDA,[41] with studies showing reduction of serum bile acids and pruritus;[38] approved for Alagille syndrome in patients aged ≥12 months by the FDA.[41]
Maralixibat	**Approved** for patients with Alagille syndrome aged ≥2 months by the EMA[42] and aged ≥3 months by the FDA,[43] with studies showing reduction of serum bile acids and pruritus.[39] **Phase III** randomised, placebo-controlled trial in patients with PFIC aged ≥1 to <18 years ongoing;[44] topline data shows significant improvement in pruritus severity compared to placebo.[45]
Linerixibat	Post hoc analysis of a Phase IIb study showed significant reductions in pruritus compared to placebo;[46] **Phase III** multicentre, randomised, placebo-controlled trial in patients with PBC aged 18–80 years ongoing.[47]
Volixibat	**Phase II** randomised, placebo-controlled trials for patients aged ≥18 years with PBC[48] and PSC,[49] ongoing.

EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; IBAT: ileal bile acid transporter; PBC: primary biliary cholangitis; PFIC: progressive familial intrahepatic cholestasis; PSC: primary sclerosing cholangitis.

the patient, and we need to have a really good physician-patient relationship." This includes sharing goals and action plans. Bonder suggested that when managing people with PBC who are experiencing pruritus and fatigue, to focus not only on laboratory test results, and not be shy to ask and discuss these symptoms. Houghton recounted the value of having telephone consults every 2 weeks between 3-monthly clinical visits, and how they use these as an opportunity to explore how a treatment prescribed for pruritus is working, and change it if needed. This means, Houghton mentioned, that "when they come back to the clinic, we're getting closer to itch management, rather than having a 3-month gap with no contact with any physicians."

Houghton shared how, in their centre in Newcastle, they have the 'TRACE' approach to patient management in PBC: TReatment of exacerbating factors, such as pruritus, anaemia, hypothyroidism, or vitamin D deficiency; Amelioration of associated problems, such as autonomic dysfunction, sleep disturbance, or depression; Coping strategies, including education, social interactions, and regular exercise; and Empathy.[7,53] "You're probably all aware of this," said Houghton, "but whether you can do it is another thing," with time being a limiting factor in a usual consult. As such, the Newcastle Hospitals NHS Foundation Trust has a dedicated fatigue clinic where they have time to discuss this symptom and its exacerbating factors. Here, long-term management is discussed, taking into account the broader impacts fatigue can have on a person's daily life. This may be carried out by a nurse specialist, who, as Houghton states, "may have more time, and (to whom) patients will often tell things that they won't tell a doctor."

Bonder also discussed how patients should also be guided to advocacy groups, such as the PBC Foundation,[54] for support, and to help manage symptoms. "Sometimes my patients are shy to share common symptoms with me, but when they go to patient advocacy websites or social media pages, they are helping to get resources, and at the next appointment they are happier to share symptoms."

Conclusion

Cholestatic pruritus is common in patients with PBC, and should be assessed and discussed by a healthcare professional at every visit, as it is often under-recognised and under-treated. This is despite how it can sometimes dramatically impact a patient's QoL, including associations with sleep disturbances, fatigue, and depression. There are several tools, including those specific to PBC, to health-related QoL, and to pruritus, that could aid assessment and discussion. Several pruritogenic compounds have been implicated in the development of cholestatic itch, including serum bile acids. Treatments leading to reduction of bile acid levels appear to be associated with clinical improvement of itching, and are currently in development for PBC-related pruritus. Treatment is through provision and suggestion of behavioural modifications, and a stepwise approach to medical management.

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Abstract Highlights

The following selected abstracts were the pinnacle of those showcased at the European Association for the Study of the Liver (EASL) Congress 2023, exploring current topics ranging from the gut microbiome diversity and cirrhosis, to hepatitis and hepatocellular carcinoma.

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Advanced Hepatocellular Carcinoma: Myeloid IL-8 Enrichment and Immunotherapy Resistance

DURABLE response to treatment in patients with advanced hepatocellular carcinoma (HCC) is confined to a small fraction of patients, despite emerging therapeutic options, including immunotherapy. The ineffectiveness of immune checkpoint blockade (ICB) and resistance acquisition caused by the immunosuppressive drivers, such as inflammatory cytokines and myeloid cells, had to be tackled. A research team at The Chinese University of Hong Kong, China, therefore sought to analyse the role of myeloid IL-8 in ICB-resistance mechanisms, aiming to intervene the IL-8 pathway through the inhibition of its receptor using a CXCR2 antagonist.

Patients with advanced HCC were recruited prior to pembrolizumab therapy, resulting in the inclusion of 26 participants. Baseline and on-treatment biopsies were collected, with single-cell RNA transcriptomic analysis performed. Simultaneously, circulating IL-8 levels were quantified in peripheral blood samples.
To evaluate the efficacy of CXCR2 pathway inhibition using AZD5069 in potentiating ICB response, an orthotopic mouse model with ICB resistance was used. The mouse model was generated through serial *in vivo* passaging of anti-PD-1 residual tumour. High-parameter flow cytometry was used to profile the immune landscape in the tumour microenvironment.

"Biopsies were collected, with single-cell RNA transcriptomic analysis."

Results showed that patients with a higher baseline plasma IL-8 had worse overall survival than those with lower IL-8 (hazard ratio [HR]: 2.899; 95% confidence interval [CI]: 1.112–7.558; p=0.0294). Single-cell RNA sequencing suggested IL-8 originated from myeloid cell clusters in tissue biopsies. Specifically, the upregulated expression of IL-8 on polymorphonuclear myeloid-derived suppressor cells was strongly associated with a poorer progressive-free survival (HR: 2.327; 95% CI: 0.867–6.248; p=0.0352). Inhibition of the IL-8 receptor with a CXCR2 antagonist improved the survival benefit of anti-PD-L1 treatment in the mouse model. Mechanistically, the suppression of CXCR2 signalling hindered the recruitment of myeloid-derived suppressor cells to the tumour site. In turn, the immunosuppression in the tumour microenvironment favouring ICB treatment was reverted.

Overall, the research team demonstrated the importance of the myeloid IL-8/CXCR2 pathway in ICB resistance in a cohort with advanced HCC. This paves the way for IL-8 to become a novel prognostic target for immunotherapy. Subsequently, blocking CXCR2 could reduce myeloid-derived suppressor cell trafficking, and overcome ICB-resistance in a pre-clinical HCC model. This could be a promising combination regimen in future.

Role for Faecal Microbiota Transplant in Advanced Liver Cirrhosis?

REDUCTION in gut microbiome diversity, alongside gut barrier damage and bacterial translocation, occurs in patients with liver cirrhosis, resulting in an increased infection risk and impaired microbial metabolism of ammonia. The latter can lead to hepatic encephalopathy.

A group of researchers led by Lindsey Edwards, King's College London, UK, conducted a placebo-controlled, single-blinded, randomised controlled feasibility trial to determine whether faecal microbiota transplant (FMT) could improve intestinal barrier function, mucosal immunity, and microbial ammonia metabolism in patients with advanced liver cirrhosis (defined as Model for End-Stage Liver Disease score of 10–16).

Stool and blood samples were taken at baseline to evaluate the impact of FMT on gut microbiota modulation and patient inflammatory status. Patients were randomised on a 3:1 basis to receive either liquid frozen FMT or placebo. In total, 32 patients were endoscopically delivered 50 g of liquid frozen FMT directly into the jejunum. Stool and blood samples were subsequently collected at Days 7, 30, and 90 to evaluate changes in the microbiome and inflammation levels.

Using metagenomic sequencing, the authors found a significant donor engraftment and increased recipient species richness following FMT. FMT also resulted in significantly reduced carriage of *Enterococcus faecalis* and other pathobionts, which are over-represented in patients with liver cirrhosis; reduced inflammatory biomarkers; and increased gut barrier repair markers.

Furthermore, reductions in 30-day plasma ammonia were seen in those treated with FMT ($p=0.0006$), and 30-day faecal ammonia was higher in the FMT group than the placebo group ($p=0.0110$ and $p=0.0250$, respectively). Faecal proteomics showed increased denitrification and ammonification microbial enzymes in the stool of patients treated with FMT compared with those treated with placebo ($p=0.031$), plus an increase in enzymes involved in nitrogen assimilation and excretion via the urea cycle.

> **"Reductions in 30-day plasma ammonia were seen in those treated with FMT."**

The researchers concluded that the findings highlight the impact of FMT on pivotal factors in hepatic encephalopathy pathogenesis. FMT led to increased ammonia metabolism by reducing serum microbial-associated ammonia production, increasing faecal ammonia excretion, and enhancing anaerobic L-aspartate metabolism. FMT also altered the gut microbiota, and promoted gut barrier inflammatory repair. ●

Improving Outcomes in Patients with Hepatitis C and Hepatocellular Carcinoma

IMPROVED clinical outcomes and survival rates have been uncovered in patients with chronic hepatitis C and hepatocellular carcinoma (HCC) by achieving sustained virological response. The current research was presented at the EASL Congress 2023, aiming to provide real-world data on virological response and overall survival in patients with hepatitis C-related HCC, who were treated with direct acting antiviral therapies at differing time points.

This investigation was a retrospective cohort study including patients who were hepatitis C positive, and were diagnosed with HCC, managed at King's College Hospital, London, UK, between January 2015–2020. Follow-up data was collected until end points, including death, liver transplantation, or April 2022. Patients with historical or active HCC were included, and information about tumour stage and treatment modality were collected, with tumour treatment defined as curative (ablation, resection, or liver transplantation) or non-curative (transcatheter arterial chemoembolisation, selective internal radiation therapy, stereotactic body radiation therapy, or systemic therapy). Primary outcome was comparison of sustained virological response in both HCC groups, and secondary outcome was measuring overall survival.

The cohort was made up of 98 patients, 81 (83%) of whom had active HCC at the time of direct acting antiviral therapy and 11 (17%) with historical HCC. In total, 85% were cirrhotic with compensated liver disease, and 52% received curative HCC therapy. Overall, participant sustained virological response rate was 82%, but this decreased to 76% in patients with active HCC.

Multivariate analysis highlighted that the presence of active HCC at time of hepatitis C virus therapy (hazard ratio [HR]: 5.46; 95% confidence interval [CI]: 1.25–23.82; p=0.024) and the number of HCC nodules (HR: 2.19; 95% CI: 1.08–4.41; p=0.029) were the only factors associated with not achieving sustained virological response. Failure to achieve sustained virological response (HR: 9.9; 95% CI: 2.16–46.01; p=0.003), presence of advanced chronic liver disease (Child Pugh B/C: HR: 3.7; 95% CI: 1.46-9.58), and administration of non-curative treatments (HR 3.2; 95% CI: 1.19–8.44) were associated with mortality. Overall survival was higher in those who achieved sustained virological response (130 m; 95% CI: 85–174), and this was consistently irrespective of treatment timing (historical HCC: 119 m; 95% CI: 102-135; active HCC: 78 m; 95% CI: 67-88), tumour stage (Barcelona Clinic Liver Cancer [BCLC]: A 104 m; 95% CI: 93-116; BCLC B/C: 60m; 95% CI: 63-85), and treatment intent (curative: 117 m; 95% CI: 107–128; and non-curative: 75 m; 95% CI: 59–91; log-rank test p=0.003).

The researchers of this investigation acknowledged that the optimal timeframe for delivering antiviral therapy in those with active infection remains unclear, and warrants follow-up in future study. They were able to conclude that treating patients with hepatitis C and HCC is feasible with acceptable sustained virological response rates. Other key points from this study were that failure to achieve sustained virological response is one of the main factor associated with mortality, and overall survival is higher in those who achieve sustained virological response, independent of tumour stage or treatment modality.

Utilising Spatial Proteotranscriptomics in Patients with At-Risk Non-alcoholic Steatohepatitis

During the EASL Congress 2023, Dina Tiniakos, Newcastle University, Translational and Clinical Research Institute, UK, presented a study which aimed to resolve the spatial heterogeneity of the macrophage population in at-risk non-alcoholic steatohepatitis (NASH), and their relationship to histopathological features.

The researchers performed GeoMx® Human Whole Transcriptome Atlas (Nanostring, Seattle, Washington, USA) profiling on eight biopsies from patients with NASH fibrosis Stage 3. They selected the regions of interest based on the presence of portal inflammatory infiltration, steatosis with lobular inflammation and/or lipogranulomas, and parenchyma without steatosis. For segmentation of different macrophage, immune cell, and epithelial cell populations from each region, fluorescent CD6, CD45, and pan-keratin markers were used. In total, 80 segments were processed for high throughput RNA sequencing.

The authors explored the clinical relevance of the identified differentially expressed genes in extant bulk RNA sequencing data from 206 patients with non-alcoholic fatty liver disease. By using the Multiple Iterative Labelling by Antibody Neodeposition (MILAN) method, the key targets were validated on a protein level. An expert liver pathologist scored all the samples, referring to the semi-quantitative Nonalcoholic Steatohepatisis Clinical Research Network (NASH-CRN) Scoring System.

By comparing parenchymal steatohepatitis-associated (SH-) macrophages with portal (PT-) macrophages and Kupffer cells from parenchyma without steatosis, they identified 352 and 218 differentially expressed genes, respectively. SH-macrophages showed features of both monocytes (high expression of *LSP1*, glycoprotein NMB, and lysozyme) and mature macrophages (high *MSR1* expression), when compared to Kupffer cells in areas without steatosis. Additionally, metabolic- and phagocytosis-related genes were heightened in SH-macrophages.

With regard to the clinical relevance of key markers in the bulk RNASeq data, *CCL19* expression was linearly collated with the fibrosis stage, lobular inflammation, and hepatocyte ballooning scores; however, this was not observed with the steatosis grade. *GPNMB* and lysozyme mRNA expression displayed predominantly NASH activity, attributable to the significant association with steatosis, lobular inflammation, and hepatocyte ballooning scores, but not with fibrosis.

Tiniakos and colleagues demonstrated a steatohepatitis-associated macrophage subpopulation in patients with at-risk NASH. By comparing to portal macrophages and Kupffer cells from non-steatotic liver parenchyma, they identified unique characteristics to highlight macrophage heterogeneity. Tiniakos also demonstrated the clinical relevance of steatohepatitis-associated macrophages in the grading and staging of the non-alcoholic fatty liver disease spectrum.

"The study identified unique characteristics to highlight macrophage heterogeneity."

Albuminome Signatures: Predicting Severity and Early Mortality in Acute Liver Failure

BIO-MOLECULAR analysis of serum albumin unveils signatures indicative of severity (need for emergency liver transplantation) and early mortality in acute liver failure (ALF), according to researchers from the Institute of Liver and Biliary Sciences (ILBS), New Delhi, India.

Mortality associated with ALF corresponds to changes in plasma albumin function and levels. To assess changes in albumin and the relationship to ALF disease severity and mortality further, the authors recruited 200 patients with a diagnosis of ALF, and 25 healthy controls. Patients were split into a training cohort, comprised of non-survivors of ALF (n=32), survivors of ALF (n=8), and health controls (n=5); and a test cohort for validation, comprised of the remaining recruited patients.

In the training cohort, albumin samples were purified and analysed for modification, functionality, and bounded multi-omics signatures. Subsequently, validation was performed in the test cohort using five machine learning algorithms.

> **"Validation was performed in the test cohort using five machine learning algorithms."**

Albumin oxidative state, plasma oxidation, and glycosylation was higher in patients with ALF, particularly non-survivors of ALF ($p<0.05$).

Multivariate partial least squares-discriminant analysis and α/β-diversity indices of purified albumin from non-survivors of ALF showed significant multi-omics alterations ($p<0.05$). The bio-molecular albumin profile for non-survivors of ALF displayed significant increases in bound biomolecules linked to inflammation, amino acid metabolism, bacterial peptides, bile acids, mitochondria breakdown, and advance glycation end-products signalling. Increased bacterial taxa functionality was also found to correlate with serum triglyceride, metabolites, and phosphatidylserine in non-survivors of ALF ($R^2>0.7$; $p<0.05$).

Multi-omics signature-based probability of detection was >90% for non-survival in ALF, which correlated with clinical parameters and albumin functionality ($R^2>0.85$). There was a 98% diagnostic efficiency in metabolite probability of detection for ALF early mortality prediction (area under the curve: 0.98; 95% confidence interval: 0.95–1.0; $p<0.05$). In non-survivors of ALF, increased binding of L-acetylcarnitine, L-carnitine, N-(-3ydroxybutanoyl)-L homoserine lactone, nicotinic acid, and pregnenolone lactone to albumin was seen. Validation accuracy for early mortality prediction was >98%.

The authors concluded that albuminome signatures can help differentiate patients with ALF who are at greater risk of early mortality, or need emergency liver transplantation. Therefore, this could potentially be used to aid clinicians in clinical decision-making. ●

Congress Interviews

The following interviews take a look at the careers of two leading experts who were involved at the EASL 2023 Congress, providing updates on a broad range of topics from liver transplant, liver cancer, and cirrhosis, all the way to imaging and interventional radiology within hepatology.

Featuring: Marina Berenguer and Irene Bargellini.

Marina Berenguer

Professor of Medicine, University of Medicine, Valencia, Spain; Head of the Hepatology and Liver Transplantation Unit, Servicio de Medicina Digestivo, Hospital Universitari i Politècnic La Fe, Valencia, Spain

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Q1 Was there a particular event or person that encouraged you to pursue a career in hepatology?

I started doing gastroenterology because of my father, who was a gastroenterologist, and who started the Liver Transplant Unit in Valencia, Spain, together with a liver surgeon colleague. This unit was opened just a few years before I became a resident. It was exciting to see how patients who were extremely sick could start a near normal life only 1 month after the transplant. At that time, quite a few years ago, there were not many effective therapies available in the field of hepatology, and the management of the cirrhotic population by hepatologists had relatively low impact on survival. Most residents were mostly interested in endoscopy or gastroenterology, and hepatology was considered less attractive as a speciality because of this lack of effective therapies. After a few good experiences with transplant patients, I knew I wanted to become a 'transplantologist' in the Hepatology Unit.

Q2 You have been involved in the creation of various consensus documents on viral hepatitis and liver disease. How do these documents impact care for affected patients?

Consensus documents are very important for several reasons. First, they summarise what we know and are based on evidence created over many years. Second, they serve as a legal document that every physician can rely on when applying certain practice or therapies in their respective countries. They also help with pushing the machinery; this was very clear with the direct-acting antivirals (DAA) against hepatitis C. When they were initially launched, there was a huge debate regarding indications due to the high price and reluctance from health care payers. In fact, the penetrance of DAAs in the different European countries was done at different speed. Germany started first, but other countries took much longer, due to cost discussion with authorities. Guidelines and Consensus Documents can help patients and physicians by 'pushing' health authorities to accept new standards of care.

Q3 One of your recent papers looked at long-term outcomes after living donor liver transplantation compared to donation after brain death in autoimmune liver diseases. What were some of the main findings?

This was a multicentre study, with many authors, using the European Liver Transplant Registry (ELTR). We were interested in the outcome of patients undergoing liver transplantation for several autoimmune liver diseases (autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis), particularly focusing on post-transplant outcomes with donors who were either brain-diseased or live donors. We found that, particularly for patients with primary sclerosing cholangitis, outcomes seem to be worse with live donors. We are unsure of the cause, but it might be related to the fact that this disease is based on injured biliary ducts. In live donation, the anastomosis between the donor and the recipient biliary ducts is more difficult, and this may have an impact on post-transplant outcomes. Our data showed that live donors were an excellent option for autoimmune hepatitis and for primary biliary cholangitis, but not so much for primary sclerosing cholangitis.

Q4 What are the biggest challenges for the European Association for the Study of the Liver (EASL) in their goal to promote the highest standard of practice in hepatology and benefit patients?

Personally, I believe that currently EASL is one of the strongest societies in the field of hepatology. They not only target hepatologists but also health allied players, industrial partners, and incorporate patients' associations in their discussions regarding standard of practice. The future of medicine, the future of hepatology, and the future of medical societies is uncertain. There is a lot of competition, digital technologies are permeating the society, the development of drugs is a difficult pathway, and societies will struggle to maintain their attractiveness, as well as being economically solvent. There is also the question of what meetings will be like in the future. There are many factors to consider, including cost, sustainability, carbon imprint, interest of the members, interest of industries in the classical meeting, and e-technologies. EASL will have to adapt to the challenge as it has successfully done for years.

"I believe that currently EASL is one of the strongest societies in the field of hepatology."

Q5 Having authored and co-authored multiple peer-reviewed articles, which parts of your research do you feel have had the greatest impact on practice, and what are you most proud of?

The biggest impact has been on hepatitis C and liver transplantation, because that is where my major research lies. There are two papers that I love. The first showed that by using specific donors with certain characteristics the outcome of patients undergoing liver transplantation for hepatitis C could be significantly enhanced. This led to several centres to apply some rules when selecting the donors in hepatitis C-related indications, which eventually may have had a direct impact on patient outcomes. The second paper looked at ways of enhancing the efficacy of interferon-based therapies when we did not have DAAs, and what measures could be put in place to benefit the highest number of patients with the lowest number of side effects and problems. Again, this was something that benefitted the patients. I am proud of some other papers because they have helped my colleagues to grow in their careers. There are different types of 'successes': personal benefit (the career, for instance), benefit for the patients, and benefit for the colleagues, which is also very rewarding.

Q6 Could you highlight some of the key information you presented at the EASL 2023 Congress, on topics ranging from hepatocellular carcinoma to liver transplantation for acute-on-chronic liver failure?

We had the chance to present the results of several studies, many of which were collaborative multicentre studies in Spain. One study was on the use of anti-coagulant in the cirrhotic population, and how these drugs are safe in this population and can lead to improved outcomes. Another was a study on risk-stratifying patients with advanced liver disease following the cure of the hepatitis C virus infection with the new direct antiviral agents. Although the virus is eliminated, there

is a persistent risk of developing a liver cancer, and so these patients need to be monitored in the long-term. In the study, we applied different models that have been developed to risk stratify the patients in our population and showed the usefulness and limitations of these models.

We also had presentation on hepatitis D, a virus without treatment until very recently. We now have new drugs that are being developed and approved by the authorities, but we need to make sure that these drugs reach the patients, and over the years, several of these patients have been lost in the system and have not been followed carefully in clinics because we did not have much to offer. It is now time to link these patients back to our clinics. To achieve this, we went through a microbiology registry of all the microbiological results in the region where I work, and we were able to link back to care a proportion of patients, as well as make new diagnoses. Another part of the study focused on undocumented migrants who have never been tested. We specifically went to non-governmental organisations and used non-invasive tests. I did not present on this part of the project because it is still ongoing, but it has been very rewarding because we have detected infected individuals who were unaware of the infection and were able to link them to care.

Q7 Over the course of your career to date, what are the most significant changes you have observed in liver transplantation? Are there any noteworthy advances on the near horizon?

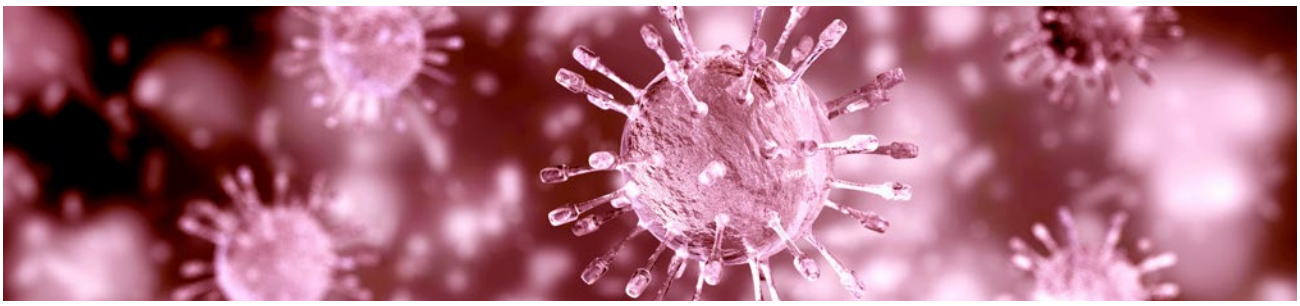
There have been huge changes with an impact on the greatest challenge in liver transplantation today, which is to find organs for all recipients at need. This gap has kept rising over the years to ultimately reaching a certain plateau, at least in some countries due to several reasons. The major one is the impact of DAAs on the number of patients with hepatitis C at need for liver transplantation either because of decompensated cirrhosis or liver cancer. Hepatitis C-related liver disease was, for many years, the first indication for liver transplantation, and is now a relatively rare indication. In countries like Spain, the numbers have dropped so much that our waiting lists are now much shorter and candidates typically wait less than 6 months.

Secondly, for many years, we only retrieved organs from donors who were brain-dead. Now, we are using organs from donation after circulatory death. This has also had an impact on the number of available donors.

Finally, the third reason is the use of machines that perfuse the organs and help surgeons to decide which organ is of sufficient quality to be successfully implanted, and also that help in maintaining the quality of the organs for several hours so that the timing of transplantation can be optimised. In the future, we may even be able to treat these organs while they are put on these machines, such that suboptimal organs may become usable by successful reconditioning.

Q8 What advice would you give to those who are starting out in the field of hepatology?

I would tell them to just enjoy this speciality. It is a very complicated field but extremely attractive; many changes have been happening in recent years. Now we have drugs that can be successfully used in several diseases. The liver is a hugely complicated organ. I would say it is much more complex than, for example, the heart, providing many research opportunities that are challenging. It is a beautiful career, so I would really encourage everybody to go into hepatology and liver transplantation if they can, because it is very rewarding.



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Q1 Following your medical degree, what sparked your interest in oncologic imaging and later liver imaging?

The main reason why I decided to become a radiologist was my interest in interventional radiology. I was attracted by the possibility of getting access to and treating different types of diseases (vascular, tumoural, etc.) with a minimally invasive approach in a field that is continuously evolving, extremely dynamic and innovative, and of increasing interest for other physicians. Then, the main focus of my residency programme at the University of Pisa, Italy, was on liver tumours and interventions, and that is the reason why over the years I specialised more in this field, including pre- and post-procedural radiological assessment of treatment response, which is an essential part of our work to understand the outcomes of our treatments, how to improve them, and what to offer to the patients in case of partial or no response.

Q2 With over 100 publications to your name, which areas of hepatology research do you believe warrant greater attention?

As already mentioned, I mostly focused on primary liver tumours, for which treatment has rapidly evolved over the past few years with the introduction of newer drugs. Today, there is an increasing need for understanding the biology of these complex and heterogeneous tumours by linking clinical, radiological, and pathological data in an attempt to optimise and personalise treatment strategies, which will inevitably become more and more combined treatment strategies.

Q3 You recently co-authored a study entitled 'Prognostic value of baseline imaging and clinical features in patients with advanced hepatocellular carcinoma'. What were the key findings?

This is one the papers that have been published analysing the results of the SORAMIC1 trial, a European study randomising patients with advanced stage cancer to receive either sorafenib alone or sorafenib and radioembolisation. The study failed in demonstrating an overall survival advantage of adding radioembolisation to systemic therapy. However, it provided a lot of useful information that was analysed to understand which patients could benefit from this combination therapy, or conversely for which patients sorafenib and radioembolisation could be even detrimental. The paper presents a number of clinical (such as poorer liver function) and radiological features that should be taken into account when selecting patients. In particular, from a radiological point of view, it confirms that there are some radiological features that are indicative of a more aggressive tumour behaviour, which do not just include tumour size and presence of satellite nodules (already known), but also peritumoral arterial enhancement and peritumoral hypointensity in the hepatobiliary phase. As previously mentioned, there is now a need to link some of these radiological features to a pathological signature that is not yet clearly identified.

> **"There are some radiological features that are indicative of a more aggressive tumour behaviour."**

Q4 What are the most significant changes you have seen in the field of hepatology during your time working within the field?

Over the last decade or so, there have been very important discoveries in the field of hepatology, such as the newer antiviral therapies that have dramatically modified the history of viral hepatitis and, consequently, the possibility of managing patients with concomitant hepatocellular carcinoma. On top of that, as already mentioned, systemic treatments of liver tumours are rapidly evolving and significantly improving patients' prognosis.

Q5 You chaired a session at the European Association for the Study of the Liver (EASL) Congress 2023, entitled 'Treatment of early stage hepatocellular carcinoma in 2023'. What were the key take-home messages?

I believe that the most interesting message of the session (which was very interesting with many questions from the audience and a lot of discussion) was that, despite the fact this is considered a very well-defined stage, when it comes to clinical practice it may be difficult to choose the most proper treatment approach for that specific patient group, with the possibility of offering different types of procedures (surgical, ablative, transarterial, and even systemic), knowing that to a certain extent the immediate results may not differ much (with the exception of transplantation). The session wanted to stimulate debate on how to move forward to identify clinical, pathological, and radiological features that could enable us to allocate patients to the most proper treatment, considering how the initial choice could have an impact on subsequent treatment options. On top of this, the very recent results of the IMbrave 050 trial2 have been presented and were discussed. This is the first positive study of systemic therapy in the adjuvant setting (atezolizumab plus bevacizumab after resection or ablation), although the interim results that have been presented are not yet mature enough to draw a definitive conclusion.

Q6 As a radiologist, what were your highlights from the EASL congress?

I was very proud, as a radiologist, to be invited to such a high-level hepatological meeting. To me, participating to non-radiological congresses is very helpful to have an update and a better understanding of what we as radiologists and interventional radiologists could offer. It is always challenging but inspiring.

> **"I was very proud, as a radiologist, to be invited to such a high-level hepatological meeting."**

Q7 EASL introduced interactive workshops as a new session type in 2023. How successful do you believe they were in encouraging participation and fostering engaging discussions?

The hands-on workshops were a real success. Attendees were very interested in learning some procedures, and in my workshop, we dealt with transjugular biopsies, hepatic venous pressure gradient measurement, and transjugular intrahepatic portosystemic shunt. Many questions were raised and the interaction in small groups is always very helpful.

Q8 How influential is EASL in the ongoing education of clinicians and, ultimately, the management of patients?

This is a top-level meeting that always attracts many physicians and not just from the hepatological field. Indeed, what makes EASL almost unique is the increasing involvement of specialists from other fields, with not only doctors but also nurses and technicians, to cover the entire spectrum of patients' needs and continuously promote multidisciplinarity. ●

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Interview

In the following interview, Nancy Reau, an experienced hepatologist, shares insights from her career specialising in complex liver disease. Reflecting on the changes she has observed in her journey to date, she provides her perspective on the likely future direction of this field.

Featuring: Nancy Reau

Nancy Reau

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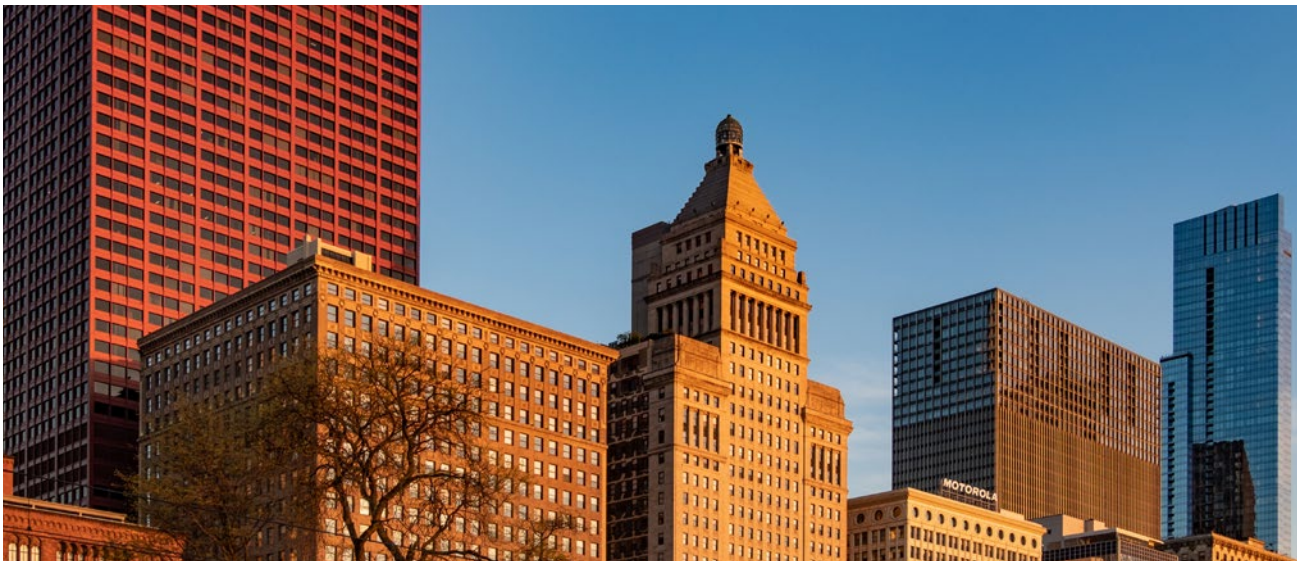
Q1 Was there a particular event or person that inspired you to pursue a career in medicine?

My father always wanted me to be a doctor. He was a police officer and would come home late at night, talking about forensics and autopsies. My best friend in grade school had doctor parents, a neurologist and neurosurgeon. I think the cool magazines in their house and my father's enthusiasm piqued my interest in medicine. It wasn't until college, where I realised that my degree in neuroscience had limited job opportunities, that I truly decided to become a doctor. I haven't regrated that decision since.

Q2 What is it that interests you most and has led you to specialise in the treatment of complex liver diseases?

I was never going to be a very good primary care doctor. I always wanted to know everything about the condition in front of me and didn't want to transfer my patient to a subspecialist just when I thought I had an intervention to offer. Still, I really enjoyed helping people navigate a path toward health, transplant, or supportive care. When I first became interested in liver disease there weren't many therapeutic options other than transplant, but not everyone wants or is a candidate for this life saving therapy. Over my career, we have seen approval of therapies that can cure hepatitis C; We see an opportunity

"The constantly evolving balance between serious disease and scientific innovation is the reason I am a liver specialist."



to offer finite therapy to those with hepatitis B; and we have seen an influx of individuals at risk for advanced liver disease from alcohol or non-alcohol associated liver disease, with an avalanche of potential therapeutics. The constantly evolving balance between serious disease and scientific innovation is the reason I am a liver specialist.

Q3 With over 15 years of experience in both hepatology and gastroenterology, what are the most significant changes you have observed in these specialties over the course of your career?

The conversation of cure. Rarely can you diagnose and then eradicate a disease that causes a chronic condition or illness. Given the amazing drug innovation with hepatitis C, this has challenged us with reimaging hepatitis B and D as curable.

When I was in training, if you wanted to know how diseased the liver was you had to obtain a liver biopsy. Now, with multiple reliable non-invasive options for fibrosis assessment; staging is rarely done with a liver biopsy.

The prevalence of liver disease, which used to be rare. Now one in four Americans have fatty liver disease from metabolic disease. Alcohol use disorder is increasing, along with liver related complications, and liver cancer rates continue to increase. Given these statistics, nearly every American is impacted by liver disease or are at risk of liver injury.

Q4 Having authored and co-authored more than 100 peer-reviewed articles and several books, which parts of your research do you feel have had the greatest impact on practice, and what are you most proud of?

It is rare to have a publication that impacts practice. However, I do think that recognising early treatment response and futility had a significant role in hepatitis C management when we were using pegylated interferon-based therapy. These rules may resurface with hepatitis D, or even in our non-alcoholic fatty liver disease (NAFLD) therapies when you want to minimise exposure to a futile therapy. Guidelines have a huge impact not just in practice management but by setting the standard of care. I was very fortunate to be one of the original authors on the American Association for the Study of Liver Diseases (AASLD) / Infectious Diseases Society of America (IDSA) hepatitis C guideline document. I also am an author and reviewer for UpToDate.[1] This platform is so widely used that you know the authors are impacting practice patterns.

Q5 Are there any innovative approaches/technologies for organ, and more specifically liver, transplantation you expect to transition into common practice in the future?

We need to optimise marginal organs. Our donors reflect the general populations, meaning that they are both older and impacted by metabolic diseases. Metabolic syndrome increases risk of

fatty liver disease; however, a liver with steatosis may not do well after liver transplantation. There are several exciting ideas on how to make these organs safer for transplant.

We are also seeing increased utilisation of organs that would have previously been considered high risk. Hepatitis B virus is controllable and Hepatitis C virus is curable. These organs are great options for some recipients.

I also think we need to find ways to use more of our organs that are donated after circulatory death. Cardiac death is very stressful for the liver, but not all organs perform badly. Finding a way to use this valuable resource without compromising the outcome is very important.

Lastly, until we have synthetic liver options. Living related donation should be increasing but remains a minority of our transplant population. This is a great alternative for individuals who are not severely sick but still need transplant.

Q6 Which topics within the field of hepatology do you feel warrant further study? Are there any gaps in literature you feel most urgently need to be addressed?

The obvious gap is identifying fatty liver disease from both metabolic syndrome/obesity and alcohol use disorder. I think the most important conversation centres around prevention. We need to identify those at risk and aggressively work to prevent, stabilise, and reverse their disease. There are also significant genetic risk factors. Our newest NAFLD guidelines recommend screening first degree relatives of those with NAFLD associated cirrhosis for fatty liver disease. This is incredibly important and under recognised.

Q7 What advice would you give a younger clinician, taking their first steps to become a practicing clinician and educator now?

Enjoy what you do but make sure it is part of your long-term vision. I'm lucky, I always seemed to be in the right place at the right time. I had amazing mentors and sponsors and it really felt like I was handed a gift when I was recognised for my expertise. You need to work hard, but you don't need to do everything that everyone wants you to do. That's where having a network is imperative. It's like tumour board. Sometimes the answer is easy, and you don't need the collaboration. But sometimes you need to bounce your ideas off your friends. You don't have to take their advice, but it really helps place the situation into context.

The other piece of advice I would offer, is rank your value. It is well established that females tend to make about 20 cents less per dollar than their male counter parts. But line up your priorities. If your salary is most important, you will be able to negotiate reimbursement that is equal to your peers (irrespective of gender). But, if flexibility in your schedule is more important, this might come at a financial cost. I was fortunate as my husband was also a doctor, so we didn't rely on my salary. But my husband was a surgeon, so when our children were small, we relied on my presence. I knew I was 'underpaid', but that was worth the flexibility in hours and call. By negotiating flexibility in my time, I was not only able to be with my children, but I also was able to do academic work that allowed me to be promoted in line with peers.

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Biomarkers for Liver Disease

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Imaging in NASH and NAFLD

Blood tests, MRI, and ultrasound are used to determine liver function.

- Currently liver biopsy is required to diagnose suspected NASH.
- There is growing support for the idea patients with NAFLD can be diagnosed and staged adequately using non-invasive strategies, and liver biopsy should be exclusive to subjects with diagnostic uncertainty.

Gaps in research and future directions

1 **Projected increase in global burden of liver disease from NAFLD has shown non-invasive detection and monitoring a major unmet need.**

New, widely applicable non-invasive diagnostics are urgently required and would eliminate need for a liver biopsy.

Differentiating benign steatosis from progressive NASH is a significant challenge.

2 **Defining the optimal combination of imaging and blood-based biomarkers is warranted in future study.**

Establishing cut-off points will help guide the management of patients.

Multicentre longitudinal study is required on the impacts of non-invasive imaging on histology and liver-related events, and to minimise reliance on biopsy.

Due to the lack of a simple, widely available biomarker for NASH, a pragmatic diagnostic and staging approach should be adopted.

Liver Biopsy

- Until recently, imaging biomarkers have only shown modest diagnostic accuracy for NASH.
- Histology by an expert is the gold standard for diagnosing NASH and staging liver disease in NAFLD.

- It is expensive, invasive, and associated with complications
- Cannot be applied to large scale screening programmes, and currently only used for high-risk groups.

Comparison to New Biomarkers

MRI-PDFF

- Shows promise as an emerging quantitative biomarker that accurately measures liver fat, and is more informative than liver biopsy following longitudinal changes

Multi-parametric MRI

- Shows promise assessing hepatic steatosis, inflammation, and fibrosis
- Helpful, sensitive, and accurate non-invasive method for identifying individuals with active and advanced stages of NAFLD

Key

NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; MRI-PDFF: MRI-derived proton density fat fraction.

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Intrahepatic Splenosis in a Patient with Autoimmune Hepatitis with No History of Splenectomy or Abdominal Trauma

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Abstract

Splenosis should be suspected when a patient has a history of trauma or abdominal surgery. Intrahepatic splenosis is a rare disease that is often difficult to distinguish from liver malignancy, especially hepatocellular carcinoma. The cause of intrahepatic splenosis may be though the auto-transplantation of splenic tissue on the surface of the liver. The authors report a case of intrahepatic splenosis that presented as a liver tumour in an 81-year-old female treated for autoimmune hepatitis, who had no history of splenectomy or abdominal trauma. Laparoscopic hepatectomy was performed and the specimen demonstrated characteristic histopathological findings of the spleen. Only one case of a patient who had no history of splenectomy or abdominal trauma has been reported in the literature. It may be hypothesised that erythropoiesis induced by local hypoxia in the chronic hepatitis may cause the growth of splenic erythrocytic progenitor cells, which have migrated via portal vein to the liver.

Key Points

1. Generally speaking, intrahepatic splenosis (IHS) has been thought to occur after splenectomy or abdominal trauma. In this case report, IHS occurred in the patient who had no splenectomy or abdominal trauma.

2. Here, the authors explain the imaging diagnosis of IHS, and differential diagnosis from hepatic malignancy. The cause of IHS was inferred from previous literature.

3. When an atypical hepatic tumour is found, it is important to keep in mind that IHS could be one of the differential diagnoses, even if the patient has no history of splenectomy or abdominal trauma.

INTRODUCTION

Intrahepatic splenosis (IHS) is thought to be formed by the intrahepatic proliferation of splenic tissue by autograft after splenic injury or splenectomy. It is important to include IHS in the differential diagnosis based on splenic injury and history of abdominal surgery, as it can be difficult to differentiate it from hepatic malignancy, especially hepatocellular carcinoma (HCC), on imaging diagnosis. In this report, the authors describe a case of IHS diagnosed by pathological examination in a patient with no abdominal trauma or history of surgery.

CASE REPORT

An 81-year-old female was being observed by their primary care physician for autoimmune hepatitis. The patient was found to have elevated liver enzymes and was referred to the authors' internal medicine department on suspicion of HCC. The patient was asymptomatic, and had no history of any abdominal trauma or surgery.

Patient History

In early 2013, the patient was examined for abnormal liver function. Their antinuclear antibody was 1:1280; their IgG level was 3475mg/mL; and their hepatitis virus markers were negative. There was no other cause of hepatitis. As a result, the patient was treated with ursodeoxycholic acid as a patient with autoimmune hepatitis. The patient's details were taken on admission, including height: 157 cm; weight: 47 kg; clear consciousness; body temperature 36.1 °C; blood pressure 151/87mmHg; pulse 88 /min; well-conditioned; no anaemia or yellowing of the ocular conjunctiva; and a flat, soft abdomen. Laboratory findings on admission showed a mildly elevated aspartate transaminase of 35 IU/l and lactate dehydrogenase of 254 U/l. Both hepatitis B surface antigen and hepatitis C virus qualitive were negative, and tumour markers carcinoembryonic antigen, α-fetoprotein, and protein induced by vitamin K absence-II were within the reference values.

Abdominal contrast CT was performed. An examination in early 2017 showed a 13 mm large low-density area in segment VIII (S8) of the liver, faintly contrasted in the arterial and portal phases, and indistinguishable from normal tissue in the equilibrium phase. The enhancement pattern was different from typical HCC, and more like haemangioma. At this point, the authors diagnosed a haemangioma of the liver, and followed-up 10 months later with a CT examination in early 2018. The mass had increased to 30 mm. In the arterial phase, part of the margin was faintly enhanced, and the margin was predominantly faintly enhanced in the equilibrium phase (Figure 1). The contrast effect was stronger than the previous CT examination.

Abdominal gadoxetic acid-enhanced MRI (Gd-EOB-MRI) findings include a 30 mm large mass in S8, showed as a pale contrast effect on a part of the limbus in the arterial phase and a partially missing image in the late phase. The hepatocellular phase also showed low intensity and diffusion-weighted imaging, which revealed a slightly high signal area (Figure 2). These findings were consistent with HCC. Abdominal ultrasonography: a heterogeneous mass was seen in S8 of the liver. Colour doppler showed no blood flow signal within the mass.

Treatment and Course

Based on the above examinations, the mass was growing, and HCC could not be ruled out, so the patient underwent laparoscopic partial hepatectomy in spring 2018. The liver surface was uneven due to coarse regenerative nodules, giving the appearance of chronic hepatitis. The surface of the mass in S8 was white, depressed, and trailing. There was no mass in the abdominal cavity.

Pathological Examination

The mass was 20 mm in size, had a capsule, and was reddish brown with white cord-like material (Figure 3A). The surface of the mass was depressed (Figure 3B). Microscopic examination showed a thick connective tissue capsule, some arteriovenous inflow from the liver, one fibrous nodule containing arteriovenous vessels thought to be a splenic column, and an associated lymph follicle (Figure 3C). The histopathological findings confirmed that the lesion was composed of typical splenic tissue (i.e., IHS). In the background liver, mononuclear cells infiltrated around the portal and periportal areas, which was consistent with autoimmune hepatitis (Figure 3D). Post-operative course was uneventful, and the patient was discharged on post-operative Day 8.

DISCUSSION

Splenosis was first described in 1939, when Buchbinder et al.[1] named the splenic tissue that remained viable in the abdominal cavity after splenectomy following traumatic splenic injury as splenosis. It is an ectopic autograft, unlike a congenitally developed accessory spleen, and all patients have a splenic history of trauma or abdominal surgery. Some reports estimate that as many as 26–65% of patients with splenic rupture develop splenosis.[2,3] They are often discovered 10–20 years after splenic injury or abdominal surgery, and the number varied from 1–400 in the literature.[4] The omentum, mesentery, and serosa of the intestinal tract are common sites for splenosis.[5,6] There are some case reports that have occurred in the thoracic cavity.[7,8]

IHS is very rare, and even with today's advanced diagnostics there are still cases mimicking as hepatic malignancies.[9-13] Toh et al.[14] demonstrated a review of 59 cases in their study between 1939 and 2019. IHS should be diagnosed by the triad of history of splenectomy or abdominal trauma, absence of risk factors for liver malignancy, and typical contrast pattern on imaging studies.[14,15] (The contrast pattern of CT and MRI is described below.)

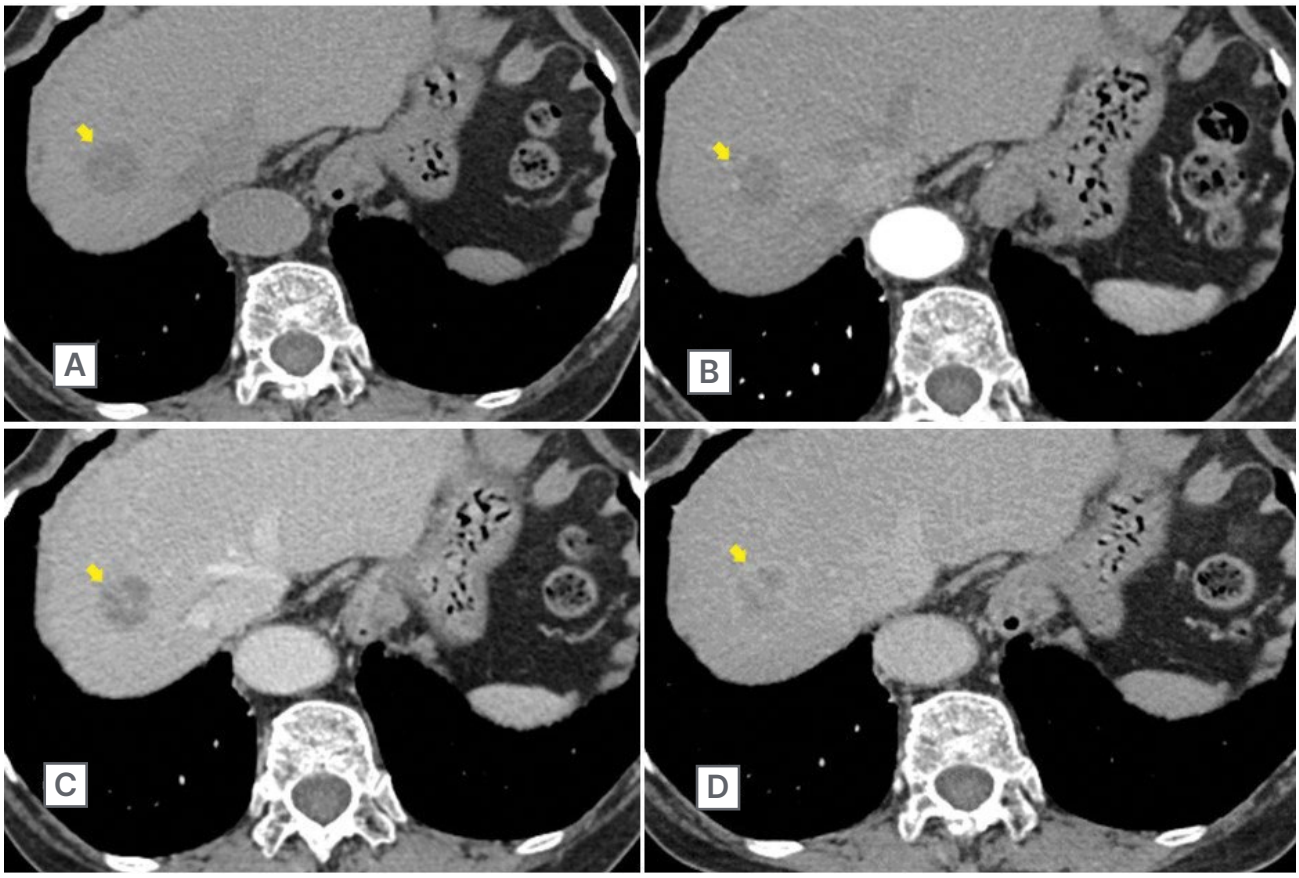
The mechanism of IHS is generally thought to be the growth and proliferation of disseminated splenocytes, like other cases of splenosis on the serosa of the organs.

What then should be the explanation in this case? IHS without a history of abdominal trauma or surgery has only been reported in one case.[16] In that case, chronic hepatitis C infection was present in the background liver. Kwok et al.[17] suggested the particular mechanism of IHS. They hypothesised that erythrocytic progenitor cells somehow strayed into the liver via the portal vein after splenic trauma, and ectopic splenomegaly was induced by erythropoiesis due to local hepatic hypoxia.[17] In this mechanism, the presence of background viral hepatitis or other liver disorder may be a factor in causing intrahepatic hypoxia.[18,19] In a present case, the background liver was histologically severe hepatic degeneration by autoimmune hepatitis. Intrahepatic hypoxia could have occurred, and there was thought to exist a potential of IHS.

In terms of imaging diagnosis, this case did not show any characteristic findings of HCC on contrast-enhanced CT scan, but the T2-weighted image of Gd-EOB-MRI showed mildly high signal in the arterial phase, the hepatocellular phase showed a loose image, and diffusion-weighted imaging showed high signal, which led to suspicion of HCC. Therefore, the patient was suspected to have HCC. Moreover, the background of autoimmune hepatitis was a possible risk factor for HCC. Fine needle biopsy is one of diagnostic methods for histopathology, but there is a risk of peritoneal dissemination.[20] Liver biopsy should be avoided as much as possible, and the authors decided on a partial resection of liver. Nowadays, laparoscopic surgery is performed as a safe and minimally invasive procedure.[21,22]

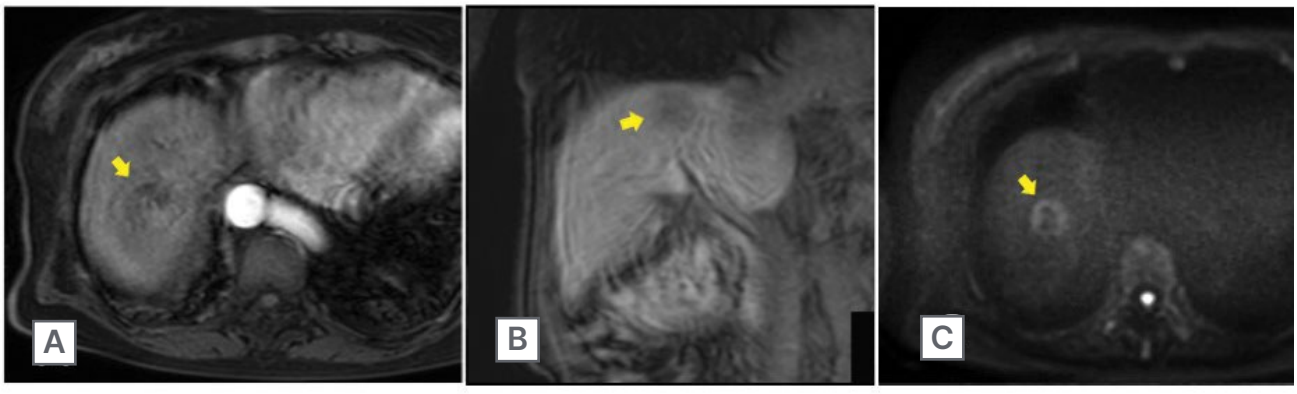
IHS was reported to present a variety of images in the literature. Varghese et al.[23] reported that CT demonstrated 'archiform' enhancement pattern in the arterial phase and homogenous filling-in enhancement on portal venous and delayed phases.[23] However, in another case, there was heterogeneous hyperenhancement in the arterial phase, isodensity in the portal venous phase, slight hypodensity in the delayed phase, and delayed enhancement of the capsule.[24] CT imaging in each case is so varied that diagnosis can only be made with the use of other modalities. Gd-EOB-MRI is often used for differential diagnosis of hepatic malignancy; however, MRI could not rule out malignancy based on the findings of low signal in the hepatocellular phase and high signal in the diffusion-weighted image.[25]

Figure 1: Abdominal contrast CT scan in March 2018.



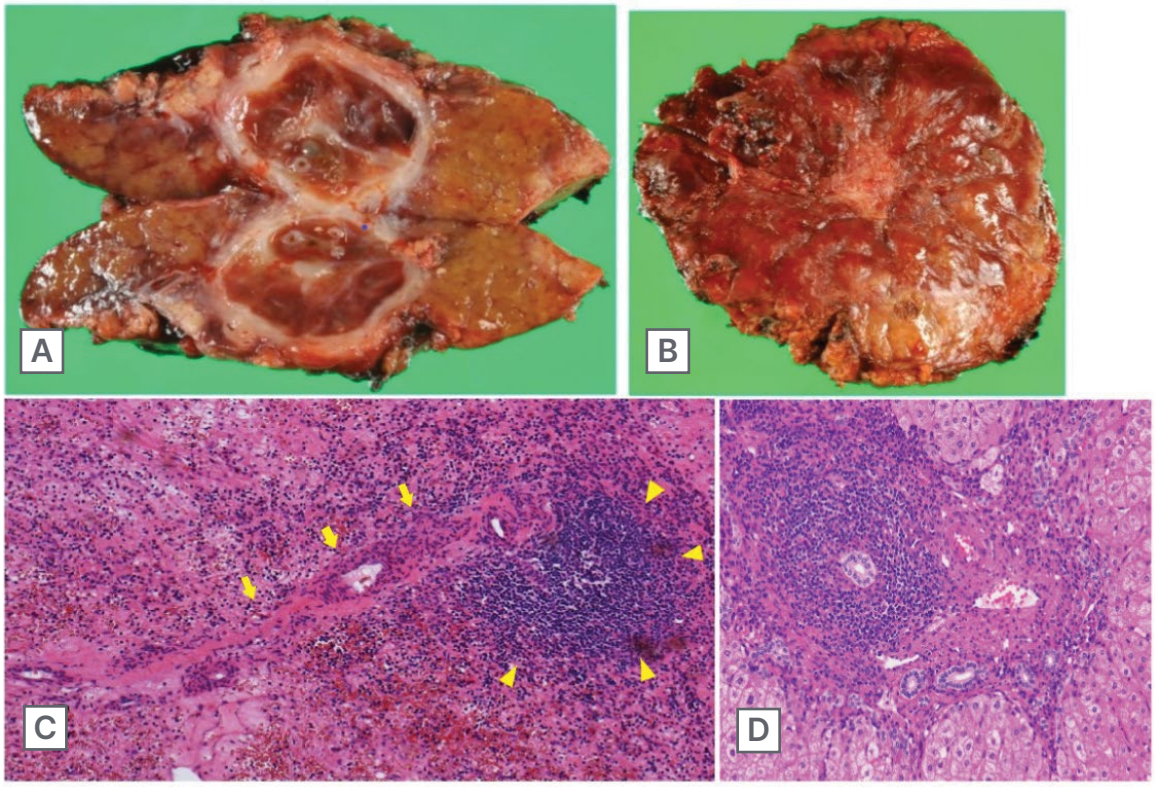
This scan showed a 30 mm large mass lesion (arrow) in segment VIII of the liver (**A**). The enhancement effect progressively increased in the arterial phase (**B**), portal phase (**C**), and equilibrium phase (**D**).

Figure 2: Gadoxetic acid-enhanced MRI scan of the abdomen.



Scan of the abdomen showed a 30 mm large mass lesion (arrow) in segment VIII. In the arterial phase, the lesion had a faint contrast effect at the margins (**A**), and in the late phase changed low signal (**B**). Diffusion-weighted imaging revealed slightly high signal area (**C**).

Figure 3: Cut surface of the resected specimen.



Analysis of the cut surface showed an encapsulated, round shape mass and 20 mm in diameter (**A**). The liver surface was uneven due to coarse regenerative nodules, giving the appearance of chronic hepatitis, and the surface of the mass was depressed (**B**). Histopathological examination revealed a fine fibrous structure containing large amounts of blood, with a single splenic arteriovenous-like structure (arrow) and associated lymph follicular formation (arrowhead) (**C**). The background liver revealed dense portal and periportal mononuclear cells infiltrate, forming interface hepatitis that is a relatively typical finding of autoimmune hepatitis (**D**).

There are some recent cases that were diagnosed with splenosis by MRI with other modalities that have been reported.[26-28] Sonazoid contrast-enhanced ultrasonography has been reported to be useful in differentiating HCC.

In the early arterial phase, the nodule was more enhanced compared with the surrounding liver parenchyma, and in the late vascular phase (Kupffer phase), the enhancement sustained compared with that of the surrounding area and did not show obvious defects as in HCC.[29]

Some cases have been reported where the use of Tc99m heat-denatured red blood cells scintigraphy allowed diagnosis confirmation, demonstrating phagocyte ability in the ectopic splenic tissue.[30] Moreover, single-photon emission CT/CT after isotope administration increased specificity of planar imaging.[31-35] However, Tc99m heat-denatured red blood cell scintigraphy has demonstrated superior sensitivity in the identification of residual or heterotopic splenic tissue, but preparation is complicated, and *in vitro* technique of isotope labelling is necessary. Kawada et al.[36] reported a more convenient method using Tc99m sulfur colloid (conventional spleen scintigraphy), which is useful for differential diagnosis.

Although this scintigraphy is easy and cost-effective, it is somehow difficult to distinguish between liver parenchyma and the ectopic splenic tissue. In this case, the patient did not have a history of splenectomy or abdominal trauma. IHS did not come to mind as a differential diagnosis, so splenic scintigraphy was not even considered.

In conclusion, IHS is a differential diagnosis that should be kept in mind when an atypically enhanced hepatic lesion is encountered in a patient with previous splenic trauma or splenectomy. It should be noted that IHS can occur even in very rare cases without splenectomy or abdominal trauma, as in the case presented here.

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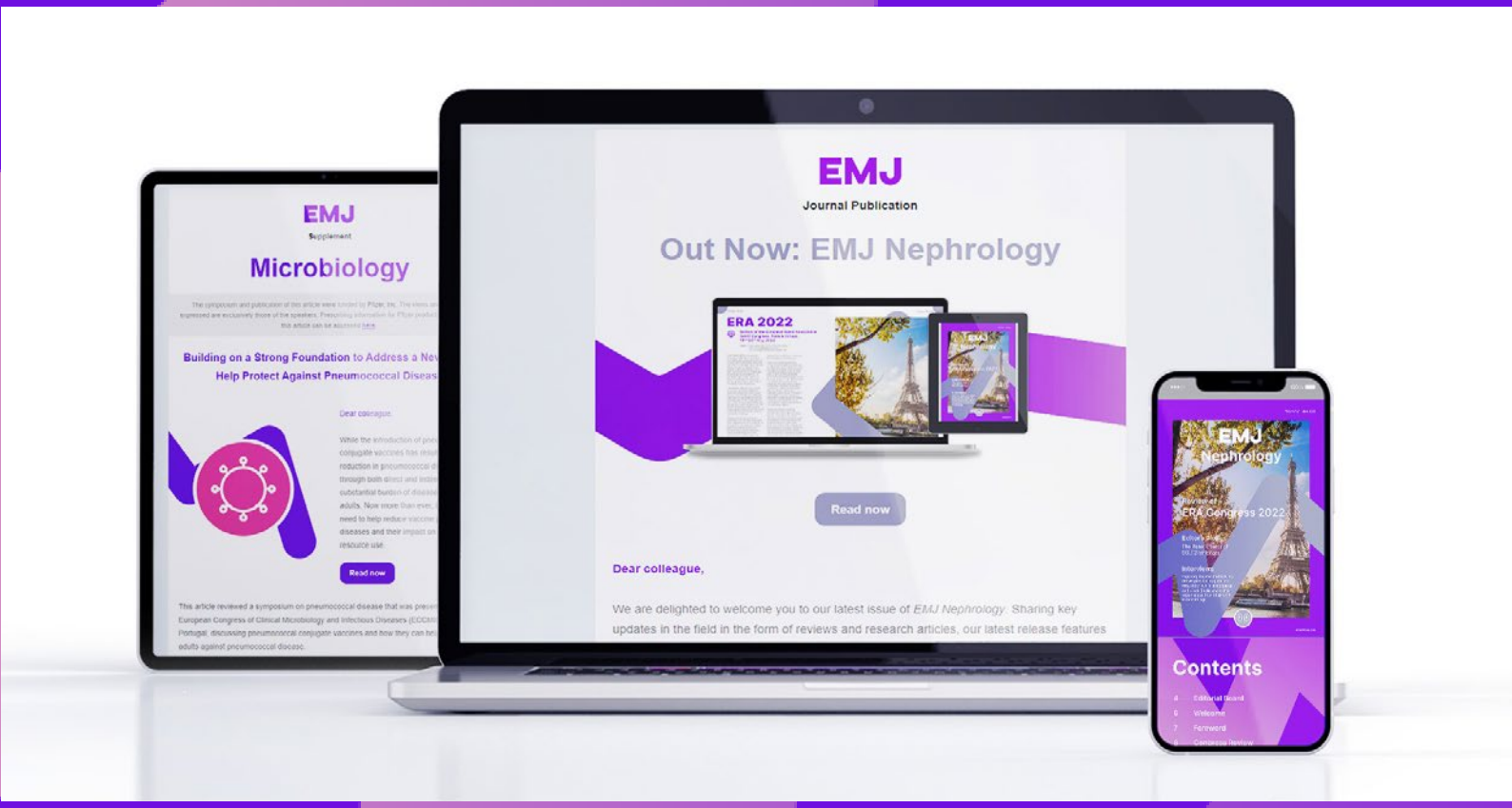

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