Highlights from Hepatology 2015:
From Chronic Hepatitis to Hepatocellular Carcinoma

Therapeutic Strategies in Diseases of the Digestive Tract – 2015 and Beyond
Pluripotent stem cells can be differentiated in vitro and transplanted in vivo to form mature and functional human intestine. The image, provided by the Helmrath laboratory (Cincinnati, USA), depicts pluripotent stem cell-generated human small intestine 8 weeks after engraftment into a NSG mouse; with human intestinal DNA (pink), total DNA (blue), smooth muscle (green) and recipient kidney (red).
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At Falk Symposium 199 “Highlights from Hepatology 2015: From Chronic Hepatitis to Hepatocellular Carcinoma”, it became clear that a major breakthrough had been made in the treatment of hepatitis C. The numerous unmet medical needs in the treatment of viral hepatitides were also highlighted, however, including the development of a prophylactic vaccine against hepatitis C (HCV) and virostatics, which are used to achieve high sustained virologic response (SVR) rates in patients with hepatitis B (HBV) infections. The significance of hepatitis E (HEV), which can have a chronic progression in immunosuppressed patients in particular, is underestimated.

With advances in the treatment of viral hepatitides, focus is shifting to other causes of fibrosis of the liver, cirrhosis of the liver and hepatocellular carcinomas, in particular to non-alcoholic steatohepatitis, which is becoming increasingly prevalent. Currently, there is no established treatment, which makes it all the more important to deal with the complications of cirrhosis of the liver correctly, above all variceal bleeding and ascites, which should be promptly treated with a TIPS. The prognosis for patients with autoimmune hepatitis (AIH) and primary biliary cholangitis/cirrhosis (PBC) is good if these diseases are recognized early. This is not the case for primary sclerosing cholangitis (PSC). Norursodeoxycholic acid and FXR agonists could improve this prospect, however. With regard to hepatocellular carcinomas, for which there is currently an unsatisfactory range of treatment options, focus is shifting towards immunotherapies such as checkpoint inhibitors and the depletion of regulatory T-cells. For inoperable cholangiocarcinomas, the blockade of HER2 and AKT signaling pathways is currently being tested.

The Falk Symposium 200 “Therapeutic Strategies in Diseases of the Digestive Tract – 2015 and Beyond” covered a wide range of current developments in the treatment of diseases of the entire gastrointestinal tract, from the esophagus to the stomach, pancreas, bowel and liver. Barrett’s esophagus, Barrett’s neoplasia and the relevance of eosinophilic esophagitis, which is attracting more and more interest, dominated discussions of the upper digestive tract. Deciding whether or not to treat early Barrett’s neoplasia with endoscopic resection is critical in particular. Helicobacter pylori still determines processes in the stomach. Eradication as a preventative measure in asymptomatic patients is no longer called into question. However, established treatment regimes do not always work, in which case alternative options must be sought.

The pancreas is often forgotten, yet pancreatic carcinomas are still a catastrophic diagnosis for patients. Even targeting treatments, which are effective against numerous carcinomas, do not provide a significant breakthrough here. This makes it all the more important not to overlook autoimmune pancreatitis or misdiagnose it as a carcinoma.

Since defective intestinal barriers have been recognized as an underlying cause of inflammatory bowel disease, researchers have been intensively searching for medications to eliminate this defect. New options include phosphatidylycholine and defensins.

For chronic liver diseases, it is important to ask what can be done if fibrosis of the liver has already developed. Current treatment attempts include the blockade of TGF-β and the inhibition of cannabinoid receptors.

In addition to individual presentations, it was the highly engaging discussions in particular that characterized both symposia: discussions to critically evaluate existing data, provide impetus for new research projects and directly improve patient care.
Autoimmune diseases of the liver: good prognosis if diagnosed early

The prognosis is good: In most cases, patients with autoimmune hepatitis or primary biliary cholangitis/cirrhosis can be effectively treated and have an almost normal life expectancy. The precondition is that these diseases are diagnosed early, ideally before the development of cirrhosis. This is not always straightforward.
Puzzle of genetic and non-genetic risk factors

An entire puzzle of genetic and non-genetic risk factors is involved in the pathogenesis of hepatic autoimmune diseases and cholestatic liver diseases, explains G. Hirschfield, Birmingham (United Kingdom). The good news is that, if recognized early, at least autoimmune hepatitis (AIH) and primary biliary cholangitis/cirrhosis (PBC) can now be treated effectively.

But this is not the case for all patients, as “we are still identifying autoimmune hepatitis too late,” criticizes C.P. Strassburg, Bonn (Germany). Wherever possible, AIH should be recognized before the patient has developed cirrhosis, as this is a determining factor for the necessity of liver transplantation and for mortality rate. Elevated LFT values are an important indication that must always be investigated further. “Normal transaminase levels do not exclude AIH, however,” stresses C.P. Strassburg, who also dispelled the widespread opinion that AIH predominantly manifests itself in young women aged between 20 and 30. According to data from 164 consecutive AIH patients, it is at least as likely to occur in older people over 50 or 60 (Al-Chalabi T, et al. J Hepatol. 2006; 45(4):575–83).

Look to extrahepatic autoimmune diseases

Diagnosis is difficult and histology alone is not sufficient. Other causes of hepatitis, including viral hepatitides, Wilson’s disease, hemochromatosis and alpha-1 antitrypsin deficiency, must be reliably ruled out. The suspicion may be substantiated in patients with elevated LFT values and a concomitant extrahepatic autoimmune disease, such as rheumatoid arthritis, diabetes mellitus, vitiligo or lichen planus. Looking at the typical autoantibodies for Type 1 autoimmune hepatitis, such as ANA (antinuclear antibodies) and SMA (smooth muscle antibodies), is also diagnostically significant (Fig. 1).

Of prognostic relevance – SLA/LP autoantibodies

Another specific autoantibody of Type 1 AIH is the SLA/LP (soluble liver antigen/liver pancreas antigen) autoantibody, which also seems to be prognostically relevant, according to a current study (Kirstein M, et al. Hepatology. 2015;62(5):1524–35). In order to determine the influence of clinical, serological and genetic parameters on the prognosis of AIH, the study observed 354 patients between 2000 and 2014.

This revealed an important result: The detection of SLA/LP autoantibodies was significantly associated with a reduced overall survival rate and reduced survival rate without transplantation. This makes it an important risk factor for short- and long-term patient outcome.

Fig. 1 Immunofluorescence imaging of autoantibodies ANA and SMA in Type 1 autoimmune hepatitis (C.P. Strassburg, Bonn)
Budesonide as a well-tolerated alternative

If AIH is diagnosed, the aim is to induce and maintain biochemical and histological remission as quickly as possible. C.P. Strassburg defines remission as the complete normalization of transaminase levels, serum IgG and histology. Standard treatment strives to induce remission using prednisone. If the patient responds well, this is combined with azathioprine to begin with and then gradually phased out.

As an alternative for patients with AIH without cirrhosis, C.P. Strassburg points to topical steroid budesonide with a hepatic first pass effect of over 90% as well as good tolerability. Budesonide has a similar efficacy to prednisone, but has a higher tolerability.

Following a change in medication from prednisone to budesonide, steroid-specific side effects fall from 40.2% to 18.4% (Fig. 2).

PBC: consider the possibility of secondary AIH

Early diagnosis is also ideal for PBC. This is because ursodeoxycholic acid (UDCA), which is the standard treatment for PBC, can achieve a survival rate without liver transplantation in responders similar to that of the normal population (Corpechot C, et al. J Hepatol. 2011;55(6):1361–7). “Response to UDCA is an important predictor of mortality and liver transplantation,” says O. Chazouillères, Paris (France) (Fig. 3).

“It is possible that at least some non-responders have secondary AIH and therefore require concurrent immunosuppressive therapy,” says A.W. Lohse, Hamburg (Germany). With a prevalence of 10–20%, this kind of variant syndrome – a term that has replaced overlap syndrome – is relatively common.

Treatment should then be determined by the inflammatory component of AIH, says A.W. Lohse, and ultimately result in triple therapy with prednisone, azathioprine and UDCA. A variant syndrome between primary sclerosing cholangitis (PSC) and AIH is also possible. This should be considered, for example, when typical AIH does not fully respond to

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\text{Figure 2: Reduction in steroid-specific side effects after changing from prednisone to budesonide during remission induction treatment for autoimmune hepatitis (Manns M et al. Hepatology 2008;48(Suppl):376-7)}
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immunosuppression and γ-glutamyl transferase and alkaline phosphatase are raised, or when patients with typical PSC show signs of AIH, such as elevated IgG, autoantibodies and increased ALT/AST.

This is treated with immunosuppressive therapy, with or without additional UDCA (Boberg K, et al. J Hepatol. 2011;54(2):374–85). Treatment should be tailored to the individual, taking into consideration treatment response and side effects, explains A.W. Lohse. There is currently no known variant syndrome between PBC and PSC.

**Bright future**

These are “promising times” for patients with cholestatic liver diseases, says O. Chazouillères – indeed, with fundamental research bringing to light new findings, research activity in this field is more intensive than ever. This begins with monitoring. For PBC, the biochemical response to UDCA should be monitored after one year and an elastograph carried out every one to two years. In PSC, the focus is on determining alkaline phosphatase as well as performing elastography in order to identify at-risk patients at an early stage and prevent the development of cirrhosis.

Researchers on their search for new, effective active ingredients against cholestatic liver disease, preferably with anti-cholestatic, anti-fibrotic and anti-inflammatory effects, still have their sights set on norursodeoxycholic acid (norUDCA), obeticholic acid and fibrates as well as budesonide. Budesonide as a glucocorticoid receptor/PXR agonist is currently being tested in combination with UDCA in an ongoing phase III trial for patients with PBC and a high risk of disease progression.

**Prognosis and response to UDCA in early PBC**

*Fig. 3  Response to UDCA in patients with PBC as an important predictor of mortality and the necessity of liver transplantation (Corpechot C et al. J Hepatol. 2011;55(6):1361-7)*

**Highlights from Hepatology 2015: From Chronic Hepatitis to Hepatocellular Carcinoma**

**Viral hepatitides: still a major health problem worldwide**

Viral hepatitides, associated with a significant morbidity and mortality rate, still rank among the world’s biggest health problems, says H.E. Blum, Freiburg (Germany). According to a 2012 publication, this trend is growing (Lozano R, et al. Lancet. 2012;380(9859):2095–128): The number of patients worldwide who have died from HBV-induced cirrhosis of the liver rose from 242,000 in 1990 to 312,000 in 2010. In 1990, acute hepatitis E claimed 35,000 lives, compared with 57,000 in 2010. The danger of liver damage caused by alcohol is also on the rise. During the same period, the number of deaths caused by alcoholic cirrhosis of the liver increased from 206,000 to 283,000.

**Degradation of cccDNA in hepatitis B: the key to success?**

The progress that has been made for hepatitis C, i.e. SVR (sustained virologic response) achieved in over 90% of patients, is still a long way off for hepatitis B. Current treatment regimes for hepatitis B, peginterferons and nucleos(t)ide analogues, are only able to achieve a HBsAg loss in 2–3% of HBeAg-positive patients and in less than 1% of HBeAg-negative patients.

Combining two nucleoside analogues only marginally improves the result, says F. Zoulim, Lyon (France).

**Milestones of hepatitis C treatment**

![Milestones of hepatitis C treatment](image-url)

**Fig. 4** Milestones of hepatitis C treatment (R.Thimme, Freiburg)
The results achieved with currently available medication are “disappointing,” according to F. Zoulim, who highlighted the necessity of long-acting therapy to at least achieve virus suppression as a further challenge. New concepts must therefore be developed as a matter of urgency.

Research is currently focusing on improving existing treatment regimes, for instance with prodrug tenofovir alafenamide, which shows better stability in the plasma. With a tenfold lower dose, the same effect can be achieved as with tenofovir. Additional areas of focus include entry inhibitors, an attack on the HBV capsid and the degradation of ccc(covalently closed circular)DNA. “The degradation of cccDNA could be the key to success,” says F. Zoulim.

**HCV infection in the era of DAAs: first cases of resistance in “very few patients”**

Chronic hepatitis C virus (HCV) infection is the most frequent cause of cirrhosis of the liver, hepatocellular carcinoma (HCC) and liver transplantation. With the development of a wide spectrum of DAAs (direct-acting antivirals), it is now possible to eliminate the virus in more than 90% of patients with interferon-free treatment regimes using various combinations of these DAAs. However, D. Moradpour, Lausanne (Switzerland), objects that more than 50% of infected patients do not know that they have the disease, making it important to screen at-risk patients, especially given the range of treatment options available. In addition to patients with clinical signs or symptoms of hepatitis, screening should also be offered to those who received blood transfusions or solid organ transplantsations before 1992, dialysis patients, those with HBV or HIV infections as well as intravenous or intranasal drug users, prisoners, people with piercings or tattoos and children of HCV-infected mothers.

D. Moradpour also raises a red flag: There are already problems with resistance, “albeit only in a very small number of patients.” He stresses the need to keep an eye on this issue, and emphasizes that, “when we treat, we need get the treatment right the first time.” In a study, 41 patients who failed to respond to an initial 8- or 12-week treatment with ledipasvir/sofosbuvir received the same combined treatment for a period of 24 weeks: 71% achieved a SVR.

**Problematic: renal insufficiency plus HCV infection**

X. Forns, Barcelona (Spain), highlights the problems associated with patients with HCV infection and concurrent renal insufficiency, who often suffer from other co-morbidities. Only a small number of studies focus on this area. Interferon-free treatment options for patients with end-stage renal disease are limited. According to X. Forns, a combination of protease inhibitor grazoprevir and NSSA inhibitor elbasvir could be an excellent strategy. This combination was examined in patients with stage 4/5 chronic kidney disease (CKD) with a genotype 1 infection.

**Standstill for hepatitis D**

Hepatitis D treatment has come to a standstill. The problem is that HDV utilizes RNA polymerase of hepatitis B to replicate and remains infective as long as HBsAg, even in minimal concentrations, is present. Nucleoside analogues are not effective and PEG-IFN only has a limited effect and carries a high risk of relapse, says M. Rizzetto, Turin (Italy): “Antiviral agents, which may reduce HBV DNA but have no impact on HBsAg, do not play a role here.”

The currently recommended treatment is pegylated interferon over 12–18 months, which induces a response in 20–25% of patients. “However, as long as HBsAg is present, a relapse may occur,” stresses M. Rizzetto. Entry inhibitors are also being tested as a new therapeutic principle of action, both alone and in combination with PEG-IFN.
HEV infection?
Be aware of neurological complications

Focus is increasingly shifting towards another, frequently forgotten virus: the hepatitis E virus (HEV). For a long time, hepatitis E was assumed to have an acute, self-limiting progression. If the acute infection progresses severely, ribavirin can be administered. In immunosuppressed patients, however, HEV infection can – contrary to previous widespread assumption – also become chronic, either asymptomatic or, less commonly, with quick progression to cirrhosis of the liver. In cases of chronic HEV infection, H.R. Dalton, Truro (United Kingdom), suggests reducing immunosuppressive therapy and commencing monotherapy with ribavirin. He stresses that the main problem of HEV infection is that it carries the risk of neurological complications, such as Guillain-Barré syndrome or brachial neuritis, which require interdisciplinary exchange with a neurologist. He also calls for HEV to be tested for before a DILI (drug induced liver injury) is diagnosed.

ASH: abstinence is a “must”

In patients with alcoholic fatty liver disease (ASH), abstinence is the most important treatment option as well as a decisive predictor of further disease progression, explains R. Bataller, Chapel Hill (USA). In a study presented at the EASL 2014, the median survival rate was 55.8 months for patients with ASH who stopped drinking compared with just 4.27 months for patients who continued to drink. Abstinence can only be achieved with a multi-disciplinary team, however, explains R. Bataller.

According to R. Bataller, ASH is best detected by transient elastography (FibroScan), which has a high acceptance rate among patients. The positive predictive value is 97% with a cut-off value of 13 kPa. He points to the ABIC score, which takes into account age, serum bilirubin, INR and serum creatinine, as a suitable tool for prognostic stratification. ASH patients treated with a TNF-β blockade experienced poor outcomes: The six-month mortality rate increased from 22% to 56%, and the incidence of serious infection from 9% to 34%.

What to do in light of the increasing incidence of NASH?

Non-alcoholic steatohepatitis (NASH) is becoming more and more common, but there is still no approved treatment for it. However, an entire spectrum of specific treatment options is currently undergoing testing in various clinical studies. These include the bile acid norUDCA, which is currently being tested in a phase II trial for NASH, as well as caspase inhibitors, FXR agonists, GLP-1 agonists and vitamin D. In experimental investigations, vitamin D was shown to have positive effects on necrotizing inflammatory processes and fibrosis in patients with non-alcoholic fatty liver disease (NAFLD), says A. Geier, Würzburg (Germany).

The benefits of a substitute for patients with NAFLD and a vitamin D deficiency are currently being investigated. Experi-
mental strategies are focusing on cytokines, in particular interleukin 1 and interleukin 17. In patients with a BMI > 40 kg/m² or > 35 kg/m² plus severe concomitant diseases, bariatric surgery may also have positive effects on NASH.

Hereditary hemochromatosis: also consider non-HFE-HH

Hemochromatosis should not be underestimated as a cause for chronic liver disease. Gene research shows that 80–90% of patients with primary idiopathic hemochromatosis are homozygous for the C282Y mutation in the HFE (high iron Fe) gene.

However, this also means that a negative hemochromatosis mutation analysis does not exclude the presence of hemochromatosis, as gene regions other than the HFE gene (non-HFE hemochromatosis) or completely different chromosome/gene areas can also be a causative factor. Before carrying out a genetic analysis for a suspected non-HFE, a liver biopsy or an MRI should be performed, recommends H. Zoller, Innsbruck (Austria).

Is cirrhosis of the liver reversible? In some cases, yes!

Is cirrhosis of the liver reversible?

For some patients at least, this does seem to be possible. For example, fibrosis markers are shown to decline following bariatric surgery to treat morbid obesity.

In patients with chronic hepatitis B, regression of cirrhosis of the liver was observed following treatment with tenofovir over five years. If new treatment regimes achieve SVR, even patients with chronic hepatitis C can experience regression of cirrhosis. Referring to the EASL’s current recommendations on hepatitis C treatment, M. Pinzani, London (United Kingdom), stresses that treatment should be prioritized in patients with severe fibrosis (F3) or cirrhosis (F4), including patients with decompensated cirrhosis.

Acute inflammation  Chronic inflammation  Cirrhosis  HCC

Fig. 6 Progression of chronic liver diseases (R.Thimme, Freiburg)
Bypass the possibility of variceal bleeding with TIPS

Variceal bleeding, ascites, encephalopathy and spontaneous bacterial peritonitis are the main complications of decompensated cirrhosis of the liver. Prophylactic antibiotics, intravenous administration of vasopressors and ligatures have improved the prognosis after variceal bleeding. Current data advocate the use of TIPS (transjugular intrahepatic portosystemic (stent) shunt) in the early stages of treatment: 63 patients with Child C or Child B cirrhosis of the liver with an active hemorrhage received either a TIPS within the first 72 hours or standard treatment. In a follow-up over 16 months, mortality was shown to be significantly reduced (12% vs. 39%) following early insertion of a TIPS. A TIPS should be used as a pre-emptive measure before the hemorrhage can no longer be controlled, says G. Garcia-Tsao, New Haven (USA). According to current consensus, a TIPS with a PTFE-covered stent should be considered for patients at high risk of treatment failure, ideally within 24 hours (de Franchis R, et al. J Hepatol. 2015;63(3):743–52).

TIPS also an option for extensive ascites

During ascites treatment, care must be taken to avoid a rapid reduction in plasma volume. Performing an albumin infusion after paracentesis reduces the mortality rate. In the case of massive ascites, however, it may be better to place a TIPS, says A.L. Gerbes, Munich (Germany). A meta-analysis of 4 randomized controlled trials revealed a better survival rate in comparison to paracentesis.

Candidates for TIPS are patients with bilirubin < 3–5 mg/dL, without encephalopathy, without a HCC or other liver tumors, with open portal veins and efferent liver veins as well as compliance with the required medication and dietary recommendations. If just one of these criteria is not met, large-volume paracentesis followed by albumin infusion should be performed.

Microbiome affects liver sensitivity to noxious substances

Excessive alcohol consumption increases the risk of liver disease. One possible reason for this could be a modified microbiome. G. Perlemuter, Paris (France), found that alcoholics had a specific dysbiosis, which is accompanied by severe alcoholic hepatitis. His research group transferred intestinal microbiome from patients into aseptic mice, and found that this increases liver sensitivity to harmful noxious substances.

This suggests that the intestinal microbiome helps to determine how the liver reacts to alcohol. A decline in bacteroides is accompanied by an increase in liver damage. If probiotics or fecal microbiota transplantation can inhibit the decline of bacteroides, this will prevent steatosis and inflammation.
**The importance of genetics**

The better our understanding of a disease's genetic background, the better we can understand and classify the pathophysiology and develop strategies for diagnosis and treatment. As a typical example, F. Lammert, Homburg (Germany), shows that an ABCB4 defect can cause a wide range of diseases, from heterozygous mutations, which can lead to mild chronic cholestasis, to homozygous mutations, which may cause decompensated biliary cirrhosis.

**Vaccine against hepatitis C – still a necessity**

A therapeutic vaccine against hepatitis C is no longer required. However, C. Neumann-Haefelin, Freiburg (Germany), stresses the increasingly urgent necessity of a prophylactic vaccine against hepatitis C, despite modern DAAs, which promise high SVR rates. "These expensive medications will not be available in most countries," he says, with reference to the high prevalence rates of HCV in parts of Africa, South America and Asia. In contrast to hepatitis B, which has an acute, self-limiting progression in 95% of adult patients, the majority of HCV infections develop into a chronic condition. HCV-specific CD8+ T-cells play a decisive role in the immune response of patients with a hepatitis C infection. These fail to eliminate HCV for two reasons: T-cell exhaustion in 30–50% and viral escape mutations in 50–70% of cases.

**NASH: dietary changes improve histology**

The development of cirrhosis and fibrosis of the liver is a highly dynamic process that can usually be reversed, says F. Tacke, Aachen (Germany). In patients with NASH, dietary changes associated with weight loss can improve biopsy-derived liver histology within a year, according to the results of a current study. Other studies are currently examining the effects of FXR agonist obeticholic acid and CCR2/CCR5 inhibitor cenicriviroc on patients with NASH and fibrosis. Matrix-targeting active ingredients, such as anti-LOXL2 antibodies, are also being examined.

**ALF: thyroid gland function of prognostic relevance**

In Germany, acute liver failure (ALF) is predominantly traced back to medication, above all paracetamol. In around 10% of patients, HEV infection can be identified as the cause. However, "in a significant minority, the reason for ALF remains unclear," explains A.E. Canbay, Essen (Germany). At 80%, the mortality rates are high. Thyroid gland function is also relevant for prognosis. A current study has shown a significant link between low T3 levels and poor disease outcome in patients with ALF. 83% of patients with hypothyroidism had to undergo liver transplantation (LTX) or died; only one patient went into spontaneous remission. The opposite was true for patients with euthyroidism: 86% of patients went into spontaneous remission, while 14% died or needed a liver transplantation.
HCC: identifying mutations using genomics

80–90% of HCC cases occur in a cirrhotic liver. Genetic heterogeneity is high. “Each tumor is the result of a unique combination of mutations,” explains J. Zucman-Rossi, Paris (France). The HCC is often infiltrated with lymphocytes. The greater the lymphocytic infiltration and therefore the number of CD8+ T-cells in the liver, the greater the proportion of recurrence-free, and overall survival of, patients.

This highlights the potential of immunotherapy for patients with HCC, which is already being used in the treatment of malignant melanoma, for instance, according to R. Thimme, Freiburg (Germany). Potential strategies are the depletion of regulatory T-cells or a PD-1 blockade, which has been shown to have partial effects in studies to date. Several checkpoint inhibitors are already being tested as forms of immunotherapy for HCC in phase I/II studies.

mRECIST instead of RECIST

How should HCC treatment success be determined? R. Lencioni, Miami (USA), advocates the use of mRECIST instead of RECIST (response evaluation criteria in solid tumors) to determine HCC treatment response, i.e. a modified version that is increasingly being used in HCC research. With mRECIST, it should also be possible to determine the effects of systemic and liver-centered treatment types.

Trastuzumab and AKT: blockade in inoperable cholangiocarcinoma

Cholangiocarcinomas account for up to 15% of all primary liver carcinomas. The risk factors are unclear. Resection is the first-line treatment. However, 70–90% of carcinomas are inoperable at the time of diagnosis. As a result, the search for effective medication is crucial. In a preclinical controlled study on a TKI (tyrosine-kinase inhibitor)-resistant xenotransplantation model, trastuzumab, which addresses the HER2 receptor, was tested on its own and in combination with celecoxib over a period of four weeks. The combined treatment reduced the size of the tumor more effectively than the monotherapy options, thus also extending the overall survival rate, says J.B. Andersen, Copenhagen (Denmark). AKT inhibitor MK2206 was examined in a similar model, and was also shown to reduce tumor volume and weight.
Single HCC: never too large for resection

The Barcelona Guidelines, referred to by P.E. Majno, Geneva (Switzerland), provide orientation in the treatment of HCC. According to these guidelines, liver resection is clearly indicated when patients have a single tumor, do not have portal hypertension and have normal bilirubin values. The size of the tumor is irrelevant when making decisions about the course of treatment: “Size is never a contraindication for surgery. Never tell your patients that their tumor is too large,” stresses P.E. Majno.

In the case of multiple tumors, resection should be given more serious consideration, as the relapse rate is higher than in the case of a single tumor. In a study conducted at the Women’s Hospital in Tokyo, the five-year survival rates were considerably higher following resection of large, solitary HCC than following the removal of multiple tumors (79% vs. 31%). The contraindication for resection if portal hypertension is present is due to poor long-term results.

Prize-winning posters at the Falk Symposium 199

3 poster prizes were awarded at the Falk Symposium 199. The Falk Foundation award was presented to the prize winners by Prof. Dr. Robert Thimme, Freiburg, one of the scientific organizers of the symposium:

The 1st prize went to M. Krawczyk, Homburg (Germany), for his work: “Reduction of caloric intake overrides the prosteatotic effects of the PNPLA3 p.1148M variant in patients with fatty liver: Ultrasound-based prospective study”.

The 2nd prize was awarded to D. Boldbaatar, Ulan Bator (Mongolia), for the work: “Prevalence of acute hepatitis D in Mongolia” and to Z. Delgersaikhan, Ulan Bator (Mongolia), for the work: “High prevalence of HDV infection in Mongolia”.

The 3rd prize went to M. Corrigan, Birmingham (United Kingdom), for her work: “Primary biliary cirrhosis and quality of life – Results from a UK patient survey”.

From left to right: Prof. R. Thimme, Freiburg, prize winner, Dr. R. Greinwald, Falk Foundation
Editor:  
Professor Thimme, the new direct-acting antiviral agents used in the interferon-free treatment of chronic hepatitis C have been dubbed a “small revolution”. However, they are not indicated for every HCV-infected patient. When do you use them?

Professor Thimme:  
We administer them to patients with chronic hepatitis C and established liver disease, i.e. advanced fibrosis or cirrhosis of the liver, as well as to patients with extrahepatic manifestations, such as renal disease or other problems. I would currently refrain from administering them to patients with normal LFT values, as we are still learning about these substances. Besides, new medications will come and bring the costs down.

Editor:  
Do DAAs solve the problems of hepatitis C?

Professor Thimme:  
There is currently a euphoric atmosphere among hepatologists, as these drugs represent an enormous breakthrough. It is a great achievement. However, we need to consider the fact that some patients do not respond to DAAs. This – albeit very small – group often shows resistance and we need to wait and see to what extent this resistance will dominate day-to-day clinical practice. This mutation resistance often targets several substances at the same time, which means that changing the active ingredient will not solve the problem.

Editor:  
Would you nevertheless be in favor of screening at-risk groups for hepatitis C infection and, if necessary, carrying out targeted treatment?

Professor Thimme:  
I think this is a very sensible approach, also in order to prevent the virus from spreading. From my experience, the classic at-risk groups include intravenous drug users and men who have sex with men. They should certainly be screened.
Editor:
A prophylactic vaccine would still be the most effective way to eradicate the virus. However, developing such a vaccine seems to be difficult.

Professor Thimme:
It is true that we need a prophylactic vaccine, and we are on the right track. In the last few years, we have found vectors that induce a better immune response than in the past. They also achieve a strong immune response against hepatitis C in healthy individuals. The international HCV meeting took place in Strasbourg. During the meeting, Michael Houghton, who discovered the hepatitis C virus, announced two main goals in the treatment of hepatitis C: reducing treatment costs to make treatment accessible to everyone, and developing an effective prophylactic vaccine. Scientists will therefore continue to work on the development of such a vaccine and, in the long term, they will succeed.

Editor:
At the symposium, the danger of hepatitis E was highlighted several times. How relevant do you think this is?

Professor Thimme:
It is true that hepatitis E infection is a much rarer disease than hepatitis B or C. However, its significance stems from the fact that it can trigger chronic hepatitis, particularly in immunosuppressed patients. In this regard, the textbooks actually need to be changed. Blood donors are currently not being tested for HEV. There are examples of HEV being transmitted via blood transfusion. In the next few years, we will observe an increase in prevalence due to intensified screening. The good news is that most patients eliminate HEV, which means that chronicity is still rare. Patients with acute hepatitis should definitely be tested for HEV, as well as patients showing chronically elevated LFT values under immunosuppressive therapy.

Editor:
Immunotherapy is currently the focus in many areas of oncology. Checkpoint inhibitors have achieved high response rates in malignant melanomas in particular. Is this strategy also relevant for hepatocellular carcinomas, for which there is a somewhat limited range of treatment options?

Professor Thimme:
The first data on the use of checkpoint inhibitors for hepatocellular carcinomas were presented at last year’s American Society of Clinical Oncology meeting. At 19%, the response rates are limited in comparison to those for malignant melanomas. Nonetheless, this is a crucial indication that immune response stimulation would also be a viable option for HCC. For this, we need to understand which type of immune response we need to induce in order to attack this tumor. Combination therapies are therefore also being tested, such as the combination of two checkpoint inhibitors which target PD1 and CTLA4 and the combination of immunotherapy and standard treatment, such as chemoembolization. These are all very interesting approaches; now we just need to wait for the first results. Another approach is the depletion of regulatory T-cells, which keep the immune response at bay. One of the reasons why tumors grow is a high concentration of regulatory T-cells in the tumor tissue or surrounding area. If these are removed, i.e. using cyclophosphamide or target-ed antibody treatment, the tumor-specific immune response is found to increase. This approach is still in the early stages, however.

Professor Thimme, thank you very much for the interview.
Recent years have seen considerable advances in the diagnosis and treatment of diseases affecting the digestive tract. The 200th symposium on “Therapeutic Strategies in Diseases of the Digestive Tract – 2015 and Beyond” covered topics representing the entire spectrum of current developments in gastroenterology – from the esophagus to the stomach, pancreas, liver and bowel. These developments show that research is making progress all the time, and with it the range of treatment options that increase quality of life and often improve patient survival rate.
Esophagus: everything revolves around Barrett

Barrett’s esophagus, Barrett’s neoplasia and the relevance of eosinophilic esophagitis, which is attracting more and more interest, dominated discussions of the upper digestive tract. It may be possible to prevent Barrett’s esophagus by using oxaliplatin, irinotecan and 5-fluorouracil. This achieves an overall survival rate of around 11%.

Stomach: strategies against resistant germs

In the stomach, Helicobacter pylori is still the main subject of discussion. The discussion is now not whether to treat, but how to treat, as not all patients respond to established strategies. Here, focus is increasing shifting towards quadruple therapy as an alternative option. Drugs can also upset the stomach. For example, cannabis smokers are at risk of developing cannabinoid hyperemesis syndrome, which often goes undetected and is misdiagnosed as cyclic vomiting. It is easy to determine whether cannabis is involved: Patients feel the need to take cold showers.

Bringing the pancreas out of the shadows

Pancreatic carcinomas are still one of the most devastating diagnoses for patients. This is due to the fact that advances in treatment, given the five-year survival rate of 5%, are rather limited. This is due to the fact that ad- 

The FOLFIRINOX regime, a combination of oxaliplatin, irinotecan and 5-fluorouracil, is currently the standard treatment. This achieves an overall survival rate of around 11 months (gemcitabine: just under seven months). Due to the disastrous progression, it is also catastrophic when autoimmune pancreatitis is misdiagnosed as cancer of the pancreas. In addition to high psychological pressure, patients then also face unnecessary surgery. Performing a differential diagnosis is therefore essential.

Preventing fibrosis of the liver from the outset

In the case of most hepatological diseases, prevention of fibrosis and cirrhosis is the primary objective. This is not always straightforward. However, that could all change in the near future as the last few years have brought rapid advances in the development of substances with anti-cirrhotic or anti-fibrotic effects. Hopes are also being pinned on FXR ligands and bile-acid mimetics, as well as the blockade of TGF-β, the inhibition of fibrocyte activation and the inhibition of cannabinoid receptors.

Irritable bowel syndrome: easy to diagnose, difficult to treat

The bowel formed one of the focuses of the gastroenterological overview, especially irritable bowel syndrome, which sends many patients to the gastroenterologist. J. Tack, Leuven (Belgium), estimates that it is the most common disease of the gastrointestinal tract. Typical symptoms are abdominal pain, dysfunction and/or bloating. It is therefore very easy to diagnose with a detailed history; however, it is important not to overlook warning signs. Treatment, on the other hand, can be somewhat challenging. It should be tailored according to the main symptoms. For J. Tack, peppermint oil is still the first-line treatment for abdominal pain, with an NNT for alleviating pain of 4 months (gemcitabine: just under seven months). Due to the disastrous progression, it is also catastrophic when autoimmune pancreatitis is misdiagnosed as cancer of the pancreas. In addition to high psychological pressure, patients then also face unnecessary surgery. Performing a differential diagnosis is therefore essential.

IL17 blockade weakens intestinal barrier

Another treatment approach is to strengthen the intestinal barrier with defensins, says J. Wehkamp, Tübingen (Germany). An interesting finding which supports the significance of the intestinal barrier in IBD is the response to an interleukin 17 blockade, which is very effective in patients with psoriasis, a chronic inflammatory skin condition. In patients with Crohn’s disease, however, it causes the clinical characteristics to worsen. According to J. Wehkamp, this is because IL-17-producing Th17 cells are essential regulators of the protective mucosal barrier. If these are blocked, the intestinal barrier will become weaker, causing IBD to progress.

Visualizing responders to TNF-α blockade

Do patients with severe Crohn’s disease respond to treatment with a TNF-α antibody? This question is highly relevant, as around half of patients are non-responders. If they receive treatment nevertheless, non-responders will be unnecessarily exposed to the risk of considerable side effects. Molecular imaging can provide a very clear picture of whether patients are responders or non-responders, explains R. Atreya, Erlangen (Germany). He conducted in-vivo molecular imag-
**IBD research – no sign of slowing down**

Future prospects for patients with inflammatory bowel disease formed one of the focal topics during a specialist press conference at the Falk Symposium 200.

For a few years now, researchers have been focusing on the underlying barrier defect, which is being used as a therapeutic target. Using a slow-release formulation of intestinal fat phosphatidylcholine (Fig. 9 and 11) to strengthen the mucosal barrier increases the rate of clinical remissions in patients with chronic ulcerative colitis: 53% (phosphatidylcholine) vs. 10% (placebo). In a randomized, placebo-controlled, multicenter study, phosphatidylcholine was shown to considerably improve the SSCAI (Simple Clinical Colitis Activity Index) in mesalazine-refractory patients (Fig. 10).

The future of IBD treatment could lie in SMAD7 antisense-oligonucleotide, which “switches off repair mechanism barriers,” explains J. Schölmerich, Frankfurt/Main (Germany).

In intestinal mucus phosphatidylcholine (PC) is reduced in patients with ulcerative colitis. Supply of PC to the colon compensates for the concentration of PC and the mucosal barrier is stabilized.

**Fig. 9** Suspected principle of action of phosphatidylcholine in patients with ulcerative colitis (mod. according to DeSchryver-Kecskemeti K et al. J Clin Invest. 1989;84(4):1355-61)

**Fig. 10** Significant improvement in disease activity in patients with mesalazine-refractory ulcerative colitis under phosphatidylcholine treatment (Kamer M et al. Am J Gastroenterol. 2014;109(7):1041–51)


In a current study, remission was induced in 65% of patients with Crohn’s disease within 15 days (Monteleone G, et al. N Engl J Med. 2015;372(12): 1104–13). “This is better than anything we have achieved to date,” explains J. Schölmerich, “but this result still needs to be confirmed.”
ing on patients with Crohn’s disease using fluorescent anti-TNF antibodies, which make it possible to detect the expression of membrane-bound TNF-α (mTNF). This method was clinically tested in a small study with 25 Crohn’s patients in which a TNF-α blockade was indicated. 13 out of 25 patients showed a clinical response to the treatment, of which 11 out of 12 had a high TNF-α expression, and just 2 out of 13 a low expression (Fig. 12). The CDAI improved significantly with a high TNF-α expression (p = 0.006). Non-responders can be detected with a probability of 92% and responders with a probability of 85%. Histologic examinations carried out by the pathologist were shown to be less clear.

**BRAF blockade for CRC: limited success**

The KRAS mutation has long been associated with colorectal carcinomas (CRC). The KRAS mutation status determines which EGFR inhibitors should be used, as patients with a mutated KRAS gene in exon 2 do not benefit from antibody therapy. W. Schmiegel, Bochum (Germany), points out that KRAS mutations are not the only relevant mutations in CRC: 11% of patients have other RAS mutations and 7% have a BRAF mutation (Fig. 13).

This mutation has a prognostic effect, but no predictive function. Patients with KRASwt/BRAFwt treated with chemotherapy and cetuximab have a median overall survival rate of 24.8 months, compared with just 14.1 months for KRASmt/BRAFmt. There are hopes that, for the BRAF mutation, the path would be paved for treatment with substances like vemurafenib, which selectively inhibit the oncogene BRAF. However, while the response rate for BRAF-positive malignant melanomas is 81%, the rate for CRC is just 5%, “as numerous other factors are involved,” explains W. Schmiegel. The results are more favorable when BRAF V600E-positive CRC is treated with combined BRAF inhibitors and EGFR inhibitors, at least according to the result of CRC xenotransplantations.

**Does LEBS change colorectal cancer screening?**

White light endoscopy supported by HD or chromoendoscopy is the diagnostic basis for exploring the intestine. But research does not stop here; there is now an entire spectrum of other procedures, increasing the reliability of diagnostics. This includes autofluorescence imaging (AFI), which is suitable for detecting neoplasias, as they show a different autofluorescence spectrum, says M. Götz, Tübingen (Germany). New screening and diagnostic procedures also include the in situ low-coherence enhanced backscattering spectroscopy (LEBS). “This has the potential to change colorectal cancer screening,” stresses M. Götz.

It has a sensitivity of 88% in the prediction of advanced adenomas; for non-advanced adenomas, the sensitivity is 71% and the specificity 72%. In order to further improve the treatment of gastrointestinal diseases, a deeper understanding of intestinal processes is required. According to M.A. Helmrath, Cincinnati (USA), there is still a lack of good models for this. He presented fascinating methods that could be used to develop “a better human intestine,” for instance by using a 3D cell culture with pluripotent stem cells.
Inflammation and stenosis characterize the clinical picture of eosinophilic esophagitis (EoE). If the inflammation is left untreated, esophagus remodelling may develop, accompanied by fibrosis and the formation of severe strictures, explains A. Schoepfer, Lausanne (Switzerland), (Fig. 14). Around two thirds of these patients will develop stenosis within 20 years.

The three “Ds” are taken into account as therapeutic measures: drugs, diet and dilation. In terms of drugs, the focus is on local treatment with topical steroids such as budesonide, which can dramatically reduce the number of eosinophils and symptoms. The active ingredient also reduces subepithelial fibrosis in the esophagus. One clear advantage of medication is that dietary restrictions are not necessary, which means that the patient can eat what he or she likes. Budesonide studies are still ongoing; the active ingredient has not yet been approved for the treatment of eosinophilic esophagitis.

On the other hand, consistent nutrition therapy also shows promising results, but requires patients to be highly motivated. Dilation can be used to remove strictures. However, it has no impact on the underlying inflammation and risks causing post-dilation pain.

Fig 14 Endoscopic image of a 28-year-old patient with untreated eosinophilic esophagitis. The image shows a severely inflamed esophagus with edema, white exudates and a stenosing ring in the lower esophagus (A. Straumann, Olten)
**Barrett’s neoplasia: When does endoscopic resection suffice?**

Endoscopic resection is the first-line treatment for early Barrett’s neoplasia. However, scientists are discussing whether this is also indicated if there is already infiltration in the superficial submucosa. In such cases, surgery is currently the gold standard. More recent studies, however, suggest that endoscopic treatment is sufficient for low-risk sm1 carcinomas. This could represent an alternative for older patients with co-morbidities in particular, according to R.E. Pouw, Amsterdam (The Netherlands).

Endoscopic procedures, such as ultrasound or diagnostic endoscopic resection, can be performed to determine whether the carcinoma is limited to the mucosa.

**Achalasia: free choice between pneumodilation or laparoscopic Heller myotomy**

G.E. Boeckxstaens, Leuven (Belgium), defines achalasia – with an annual incidence of 1/100,000 – as a lack of peristalsis and disturbed relaxation of the lower esophageal sphincter (Fig. 15). The question is then whether to treat with pneumodilation or laparoscopic Heller myotomy. According to G.E. Boeckxstaens, the doctor can choose the method he or she prefers. In a randomized controlled trial with 201 patients, which compared both procedures in the initial treatment stage of achalasia, one achieved a comparable success rate (reduction of Eckardt score by ≤ 3) for both procedures. There were also no differences in the secondary endpoints, such as pressure in the LES (lower esophageal sphincter), esophageal emptying and quality of life. G.E. Boeckxstaens warned of over-treating the illness, however: “A further aim of treatment must be to avoid over-treatment.”

**Does UDCA protect against Barrett’s esophagus?**

Gastroesophageal reflux (GERD) increases the risk of Barrett’s esophagus. Proton pump inhibitors (PPIs) have a positive effect on esophagitis, albeit without effectively alleviating the symptoms. PPIs have only been shown to prevent the development of carcinomas in patients with Barrett’s esophagus indirectly, and not in controlled studies, says R.F. Souza, Dallas (USA). She presented results which showed that Barrett’s esophagus could potentially be prevented if the composition of biliary reflux was changed. Treatment with hydrophilic bile acid ursodeoxycholic acid (UDCA) causes levels of the body’s own antioxidants to increase, thus protecting the esophagus against oxidative damage. “Changing the composition of bile acid could have a chemopreventive effect,” says R.F. Souza.

**Not to be confused: cyclic vomiting and cannabinoid hyperemesis syndrome**

Postprandial fullness, nausea, vomiting and flatulence are the cardinal symptoms of gastroparesis. There are differential diagnoses, however. In addition to gastroesophageal reflux disease and rumination syndrome, a rare eating disorder predominantly found in children, M. Camilleri, Rochester (USA), draws attention to cannabinoid hyperemesis syndrome, which is commonly misdiagnosed as cyclic vomiting. With the liberalization of cannabis, prevalence rates are increasing considerably. A typical indication is the need of these patients to take cold showers. Gastroparesis can also be iatrogenic, e.g. following fundoplication or bariatric surgery or as a result of medication like opiates.

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Fig. 15  Schematic representation of the three different stages of achalasia: 1. hypermotile stage, 2. hypomotile stage, 3. amotile stage. (Feussner H et al. München, in „Gutartige Erkrankungen der Speiseröhre“, Falk Foundation e.V.)
**Helicobacter pylori eradication prevents gastric carcinomas – preferably before atrophy**

When looking for the cause of gastric carcinomas, it is easy to find the culprit: Helicobacter pylori (H.p.) is the largest risk factor, responsible for 78% of all gastric carcinomas. H.p. is even involved in 89% of cases of distal gastric carcinomas. Data from Japan show an involvement of 98% in patients with gastric atrophy. There is therefore no doubt that eradication is the best method of prevention in asymptomatic patients.

According to current clinical practice guidelines (Sugano K, et al. Gut. 2015; 64(9):1353–67), it should be offered to all H.p.-positive patients provided there are no contraindications. This achieves the maximum benefit provided the mucosa is not yet atrophic, says K. Sugano, Tochigi (Japan).

According to F. Mégraud, Bordeaux (France), H.p. sensitivity to clarithromycin should be tested after the first treatment failure. If clarithromycin resistance is determined, he recommends quadruple therapy: “This achieves excellent effects, not least because it is not dependent on metronidazole resistance and there is almost no resistance against tetracycline.”

**Focus beyond H.p.**

Adenocarcinoma of the stomach is the third most common cause of cancer-related death worldwide, claiming more than 700,000 lives each year, according to R.M. Peek, Nashville (USA). Before new medication is developed, a deeper understanding of the interactions between H.p. and its host is required. This is because not everyone who is infected with H.p. develops a gastric carcinoma. R.M. Peek stresses that, although H.p. is the dominant germ in the stomach, other microorganisms must also be taken into account, as must environmental factors and individual patient characteristics, such as low iron levels.

**Hans Popper Award**

The Hans Popper Award went to Prof. T.H. Karlsen, Department of Transplantation Medicine at Oslo University Hospital (Norway), who expressed his gratitude with an enthusiastic talk on the pathogenesis of cholestatic and autoimmune liver diseases, from genetics to environmental factors – and back again.
The question of necrosis and infection is decisive for the prognosis and therapeutic strategy of patients with acute pancreatitis. If, as is the case in 80% of patients with acute pancreatitis, the disease has no necrotizing progression, the mortality rate is just 5%. Of patients who do develop necrosis, 70% develop sterile necrosis with a mortality rate of 12%; for infected necrosis, the mortality rate is 25%. “Surgery is an increasingly rare treatment option for acute necrotizing pancreatitis (ANP),” states T. Hackert, Heidelberg (Germany), drawing attention to a paradigm shift in the management of ANP. This is based on data from Heidelberg, which show a massive decline in open necrosectomies from 20 in 1991 to just two per year. Conservative management, such as early enteral nutrition and pain management continued for as long as possible, is the primary line of treatment for ANP. If surgery is required, i.e. in the event of infected necrosis, minimally invasive open surgery procedures are preferred. According to T. Hackert, endoscopic interventions are very successful with a low mortality rate. “Primary open surgery is obsolete, but we need it as a salvage option.”

**PYTHON study: nasoenteric feeding for patients with pancreatitis?**

Patients with severe acute pancreatitis are often fed via a nasoenteric feeding tube to prevent infections. This is not strictly necessary, says M.J. Bruno, Rotterdam (The Netherlands), referring to the results of the PYTHON study, which compared nasoenteric feeding that began within 24 hours after randomization with an oral diet which started after 72 hours. These patients were only fed via a feeding tube if they could not tolerate oral feeding. Over the six-month observation period, the risk of developing infected necrosis, bacteremia, pneumonia or of death was similar in both groups at just under 30%.

**Autoimmune pancreatitis – not to be overlooked**

G. Webster names the HISORt as useful diagnostic criteria. Despite steroid treatment, 53% of patients develop an exocrine pancreatic insufficiency, 37% an endocrine pancreatic insufficiency and 5% cirrhosis of the liver. Just under 1% of patients require surgery. It remains unclear whether it is associated with pancreatic carcinoma.

**Pancreatic carcinoma: still a disaster**

Pancreatic carcinoma is the most aggressive type of carcinoma with a five-year survival rate of 5%. There is a lack of effective treatments. Data from the Memorial Sloan Kettering Cancer Center show a survival rate following surgery of 12% after 80 months. “Surgery is palliative,” explains M.M. Lerch, Greifswald (Germany). For a long time, gemcitabine was the standard treatment. He suggests the FOLFIRINOX regime as a new treatment option for patients in ECOG grade 1. In a direct comparative study, an overall survival of 11.1 months vs. 6.8 months was achieved. With the exception of erlotinib, targeting treatments have shown very little effects up to now. Here, patients who develop a rash during treatment seem to benefit.
Also consider vasculitides!

Although rare, systemic vasculitides can also manifest themselves in the gastrointestinal tract. For example, in large-vessel vasculitides, such as giant cell arteritis and Takayasu’s arteritis, arteries in the gastrointestinal tract area may also be affected. The abdominal aorta is affected in a third of Takayasu’s arteritis cases and the mesenteric arteries in 36% of cases. In giant cell arteritis, these rates are 42% and 18%, respectively.

To prevent irreversible damage to the digestive tract, these must not be overlooked, stresses U. Müller-Ladner, Bad-Nauheim (Germany).

Major symptoms include abdominal pain, hemorrhage, intestinal necrosis and hematochezia. Large-vessel vasculitis treatment is based on induction of remission with high-dose steroids accompanied by immunosuppressants. Low-dose ASS is recommended for giant cell arteritis. For patients with Takayasu’s arteritis, reconstructive surgery should be considered during an inactive phase of the disease.

Sepsis in the intensive care unit: bilirubin of prognostic relevance

In the intensive care unit, liver dysfunction can occur for various reasons, including as the result of sepsis. Bilirubin levels are then an important prognostic predictor, says C. Trautwein, Aachen (Germany). “Jaundice in patients with sepsis-induced cholestasis is associated with prognosis.”

The higher the bilirubin value, the worse the further disease progression. Sepsis causes changes in the metabolism of bile acids. Bile acids and bilirubin in the serum increase, while bile flow decreases. This could result in atrophy of the intestinal mucosa and, ultimately, to a build-up of bacterial translocation, which plays a role in multiorgan failure.

Dysbiosis with serious consequences

Genetic predisposition and environmental factors have an effect on the intestinal microbiome, potentially leading to complex changes that could have serious consequences. This is because dysbiosis is associated with a range of illnesses, not only in the gastrointestinal area, but also in the central nervous system, for example, explains R.J. Xavier, Boston (USA).

The microbiome has therefore become a focal therapeutic target for inflammatory bowel disease (IBD), which is known to be linked with a changed microbiome with reduced diversity. One treatment attempt was fecal microbiota transplantation, which had proven to be successful in the treatment of Clostridium difficile infections. Hopes that it might also be successful here were promptly dashed, however.

“Genetics for clinicians

Clinicians often steer clear of genetics. J. Cho, New York (USA), however, has now presented five genetic disorders which she believes gastroenterologists should also be familiar with, including the link between eosinophilic esophagitis and TSLP (thymic stromal lymphopoietin). In a genome-wide association study, the gene for TSLP, which is located on chromosome 5q22, was found to be more active in patients with EoE.

In clinical practice, this especially applies to homozygous patients. Other important associations are ABO blood group and gastrointestinal diseases and the link between PNPLA3 and NAFLD.
**PBC and PSC:**

*bile acids for treatment*

FXR ligands and bile-acid mimetics are being considered as new therapeutic options in the treatment of liver diseases.

It is hoped that they will have positive effects on PBC, as well as possibly on PSC, NAFLD and NASH.

The need for such new options is great as, although ursodeoxycholic acid is an extremely effective medication for PBC and thus represents the first-line treatment, it fails to induce a response in around one third of patients.

For PSC, there is still no established treatment option. A second-line treatment for patients with PBC who do not respond to UDCA is the FXR ligand obeticholic acid – but this is not without side effects, says M. Trauner, Vienna (Austria).

Above all, patients complain of pruritus. It also causes LDL cholesterol to increase and HDL cholesterol to decrease.

Among others, norUDCA, which has a cholehepatic circulation, is currently being investigated in the treatment of PSC. To date, 164 patients have been recruited for the European multicenter phase II study. Research is also being conducted into the benefits of norUDCA for NAFLD.

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**Prize-winning posters at the Falk Symposium 200**

3 poster prizes were awarded for outstanding work at the Falk Symposium 200. The Falk Foundation award was presented to the prize winners by Prof. Dr. Pere Ginés, Barcelona, one of the scientific organizers of the symposium:

The 1st prize went to C. Günther, Erlangen (Germany), for her work: “Influence of the intestinal microbiota on expression of cell death regulators.” The 2nd prize went to R. Vasapolli, Magdeburg (Germany), for the work: “Modification of inflammatory microRNAs in gastric mucosa by aspirin, NSAIDs and proton pump inhibitors.” The 3rd prize went to A. Arslanow, Homburg (Germany), for her work: “Two-week protein-enriched low calorie diet (HEPAFAST) shows rapid improvement of fatty liver as assessed by controlled attenuation parameter.”
Counteracting fibrosis of the liver: pentraxin 2, TGF-β blockade and CB inhibition

Viral hepatitides, ASH and NASH can all lead to fibrosis of the liver. The activation of hepatic stem cells is a decisive pathophysiological mechanism. But how can fibrosis be treated in order to potentially prevent further progression into cirrhosis? D.A. Brenner, La Jolla (USA), offers various insights into this question on the basis of experimental trials. For example, human serum amyloid P (pentraxin 2), which inhibits the first steps of fibrosis, can thus inhibit fibrocyte activation and the development of cirrhosis of the liver. Another attempt is the blockade of TGF-β, which sustains the fibrosis process by activating myofibroblasts and inhibiting collagenases. Using the antagonist rimonabant to inhibit cannabinoid receptors is another way of restricting the development of liver fibrosis. On the other hand, daily cannabis consumption increases the risk of fibrosis of the liver.

HCC? Tailor treatment strategy to individual!

J. Bruix, Barcelona (Spain), presented the current BCLC (Barcelona Clinic Liver Cancer) staging and treatment strategies for hepatocellular carcinomas.

Resection, transplantation and chemoembolization, as well as administration of sorafenib, have positive effects on patient survival. The important thing is that the correct treatment is chosen for each individual patient.

NASH is on the rise

A large proportion of HCC cases are due to hepatitis C, followed by other causes such as alcohol or steatohepatitis. According to a current US study, the indication at the time of liver transplantation is HCV infection in 29% of patients, ASH in 20%, cholestatic disease in 14%, acute hepatic necrosis in 6% and metabolic liver disease in 4%. The remaining cases are unclear.

This picture will change with the treatment of hepatitis C, however, predicts J.G. Fitz, Dallas (USA): “In the next 10–20 years, NASH will become the main indication for a liver transplantation, at least in the USA.”
Evolving Therapies in Clinical Practice in IBD

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“200 international Falk Symposia – paving the way for medical advances on many levels”

Interview with Professor Dr. Jürgen Schölmerich, Medical Director and Board Chairman at University Hospital Frankfurt/Main (Germany)

“Therapeutic Strategies in Diseases of the Digestive Tract – 2015 and Beyond” was the title of the 200th international Falk Symposium.

Professor Jürgen Schölmerich, University Hospital Frankfurt, explains the success story behind the unparalleled event series.

Editor: Professor Schölmerich, 200 international Falk Symposia have taken place since 1967, each drawing in high levels of participation. What is the success story behind the events?

Professor Schölmerich: One of the main reasons for the enormous success enjoyed by the Falk Symposia has to be the fact that the events unite clinicians and fundamental researchers under one roof. They provide a platform for interdisciplinary exchange, thus creating potential for innovation. What’s more, the symposia are not influenced by corporate interests and are perfectly prepared and organized by Falk Foundation employees.

The scientific organizers independently choose the speakers they invite to the events. We are able to hunt down the world’s best scientists in individual fields – and the invitations are rarely turned down, despite the fact that speakers do not receive any financial...
compensation. This demonstrates the outstanding scientific reputation of Falk Symposia. Around the world, it is seen as an honor to be invited to present data at these events.

Editor: Which topics form the focal points at the symposia and what are past highlights?

Professor Schölmerich: Looking at how Falk Symposia have developed since their beginnings is a highlight in itself. The first symposium, which took place back in 1967, dealt with the liver and jaundice. It was followed by symposia – featuring high-caliber speakers – on intestinal diseases, and especially on intestinal absorption, a topic that was and still is completely free from corporate interests. Finally, inflammatory bowel disease was also added to the program, as well as special topics from hepatology, such as cholestatic liver diseases. In recent years, more and more symposia have been turning their attention back to the gastrointestinal tract as a whole.

Editor: How can the symposia drive forward research and improve medical care?

Professor Schölmerich: Thanks to direct dialogue between basic researchers and clinicians, new scientific findings are being applied much more rapidly than usual, allowing them to improve patient care more swiftly. Here, the Falk Symposia are a real driving force. An example of this is the development of 5-ASA from sulphasalazine – the idea of splitting the active substance from the carrier substance to make treatment more tolerable was presented early at a Falk Symposium. A similar example is the possibility of treating cholestatic liver diseases like primary biliary cirrhosis, which can also be traced back to presentations given at Falk Symposia. This represents enormous progress for patients, and could even bypass the need for liver transplantation. Bile acid research has increasingly shown that bile acids can have effects resembling those of hormones, which in turn has improved our understanding of the underlying mechanisms. Bile acids have also been developed as a medication, making the treatment of cholestatic liver diseases more effective and now also opening up treatment options for NASH.

Editor: To what extent does the 200th Falk Symposium cover hot topics?

Professor Schölmerich: The symposium does indeed look at issues on the cutting edge of research, including a presentation on the use of stem cells to replace damaged areas of the bowel. Other presentations deal with the question of how the organisms repair system can be strengthened and to what extent this strategy represents an alternative to immunosuppressive therapy.

Further highlights include discussions on the regression of fibrosis of the liver as well as advances in the treatment of chronic hepatitis. Another exciting topic is autoimmune pancreatitis, a condition that was still unknown ten years ago. The symposium will reveal the latest state of knowledge of the pathogenesis, differentiation of disease forms and treatment of this disease. POEM, an endoscopic procedure used to treat achalasia, will also be presented, along with the latest findings on HER2-positive gastric carcinomas. These examples underline our focus on exciting issues spanning all areas of gastroenterology and hepatology.

Editor: What will the future bring for Falk Symposia?

Professor Schölmerich: We very much hope that the event series will continue to run into the future. I can already reveal that more symposia have been planned up to 2017. Future symposia will focus more on the disease mechanisms than on individual special issues or individual organs. The microbiome, biomarkers as well as bowel/liver interactions will form focal points, among others. Personalized medicine will also become a topic. The scientific community is very grateful to have had such an effective platform for scientific exchange for over 48 years, and we very much hope that the Falk Symposia, with the same concept and the same success, will continue to exist in the future.
Falk Symposium 199
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Prof. Gustav Paumgartner talking to Prof. Michael P. Manns
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Speakers, moderators and scientific organizers

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Prof. Jürgen Schölmerich talking to Prof. Gerhard Rogler
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Düsseldorf, Germany
January 21 – 22, 2016

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Gut-Liver Interactions: From IBD to NASH
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March 11 – 12, 2016

Symposium 202
Evolving Therapies in Clinical Practice in IBD
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Symposium 203
XXIV International Bile Acid Meeting: Bile Acids in Health and Disease
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Symposium 204
Clinical Hepatology Practice in 2016: From Science to Therapy
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Symposium 205
New Treatment Targets in Gut and Liver Diseases
Lucerne, Switzerland
October 21 – 22, 2016

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