IN BRIEF

THERAPY

PITCHing ursodeoxycholic acid in intrahepatic cholestasis of pregnancy versus placebo

Treatment with ursodeoxycholic acid (UCDA) did not reduce perinatal outcomes in women with intrahepatic cholestasis of pregnancy, according to results in a new large, placebo-controlled randomized trial (PITCHES). 605 women were enrolled in the study from across 33 hospital maternity units in England and Wales and were randomly allocated to receive either UCDA ($n = 305$) or placebo ($n = 300$). The primary outcome, which included perinatal death, preterm delivery or neonatal unit admission for at least 4 h, was similar between the two treatment groups, 23% in the UCDA group versus 27% in the placebo group (adjusted risk ratio of 0.85; 95% CI 0.62–1.15). As UCDA does not seem to have any substantial clinical benefit in intrahepatic cholestasis of pregnancy, the authors recommend reconsidering the routine use of UCDA for this condition.

ORIGINAL ARTICLE Chappell, L. C. et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. *Lancet* https://doi.org/10.1016/S0140-6736(19)31270-X (2019)

LIVER CANCER

Increasing survival in HCV-related hepatocellular carcinoma

The benefits of direct-acting antiviral (DAA) therapy for hepatitis C in patients with hepatocellular carcinoma (HCC) have been debated. In a retrospective cohort study of 797 patients with HCV-related HCC with a complete response to HCC treatment (383 patients received DAAs, 414 patients did not), DAA therapy was associated with a significant reduction in the risk of death (HR 0.54; 95% CI 0.33–0.90). Furthermore, this association differed by whether or not patients had achieved a sustained virologic response (SVR) to DAA therapy, with risk of death reduced in those who had achieved SVR (HR 0.29; 95% CI 0.18–0.47), but not in those who did not achieve SVR (HR 1.13; 95% CI 0.55–2.33).

ORIGINAL ARTICLE Singal, A. G. et al. Direct-acting antiviral therapy for HCV infection is associated with increased survival in patients with a history of hepatocellular carcinoma. *Gastroenterology* https://doi.org/10.1053/j.gastro.2019.07.040 (2019)

TRANSPLANTATION

Preventing the development of hepatitis C in uninfected transplant recipients

Efforts to expand the donor organ pool for transplantation are ongoing, including transplantation of HCV-positive organs. Pre-emptive administration of pangenotypic direct-acting antiviral (DAA) therapy to prevent the development of chronic HCV infection in uninfected recipients of HCV-positive donor hearts was investigated in a proof-of-concept study. 20 patients underwent transplantation with a viraemic donor heart (according to nucleic acid testing) and received pre-emptive oral glecaprevir–pibrentasvir before the operation and an 8-week course after transplantation. 5 additional patients received HCV antibody-positive donor hearts without detectable circulating HCV RNA, but did not develop viraemia and so did not receive DAA therapy. DAAs were well-tolerated, rapidly suppressed HCV (median time to clearance of 3.5 days) and prevented chronic HCV infection (sustained virologic response at 12 weeks). Patient and allograft survival were 100% at a median follow-up of 10.7 months (range 6.5–18.0).

ORIGINAL ARTICLE Bethea, E. D. et al. Pre-emptive pangenotypic direct acting antiviral therapy in donor HCV-positive to recipient HCV-negative heart transplantation: an open-label study. *Lancet Gastroenterol. Hepatol.* https://doi.org/10.1016/S2468-1253(19)30240-7 (2019)

PANCREAS

Guiding pancreatic cyst management

The early and accurate detection of precancerous pancreatic cysts is a key unmet clinical need, which could reduce both unnecessary surgical morbidity and missed diagnoses. A new study now reports the development of CompCyst, a comprehensive test than can accurately guide cyst management.

The international multicentre study included a total of 862 patients with non-malignant ($n = 148$), potentially malignant ($n = 600$) or malignant ($n = 114$) pancreatic cysts, all of whom had undergone surgery (with available histopathology). Cyst fluid was analysed for somatic mutations and loss of heterozygosity at cyst-associated loci, as well as aneuploidy and protein biomarker levels, revealing various molecular features associated with cyst types.

Following equal distribution into training ($n = 436$) and validation ($n = 426$) cohorts, a supervised machine-learning approach was used to identify optimal combinations of molecular markers, clinical features and imaging characteristics that could stratify patients with benign cysts (who can be safely discharged), potentially malignant cysts (who require routine monitoring) and malignant cysts (who require surgery).

On the basis of histopathology in the validation cohort, which enabled retrospective inferences of the optimal management approach, this test — termed CompCyst — significantly outperformed conventional clinical and imaging methods for correct identification of patients suitable for discharge (60% versus 19%; $P = 0.00013$) and surveillance (49% versus 34%; $P = 0.02$), and could have avoided unnecessary surgery in 60% of the 193 patients who did not require surgery. Overall,

BILIARY TRACT

Gallstones formed by NETs

A new study published in the journal *Immunity* demonstrates that gallstone assembly requires neutrophil extracellular DNA traps (NETs) for their formation. These findings could lead to new therapeutic strategies for a disease that can substantially overburden healthcare systems.

The formation of gallstones (cholelithiasis) is a highly prevalent and severe disease, and one of the leading causes of hospital admissions in the USA. Gallstones are formed in the gallbladder in a process that involves the concentration and acidification of bile by the gallbladder luminal epithelium. This process usually increases the solubility of cholesterol and calcium salts, which are ultimately precipitated out of solution when the solubilization capacity of bile is overwhelmed, leading to the formation of the gallstone building blocks. However, not all the mechanisms leading to gallstone formation are clear and a hypothetical aggregation factor has eluded identification.

Previous studies had shown that aggregates of NETs produced by neutrophils can clot pancreatic ducts and blood vessels, leading to acute pancreatitis and sepsis, respectively. "As gallstone disease is an occlusive disease, we checked gallstones for traces of NETs," explains author Martin Herrmann.

Human gallstone-containing biliary sludge from patients receiving hepatobiliary stents was first examined using fluorescence microscopy. The sludge and gallstones showed positivity for extracellular DNA (ecDNA) and neutrophil elastase, which are markers of NETs. Using in vitro experiments, gallstones were shown to rapidly collect ecDNA when co-cultured with neutrophils, and NETs were observed to aggregate cholesterol and calcium crystals in a process requiring PADI4, an enzyme involved in NET formation.