IN BRIEF

SURGERY

Antibiotics versus appendectomy for appendicitis

To assess the efficacy of antibiotic therapy compared with appendectomy for the treatment of appendicitis, a noninferiority trial in 1,552 adults with appendicitis or an appendicolith was conducted at 25 centres in the USA. Patients were randomized to receive either a 10-day course of antibiotics or to undergo surgery. Antibiotics were noninferior to appendectomy, based on the primary outcome of 30-day European Quality of Life–5 Dimensions questionnaire scores (mean difference, 0.01 points; 95% CI −0.001 to 0.03). Of the antibiotics group, 41% of those with an appendicolith and 25% of those without had undergone an appendectomy by 90 days after randomization. Complications were more common in the antibiotics group than in the appendectomy group.

ORIGINAL ARTICLE The CODA Collaborative. A randomized trial comparing antibiotics with appendectomy for appendicitis. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2014320 (2020)

ENDOSCOPY

Intelligent and autonomous magnetic endoscopy

Demand for colonoscopy to diagnose colorectal cancer (CRC) is high, which can lead to late diagnosis and reduced survival. In addition, the ongoing coronavirus disease 2019 (COVID-19) pandemic has curtailed endoscopic procedures. Possible future alternatives include magnetic endoscopes. However, magnetic manipulation is complex, and clinical translation has proven difficult. In a new study that aimed to improve navigational performance, machine vision was used to enable intelligent and autonomous control by non-experts of a magnetic endoscope during colonoscopy. The system involved image-based autonomous navigation of the colonic lumen, but under the supervision of an operator, and consisted of a magnetic endoscope controlled by an external magnet attached to a robotic arm. It was tested in both a benchtop and in an in vivo porcine setting — in the latter, duration travelled in the colon was comparable to standard flexible endoscopy. The researchers hope that future models will enable higher levels of autonomy and ultimately provide a clinically viable alternative to conventional endoscopy.

ORIGINAL ARTICLE Martin, J. W. et al. Enabling the future of colonoscopy with intelligent and autonomous magnetic manipulation. *Nat. Mach. Intell.* **2**, 595–606 (2020)

INFECTION

SARS-CoV-2 in patients with chronic liver disease

An international registry study reports the clinical outcomes of a cohort of patients with chronic liver disease and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. 756 patients with chronic liver disease (386 with cirrhosis and 359 without) from 29 countries were included. In patients with chronic liver disease, risk factors for mortality were advancing age and alcohol-related liver disease. Mortality was 32% in patients with cirrhosis compared with 8% in those without ($P < 0.001$), and, among patients with cirrhosis, mortality positively correlated with an increase in Child-Turcotte-Pugh (CTP) class. A propensity-score-matched analysis revealed an increased risk of mortality in patients with advanced cirrhosis (CTP-B and CTP-C) compared with a UK cohort of 620 patients with SARS-CoV-2 infection but not chronic liver disease.

ORIGINAL ARTICLE Marjot, T. et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. *J. Hepatol.* https://doi.org/10.1016/j.jhep.2020.09.024 (2020)

ORGANOIDS

Developing a toolbox for drug-induced liver injury

Drugs and xenobiotics can induce unexpected harm to the liver in a process termed drug-induced liver injury (DILI), which is a major concern in clinical trials and practice. In new research, a human liver organoid (HLO)-based screening model has been developed to analyse DILI pathology with potential use in liver toxicology studies.

DILI remains a major issue during drug development. "Despite promising efficacy, developing new drugs fails at times due to unpredictable liver injury occurring during clinical trials. Unfortunately, mice and other animal models often do not precisely mimic what can happen when a human takes a medication," explains author Takanori Takebe. Previous work published by Takebe and colleagues in *Nature Medicine* had identified a polygenic risk score for predicting susceptibility to DILI mainly using primary hepatocytes. As a next step, given the difficulties of obtaining high-quality and stable primary hepatocytes, Takebe and colleagues aimed to develop a toolbox that could capture drug-induced toxicity events at high throughout using organoids.

The researchers first established a reproducible protocol to generate HLOs from pluripotent stem cell lines. Structural profiling revealed that these HLOs contained polarized immature hepatocytes with bile canaliculi-like architecture. Furthermore, the HLOs were capable of unidirectional bile acid transport; accumulation of bile acids into the organoid could be impaired by CRISPR–Cas9-based gene editing and chemical inhibition of bile salt export pump. Single-cell RNA sequencing transcriptome analysis identified diverse and zonal hepatocyte populations in the HLOs that emulated aspects of primary adult hepatocytes.

Next, a high-speed live imaging-based detection assay was developed to assess bile acid uptake and excretion in the HLOs: 15–20 organoids could be evaluated per well, with 384 wells in the high-throughput platform. To test the system, this assay was used for large-scale compound screening in which 238 test compounds at four different concentrations were assessed (32 negative controls, 206 reported DILI compounds). Dual readouts that measured viability and cholestatic toxicity had high predictive values (88.7% sensitivity; 88.9% specificity). Furthermore, multiplexed readouts incorporating assessment of mitochondrial toxicity could also be factored into the assay. Finally, the HLO system could be used to model genotype-specific susceptibility to bosentan-induced cholestasis (*CYP2C9*2* activity intermediate).


Credit: appleuzr/Getty

"[The main finding is] a living organoid-based test platform on 384 wells — each containing liver organoids — that can provide high-speed results from over 200 drug compounds with multiple concentrations," notes Takebe, adding that this testing yielded high sensitivity and specificity compared to previous primary hepatocyte-based methods. More work is needed however. "We plan to develop a genetically high-risk organoid library to establish a notable and more predictable preclinical testing system for DILI," says Takebe, "leading to a more efficient drug development cycle."

Katrina Ray

ORIGINAL ARTICLE Shinozawa, T. et al. High-fidelity drug induced liver injury screen using human PSC-derived organoids. *Gastroenterology* https://doi.org/10.1053/j.gastro.2020.10.002 (2020)
RELATED ARTICLES Koido, M. et al. Polygenic architecture informs potential vulnerability to drug-induced liver injury. *Nat. Med.* **26**, 1541–1548 (2020)