

### Improvements in post mortem techniques needed to better understand stillbirths

Analysis by a Great Ormond Street Hospital-led team looking at the effectiveness of different elements of the post mortem process shows that, in the majority of cases of stillbirth the cause remains unknown, despite full standard investigation. The series of articles highlight the need for further research to improve post mortem techniques to better detect a cause of death.

The articles (<https://doi.org/10.1002/uog.15719>) challenge the accepted thinking on the diagnosis and causes of stillbirth and earlier deaths in the womb from 12–24 weeks, and the value of specific elements of the traditional post mortem process.

### Switching between anti-TNFs without wash-out possible in patients with rheumatoid arthritis

EXXELERATE (Smolen et al, 2016), the first head-to-head superiority study of two treatments in the anti-TNF (tumour necrosis factor) class, compared certolizumab pegol (Cimzia) plus methotrexate to adalimumab (Humira) plus methotrexate in adult patients with moderate to severe rheumatoid arthritis who were inadequate responders to methotrexate.

The study did not meet its primary end points for superiority, finding no statistically significant difference in efficacy between certolizumab pegol and adalimumab in combination with methotrexate in short-term (12-week) and long-term (2-year) evaluations. However, data demonstrated that switching between these anti-TNFs without a wash-out period was beneficial to some patients.

Smolen JS, Burmester GR, Combe B et al (2016) Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. *Lancet* [https://doi.org/10.1016/S0140-6736\(16\)31651-8](https://doi.org/10.1016/S0140-6736(16)31651-8)

## Mental health interventions in pregnant women and new mothers have multiple benefits

There are clear economic and societal arguments for investing in mental health interventions for women during pregnancy and immediately after birth, suggests a report by the Personal Social Services Research Unit (PSSRU) at the London School of Economics and Political Science (Bauer et al, 2016).

Preventative measures and initiatives targeted at women already experiencing mild, moderate and severe mental illness can deliver benefits. But, as the report emphasizes, the economic and societal benefits also need to be considered in the long term.

More than one in 10 women experience depression and associated issues during pregnancy and the year after birth. The study reviewed evidence on recent 'best-practice' interventions in the UK and nations such as Canada, the USA and Australia – chiefly randomized clinical trials aimed at reducing mental health problems during the perinatal period.

Annette Bauer, PSSRU Research Fellow and lead researcher on the study, said: 'Each of the interventions included in our economic analysis led to positive net benefits for pregnant women and also from a societal perspective'.



Annette Bauer, Research Fellow, Personal Social Services Research Unit, London School of Economics and Political Science, London

While wider societal benefits were most pronounced, many interventions made strong economic cases both from governmental and health and social care perspectives. The longer-term economic advantages should be borne in mind when considering investment to prevent or address the mental health needs of mothers during the perinatal period.

Limitations and evidence gaps which give context to the study's findings include challenges in evaluating interventions around severe

mental illness, the focus on interventions that used mothers' mental health as their primary outcome, and inconsistent information available relating to each intervention.

Ms Bauer commented: 'All interventions focusing on perinatal mental health that we examined had the potential to provide good value for money. The study provides useful evidence to commissioners to support greater investment in services for the prevention of, and support for, perinatal mental health'.

Bauer A, Knapp M, Adelaja B (2016) Best Practice for Perinatal Mental Health Care: the Economic Case. [www.pssru.ac.uk/publication-details.php?id=5226](http://www.pssru.ac.uk/publication-details.php?id=5226) (accessed 29 November 2016)

## 3D video monitoring new option for sleep disorders

People with sleep disorders often have their periodic leg movements in sleep recorded using electromyography. However, the cables this requires can interfere with the patient's sleep and electrodes can become detached, compromising the quality of the data. Scientists have found that superior data can be obtained using supplementary three-dimensional (3D) scene analysis of movements (Garn et al, 2016).

Under the direction of sleep researcher, Dr Stefan Seidel, in collaboration with the Austrian Institute of Technology, intelligent software has been developed that can record and analyse even more leg movements than conventional electromyography, as well as being completely contactless, using a 3D

camera installed directly above the bed.

'This opens up new possibilities for us, not only for diagnosing and analysing sleep disorders,' says Dr Seidel. In future, 3D scene analysis could be used to supplement usual methods for monitoring epilepsy, sleep apnoea and sleep-walking, enabling the causes to be analysed much more quickly. This opens up new options for home screening of patients, especially older people or young children.

Garn H, Kohn B, Dittrich K et al (2016) 3D detection of periodic limb movements in sleep. 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Orlando, FL: 427–430. <https://doi.org/10.1109/EMBC.2016.7590731>

## Discontinuing mechanical ventilation in critically ill adults: updated guidelines

The American College of Chest Physicians and the American Thoracic Society have published new guidelines for discontinuing mechanical ventilation in critically ill adults (Girard et al, 2016). The goal of the guidelines is to help physicians and other health-care professionals determine when patients with acute respiratory failure can breathe on their own, as well as provide clinical advice that may increase the chances for successful extubation.

At any particular moment, about 40% of all patients in the intensive care unit are breathing with the help of a mechanical ventilator. However, mechanical ventilation can lead to complications, including infections and injury to the lungs and other organs.

Reducing the length of time patients are on mechanical ventilation decreases the risk of these complications, but premature removal from mechanical ventilation can produce other complications and increase mortality.

Based on a systematic review of medical studies, the committee's recommendations for acutely hospitalized adults on mechanical ventilation for more than 24 hours are:

- For patients at high risk for extubation failure who have passed a spontaneous breathing trial, extubation is recommended to preventative non-invasive ventilation
- The initial spontaneous breathing trial should be conducted with inspiratory

pressure augmentation rather than T-piece or continuous positive airway pressure

- Sedation should be minimized
- Protocolized rehabilitation directed toward early mobilization
- Managing patients with a ventilator liberation protocol
- Performing a cuff leak test in patients who meet extubation criteria and are deemed at high risk for post-extubation stridor
- For patients who failed the cuff leak test but are otherwise ready for extubation, administering systemic steroids at least 4 hours before extubation.

Dr Timothy Girard, co-lead author of the guidelines and an associate professor of medicine at the University of Pittsburgh, said the committee hoped the guidelines would help reduce variations in practice that do not benefit patients. 'We are not prescribing a specific approach to care for every patient every time,' he said. 'But we are trying to summarize the available evidence in as clear and succinct a way as possible so that clinicians know how it applies to most patients.'

Girard TD, Alhazzani W, Kress JP et al (2016) An Official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. *Am J Respir Crit Care Med* <https://dx.doi.org/10.1164/rccm.201610-2075ST>

## Memantine is the antedementia drug associated with the highest risk of pneumonia

A study including 65 481 people diagnosed with Alzheimer's disease during 2005–11 in Finland showed that those using memantine have the highest risk of pneumonia among users of antedementia drugs (Lampela et al, 2016).

People using donepezil or galantamine had the lowest risk of pneumonia; those using memantine or rivastigmine patches had a 1.6 and 1.15 times higher risk of pneumonia respectively. Patients using rivastigmine capsules had no increase in risk. The real risk may be higher, as the study only included cases of pneumonia leading to hospitalization or death.

The study is the first to compare the risk of pneumonia associated with different

antedementia drugs and drug forms. The results are not likely to be explained by differences between drugs, as rivastigmine was only associated with an increased risk of pneumonia in patch form. The increased pneumonia risk among those using memantine or rivastigmine patches may be partly because these medications are often used in patients with more advanced states of dementia, although all participants lived at home.

Lampela P, Tolppanen AM, Tanskanen A, Tiitonen J, Lavikainen B, Hartikainen S, Taipale H (2016) Use of antedementia drugs and risk of pneumonia in older persons with Alzheimer's disease. *Ann Med* <https://doi.org/10.1080/07853890.2016.1254349>

### Intestinal failure registry launched

The world's first intestinal failure registry has been launched by BAPEN, hosted on the N3 NHS Secure network ([www.e-bans.com](http://www.e-bans.com)). The registry will provide information on clinical activity and outcomes for patients managed in intestinal failure units across UK hospitals, giving a consistent national dataset to facilitate improvements in quality and clinical outcomes for patients.

### Management of older patients with chronic kidney disease

Chronic kidney disease often occurs in older age. Older patients have more comorbidities, a different physiology and a shorter life expectancy, which may impact therapeutic decisions. To face the challenges posed by this growing group of patients, the European Renal Best Practice Group has published a clinical practice guideline on management of older patients with chronic kidney disease (<https://doi.org/10.1093/ndt/gfw356>)

### Quality improvement e-learning resource for the perioperative team

The Royal College of Anaesthetists has launched a new online anaesthesia quality improvement e-learning resource – the Perioperative Improvement Science and Management module ([www.prim-ed.com/](http://www.prim-ed.com/)) – based on the College's Improvement Science curriculum.

### Monoclonal antibody reduces CDI recurrence even with hypervirulent strain

A single dose of bezlotoxumab in patients receiving standard-of-care antibiotics reduces the rate of *Clostridium difficile* infection (CDI) recurrence in patients infected with the BI strain, according to an analysis of the MODIFY I and MODIFY II trials conducted by Dr Stuart Johnson from Edward Hine, Jr. Veterans Administration Hospital, Hines, Ill. The hypervirulent BI strain is associated with worse outcomes, lower cure rates and an increased incidence of recurrent CDI.

MODIFY I and MODIFY II included 2413 adults with confirmed CDI who received a 10–14-day course of standard-of-care antibiotics. Patients were randomized to saline infusion or a single intravenous infusion of actoxumab (in MODIFY I), bezlotoxumab, or both.

BI strains were isolated from 22.0% of baseline stool samples. In patients with the BI strain, the rate of CDI recurrence was 40.5% in the placebo arm but reduced to 28.2% in the bezlotoxumab arm. By comparison, in patients infected with other strains, CDI recurrence rates were 36.7% in the placebo arm and 20.3% in the bezlotoxumab arm.

### Toxin-negative patients not a dominant source of health facility onset CDI

Toxin immunoassay-negative patients are not a significant source of *Clostridium difficile* transmission according to a study from the University of California, Davis. Investigators led by Dr Christopher Polage performed a genetic-relatedness analysis of all isolates recovered from symptomatic patients who had a stool sample submitted for *C. difficile* testing from 11 high-risk units during a 4-month period in 2014. They classified all positive patients regardless of whether they were toxin-negative or toxin-positive.

The genetic relatedness analysis was carried using polymerase chain reaction ribotyping and whole genome sequence characterization of single nucleotide polymorphisms (SNP). A cut-off of  $\leq 2$ SNP was used to define a transmission event. Directionality was inferred based on the admit/discharge/transfer date; an overlapping stay inferred direct transmission and a non-overlapping stay inferred indirect transmission.

From 398 tests from 273 patients, 98 *C. difficile* infection (CDI) events (93 patients) were identified. Isolates were recovered from 85 CDI events (81 patients), from which 101 isolates from 78 patients were ribotyped. Whole genome sequencing was performed on 65 isolates from 48 unique patients. Using the  $\leq 2$ SNP cut-off, there were only nine transmission events involving 13 patients. ‘So of these 85 CDI events, you only had 10%

that appeared to meet a relatedness criteria to some other patient,’ said Dr Polage. Further, only two of 39 (5.1%) of health facility onset CDI events analysed were related to another CDI event in the cohort.

Despite inclusion of toxin-negative patients, very few health facility onset CDI events are related to a prior symptomatic patient. The data suggest that horizontal transmission from symptomatic patients accounts for a minority of hospital onset-CDI in hospitals with active inpatient prevention programmes.

Dr Christopher R Polage, Associate Professor of Pathology and Infectious Diseases, University of California, Davis School of Medicine, California



### Rapid emergence of resistance to ceftazidime-avibactam identified

Ceftazidime-avibactam has proven to be an effective treatment for carbapenem-resistant *Enterobacteriaceae* (CRE) infections, but resistance can emerge rapidly during the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections, University of Pittsburgh Medical Center (UPMC) researchers have found. Their review of patients treated with ceftazidime-avibactam for carbapenem-resistant *K. pneumoniae* found resistance occurred in about 10%, conferred by mutations in blaKPC-3, said Dr Ryan Shields.

Of 51 patients treated with this combination at UPMC for CRE infections between April 2015 and September 2016, 42 were treated for carbapenem-resistant *K. pneumoniae*. Resistance emerged in four patients following 10–19 days of treatment, and was associated with a  $\geq 4$ -fold increase in meropenem minimum inhibitory concentrations.

Resistance was conferred by mutations in blaKPC-3  $\Omega$ -loop and adjacent sites. The presence of the mutations on highly mobile genetic elements is concerning,

and suggests dissemination of resistance if ceftazidime-avibactam is used widely, Dr Shields said.

At UPMC, ceftazidime-avibactam is a front-line agent for the treatment of CRE infection since it was approved in 2015, he said, ‘but it is not a magic bullet.’ Effective stewardship strategies and judicious use of ceftazidime-avibactam is needed, particularly the use of pharmacokinetic or pharmacodynamic-based dosing regimens to try to preserve this agent for the longest period possible.

Wayne Kuznar

## Factors associated with failure of emergency management in children with acute asthma

A Canadian team has undertaken a prospective, multicentre cohort study of children aged 1–17 years presenting to five emergency departments with moderate or severe asthma (Ducharme et al, 2016). Children received oral corticosteroids and severity-specific inhaled bronchodilator therapy.

The primary outcome was emergency department management failure (hospital admission, prolonged emergency department therapy ( $\geq 8$  hours), or relapse within 72 hours of discharge from the emergency department with admission to hospital or prolonged emergency department stay). Viral cause was ascertained by polymerase chain reaction on nasopharyngeal specimens and environmental tobacco smoke exposure by salivary cotinine concentration.

The authors screened 1893 children and enrolled 1012 eligible children, of which 973 participants were included in the analysis. Of 965 children 165 (17%) experienced management failure in the emergency department, which was significantly associated with viral detection, fever, baseline Pediatric Respiratory Assessment Measure, and presence of symptoms between exacerbations. Age,



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salivary cotinine concentration, and dose of oral corticosteroids were not significantly associated with management failure.

Viral detection (67% vs 46%,  $P < 0.0001$ ) and fever (31% vs 16%,  $P < 0.0001$ ) occurred more frequently in preschoolers than in older children. Viral detection was also associated with reduced speed of recovery over the 10 days after discharge.

Lead author Professor Francine M Ducharme from the Departments of Paediatrics and Social and Preventive Medicine,

University of Montreal, Montreal, Canada, commented: 'in addition to the severity of the acute exacerbation and chronicity of disease, viral detection and fever were important determinants of management failure, whereas age, sex, and oral corticosteroid dose were not. Viral detection was also associated with slower recovery over the next 10 days.'

Ducharme FM, Zemek R, Chauhan BF et al; DOORWAY research group of the Pediatric Emergency Research in Canada (PERC) network (2016) Factors associated with failure of emergency department management in children with acute moderate or severe asthma: a prospective, multicentre, cohort study. *Lancet Respir Med* 4(12): 990–998. [https://doi.org/10.1016/S2213-2600\(16\)30160-6](https://doi.org/10.1016/S2213-2600(16)30160-6)

## ADA published recommendations for psychosocial care for people with diabetes

The American Diabetic Association (ADA) has issued its first position statement providing comprehensive and specific guidelines for psychosocial assessments and care based on factors such as age, type of diabetes and family support system (Young-Hyman et al, 2016).

The psychosocial care position statement is based on current diabetes research and recommendations from the field of mental health.

The guidelines focus on the most common psychological factors affecting people with type 1 and type 2 diabetes, including diabetes distress, depression, anxiety and eating disorders, and emphasize that diabetes management is more successful when

lifestyle and emotional status are an integral component of diabetes care.

Commenting on the guidelines, Dr Alicia McAuliffe-Fogarty, clinical health psychologist and vice president of the lifestyle management team at the American Diabetes Association, said: 'while medical providers are trained to help people manage the medical aspects of their disease, they are not always taught to understand the impact that psychosocial factors have on people living with diabetes.'

Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M (2016) Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 39(12): 2126–2140. <https://doi.org/10.2337/dc16-2053>

## 15-year follow up of EVAR shows loss of early survival benefit

A study using data from the endovascular aneurysm repair (EVAR) randomized controlled trial (EVAR trial 1) has found that EVAR has an early survival benefit but inferior late survival compared with open repair ([https://doi.org/10.1016/S0140-6736\(16\)31135-7](https://doi.org/10.1016/S0140-6736(16)31135-7)). This loss of the early survival benefit needs to be addressed by lifelong surveillance of EVAR and re-intervention if necessary. Sac expansion needs to be tracked for all time periods and the underlying cause corrected. The authors emphasize that there is no time when it is safe to discontinue surveillance in patients who have had EVAR.

## Global elimination of hepatitis B: modelling the requirements

A simulation model of the global hepatitis B virus epidemic has been developed, incorporating data on the natural history of hepatitis B virus, prevalence, mortality, vaccine coverage, treatment dynamics, and demographics (Nayagam et al, 2016). This model was used to estimate the impact of current interventions and scaling up of existing interventions for prevention of infection and introducing wide-scale population screening and treatment interventions on the worldwide epidemic.

Scale-up of vaccination coverage, innovations in scalable options for prevention of mother-to-child transmission, and ambitious population-wide testing and treatment are needed to eliminate hepatitis B virus as a major public health threat. Achievement of these targets could make a major contribution to one of the United Nations' Sustainable Development Goals of combating hepatitis.

Nayagam S, Thursz M, Sicuri E, Conteh L, Wiktor S, Low-Beer D, Hallett TB (2016) Requirements for global elimination of hepatitis B: a modelling study. *Lancet Infect Dis* [https://doi.org/10.1016/S1473-3099\(16\)30204-3](https://doi.org/10.1016/S1473-3099(16)30204-3)