Increased risk of suicide in people with chronic fatigue syndrome

A retrospective cohort study investigated mortality in individuals diagnosed with chronic fatigue syndrome in secondary and tertiary care (Roberts et al, 2016).

Standardized mortality ratios for all-cause, suicide-specific and cancer-specific mortality were calculated for a 7-year observation period using the number of deaths observed in South London and Maudsley records compared with age-specific and sex-specific mortality statistics for England and Wales. Study participants were included if they had had contact with the chronic fatigue service (referral, discharge or case note entry) and received a diagnosis of chronic fatigue syndrome.

There was no increase in all-cause mortality in people with chronic fatigue syndrome, but there was a substantial increase in mortality from suicide. This highlights the need for clinicians to be aware of the increased risk of completed suicide and to assess suicidality adequately in patients with chronic fatigue syndrome.

Roberts E, Wessely S, Chalder T, Chang CK, Hotopf M (2016) Mortality of people with chronic fatigue syndrome: a retrospective cohort study in England and Wales from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Clinical Record Interactive Search (CRIS) Register. *Lancet* **387**: 1638–43 (doi: 10.1016/S0140-6736(15)01223-4)

Prevalence of IPF is double previous estimates

Figures released by the British Lung Foundation (www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics/what-you-need-to-know) show that approximately 32 500 people are living with idiopathic pulmonary fibrosis (IPF) in the UK. This is over twice as many as the 10–15 000 previously thought. The British Lung Foundation has called for increased prioritization of IPF care in light of the data.

New strategies to treat aspergillosis fungal infections: disrupting biofilm and loading neutrophils

Janet Fricker

Adopting two new 'strategies' could transform the way aspergillosis fungal infections are treated in clinical practice, reported a session at the 42nd Annual Meeting of the European Society for Blood and Marrow Transplantation, held in Valencia, Spain (3–6 April). The innovative strategies include disrupting the fungal biofilm and loading neutrophils with antifungal agents.

Despite a wide armamentarium of antifungal agents, invasive fungal infections, in particular aspergillosis, remain a significant cause of mortality in immunocompromised patients, including those undergoing cancer chemotherapy, haematopoietic stem-cell transplantation and solid organ transplantation. Mortality for aspergillosis ranges from 32% to 58%, and up to one quarter of patients are only identified at post mortem.

'All too often patients die while taking drugs to which aspergillosis is susceptible,' said Professor Donald Sheppard from McGill University, Montreal, Canada. 'The reality is that drugs only work if they reach their targets, and fungal infections are ingenious at creating natural barriers.'

Established fungal lesions, he explained, are characterized by extensive tissue necrosis, limiting the penetration of agents to sites of infection.

First, Professor Sheppard addressed fungal biofilms, which prevent antifungals from reaching intracellular targets. Comparing *Aspergillosis fumigatus* with the less pathogenic *A. nidulans*, Professor Sheppard and his team discovered that the amount of galactosaminogalactan present in cell walls directly correlated with virulence.

The finding that galactosaminogalactan plays a key role in biofilm formation suggested to Professor Sheppard that anti-galactosaminogalactan strategies might prove useful in treating invasive aspergillosis. The production of mutant fungi lacking Sph3, a glycoside hydrolase, showed that it was essential for galactosaminogalactan biosynthesis. In addition to being a glycoside hydrolase essential for galactosaminogalactan production, Sph3 was shown to digest galactosaminogalactan.

Delivering Sph3, explained Professor Sheppard, offers the potential to create an agent that could be effective at digesting galactosaminogalactan, thereby disrupting the biofilm. In vitro studies, he added, have shown that the addition of Sph3 enhances antifungal activity of the antifungal agents posaconazole, caspofungin and amphotericin, and also enhances their uptake.

Next, Sheppard and his team turned their attention to neutrophils, which play a critical role in host defense against aspergillosis. In vitro studies with dyes showed that posaconazole concentrates to high levels within differentiated HL-60 cells (DHL-60), used as a model system to explore neutrophil movement. The team showed that posaconazole transfers from DHL-60 cells to *A. fumigatus* hyphae on contact, and furthermore posaconazole-loaded dHL-60 cells kill *A. fumigatus* hyphae in a dose-dependent manner. In a study of neutropenic mice infected with *A. fumigatus*, neutrophils loaded with posaconazole, given intravenously 24 hours after infection, decreased the fungal burden to a greater extent than untreated mice and those just infused with normal neutrophils.

From such findings Professor Sheppard believes neutrophils loaded ex vivo with posaconazole offer a potential new approach to treat established aspergillosis pulmonary infection. 'There are likely to be two phases of posaconazole transfer. First when the neutrophils are attempting to phagocytose the hyphae, and secondly when neutrophils die and explode to release the drug,' said Professor Sheppard. The next step, he added, will be to explore both strategies in human trials. The US Department of Defense has agreed to fund the preclinical Sph3 work.

Professor Donald Sheppard, Director, Division of Infectious Diseases, McGill University, Montreal, Canada

Improved services needed to manage patients with non-viral liver disease

Susan Mayor

More than two-thirds of liver specialists consider that insufficient time and attention are currently focused on managing non-viral liver diseases despite their increasing impact, shows a survey of specialists in England.

The online survey of 50 liver specialists working at specialist units and district general hospitals around the country found that 70% considered insufficient time and attention are currently focused on non-viral diseases even though 64% considered that they are becoming a key public health priority.

'We need a shift in resource in liver disease,' commented Professor Roger Williams from the Foundation for Liver Research, Kings College London, at a roundtable discussion held at the UK launch of Intercept, a company developing new treatments for non-viral, progressive liver diseases. Liver specialists attending the meeting considered that successful management of hepatitis C means that services can be redirected to non-viral liver diseases, including rarer conditions such as primary biliary cholangitis and primary sclerosing cholangitis, as well as liver diseases associated with obesity and alcohol.

UK-PBC, a database of information on patients with primary biliary cholangitis, shows that around 80% of patients with the condition are managed by gastroenterologists rather than liver specialists. 'We have found that knowledge and awareness of primary biliary cholangitis decreases as you go from hepatologists to gastroenterologists working in district general hospitals,' reported Professor David Jones, Professor of Liver Immunology, University of Newcastle, and Director of UK-PBC.

'Greater emphasis can be given to improving basic care as well as accessing new therapies for high-risk patients,' suggested Dr Gideon Hirschfield, Senior Lecturer and Consultant Transplant Hepatologist at the University of Birmingham and a member of the UK-PBC team, adding: 'the goal should be more clearly to prevent end-stage liver disease through expert management.'

Dr Gideon Hirschfield and Professor Roger Williams

Susan Mayor's attendance at the meeting was supported by Intercept. The views expressed by the author and the specialists interviewed are their own.

Change in pain and physical function in the 3 years after bariatric surgery for severe obesity

Follow-up of the Longitudinal Assessment of Bariatric Surgery-2 observational cohort study reported changes in pain and physical function in the first 3 years following bariatric surgery, and identified factors associated with improvement.

Of 2458 participants, 2221 completed baseline and follow-up assessments. At year 1, clinically meaningful improvements were shown in 57.6% of participants for bodily pain, 76.5% for physical function, and 59.5% for walk time. Among participants with severe knee pain or disability, or hip pain or disability at baseline, 77.1% experienced joint-specific improvements in knee pain and 79.2% in hip function.

Between year 1 and year 3, rates of improvement significantly decreased to 48.6% for bodily pain and to 70.2% for physical function, but did not decrease for walk time, knee and hip pain, and knee and hip function.

Dr Wendy King, associate professor in the Department of Epidemiology at University of Pittsburgh Graduate School of Public Health, commented: 'These data can help ... develop realistic expectations regarding the impact of bariatric surgery on pain and disability.'

King WC, Chen JY, Belle SH et al (2016) Change in pain and physical function following bariatric surgery for severe obesity. *JAMA* **315**(13): 1362–71 (doi: 10.1001/jama.2016.3010)

Emergency general surgery: challenges and opportunities

Emergency general surgery: challenges and opportunities is a report from the Nuffield Trust, commissioned by the Royal College of Surgeons (www.nuffieldtrust.org.uk/sites/files/nuffield/publication/nuffield_trust_egs_report_web_0.pdf). It offers practical opportunities to improve the provision of emergency general surgery and provides health-care leaders with important points to consider when reviewing changes to emergency general surgery services.

Aspirin may help prevent cholangiocarcinoma

A hospital-based case-control study evaluating risk factors for bile duct cancer in western populations has found that regular use of aspirin was linked with a significantly reduced risk of developing cholangiocarcinoma (doi: 10.1002/hep.28529).

Evaluation of risks and benefits of treatment by young people with inflammatory arthritis

A qualitative study involved analysing in-depth interviews, audio-recordings and focus groups using techniques from grounded theory. It concluded that young people with inflammatory arthritis aspired to live a 'normal' life. They saw treatment as presenting both an opportunity for, and threat to, achieving this (doi: 10.1002/acr.22832).

26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)

Bezlotoxumab leads to fewer re-hospitalizations for *Clostridium difficile*

Janet Fricker

Taking bezlotoxumab as well as antibiotics for *Clostridium difficile* infection results in fewer re-hospitalizations, concluded a post-hoc patient analysis from the MODIFY I and II phase 3 trials. Bezlotoxumab is a selective, fully-human, monoclonal antibody designed to provide passive immunity by neutralizing *C. difficile* toxin B.

In MODIFY I, patients receiving standard of care antibiotics for *C. difficile* were randomized to a single one-time infusion of bezlotoxumab (*n*=403), an infusion of actoxumab (a monoclonal antibody against *C. difficile toxin* A) (*n*=242), a combination of bezlotoxumab and actoxumab (*n*=403), or placebo (*n*=404). After interim analysis the actoxumab arm was stopped because of a lack of efficacy.

In MODIFY II, patients receiving standard of care antibiotics for *C. difficile* were randomized to a single infusion of bezlotoxumab (*n*=407), bezlotoxumab and actoxumab (*n*=397), or placebo (*n*=399). *C. difficile* recurrence was lower in bezlotoxumab arms (*P*=0.0003 for both MODIFY I and II) and the combination of bezlotoxumab and actoxumab arms (*P*<0.0001 for both MODIFY I and II) compared to placebo.

In the first abstract (Prabhu et al, 2016), Oliver Cornely, from University Hospital of Cologne, Germany, explored the impact of bezlotoxumab on hospital readmissions in a sub-set of MODIFY I and II patients who had been recruited from 17 European countries and were inpatients at the time of randomization (*n*=521).

Dr Dale Gerding, Professor of Medicine, Loyola University, Stritch School of Medicine, Chicago

Results showed 15% of patients taking bezlotoxumab had a recurrence compared to 24.2% taking placebo. Furthermore, *C. difficile*-associated hospital readmission was 4.5% for patients taking bezlotoxumab *vs* 13.3% for patients taking placebo, and all-cause hospital readmissions were 23.0% for patients taking bezlotoxumab *vs* 26.6% for placebo.

In the second abstract (Gerding et al, 2016), Dr Dale Gerding, from Loyola University, Chicago, showed that giving bezlotoxumab to patients receiving standard antibiotic care was effective through 12 weeks in key subpopulations at high risk for *C. difficile* recurrence.

'These new studies confirm antibodies against toxins are important at preventing recurrent *C. difficile* disease,' said Dr Gerding. 'Not only does bezlotoxumab reduce recurrences but through the reduction of in hospital re-admissions the agent has the potential to deliver financial savings. From our data older patients, those with previous infections and the immunocompromised jump out as being important to target.'

Gerding DN, Kelly CP, Rahav G et al (2016) Efficacy of bezlotoxumab, the monoclonal antibody targeting *C. difficile* toxin B, for prevention of *C. difficile* infection (CDI) recurrence in patients at high risk of recurrence or CDI-related adverse outcomes. ECCMID 2016. ePoster EP0176

Prabhu V, Marcella S, Hanson ME et al (2016) Bezlotoxumab decreases CDI recurrence and is associated with a reduction in 30-day readmissions: European analysis. ECCMID 2016. ePoster P1340

High rate of colistin resistance seen in UK outbreak of carbapenemase-producing Enterobacteriaceae

Susan Mayor

Growing reports of resistance to current antibiotics, including the 'last resort' antibiotic colistin (polymixin E), for treating Gram-negative pathogens underlined the need for renewed efforts to use antibiotics responsibly and for new agents that can treat resistant strains.

Otter et al (2016) reported a high rate of colistin resistance during an outbreak of carbapenemase-producing Enterobacteriaceae (CPE) infection in a multicentre London trust in 2015. Researchers carried out whole genome sequencing on isolates from 39 of the 40 patients infected with New Delhi metallo-beta-lactamase (NDM)-producing *Klebsiella pneumoniae*. Colistin susceptibility in 38 patients was tested locally using disc diffusion and in the national reference laboratory using agar dilution.

A colistin-resistant isolate was identified in 36.0% (9/25) of the patients tested locally and in 65.8% (25/38) during testing by the national reference laboratory. The median colistin minimum inhibitory concentration for resistant isolates was 8 mg/litre (range 4–32 mg/litre). Colistin resistance appeared in two clusters, one within each of the sub-clones.

One-third (16/40) of the patients were treated with colistin in combination with other agents and 12 of these 16 were colistin-resistant. Although seven of these patients subsequently died, there was no treatment failure-related mortality.

'The therapeutic challenges presented by CPE are exacerbated by the emergence of colistin resistance,' reported the research group, led by Dr Jon Otter, from Imperial College Healthcare NHS Trust, London. 'We report a high rate of colistin resistance (65.8%) during an outbreak of CPE. The hospital laboratory failed to identify 64% of the colistin-resistant isolates, highlighting the challenges of laboratory detection of colistin resistance.'

Otter J, Gilchrist MJ, Brannigan E et al (2016) Emergence and clonal spread of colistin resistance during an outbreak of CPE in London. ECCMID 2016. Abstract 2765

Amsterdam, The Netherlands, 9–12 April

Antibiotic under-dosing in intensive care units

Susan Mayor

A Swedish study warned that a substantial proportion of patients treated on intensive care units may currently be receiving suboptimal doses of broad-spectrum beta-lactam antibiotics, with higher risk in younger patients and those with increased glomerular filtration rate (Schon et al, 2016). Researchers suggest that being aware of potential underdosing in intensive care and taking steps to reduce this risk are important in antibiotic stewardship.

The prospective multicentre study included 111 consecutive intensive care unit patients who were treated with cefotazime (*n*=38), piperacillin (*n*=49) or meropenem (*n*=24) at four sites. None of the antibiotics were given by continuous infusion. Researchers took serum samples on admission to intensive care and on two consecutive days just before the next dose of antibiotic was given and analysed serum antibiotic concentrations using mass spectrometry.

Results showed that 24% of patients (10/42) did not reach free serum minimum inhibitory concentration of antibiotic for the bacteria causing their infection for 100% of the time (100%fT). Nearly half of patients in the study (46%; 51/111) did not achieve the estimated 'worst case' minimum inhibitory concentration for susceptible bacteria for 100% of their treatment time.

Factors associated with not reaching 100%fT above the estimated minimum inhibitory concentration were younger age, increased glomerular filtration rate, low Simplified Acute Physiology Score score and continuous renal replacement therapy.

'Patients in the intensive care unit are at risk for low levels of broad spectrum beta-lactam antibiotics, which may affect treatment outcome and selection of drug resistance. Potential reasons include the increased volume of distribution and renal clearance,' reported lead author Dr Thomas Schon, from Kalmar County Hospital, Kalmar, Sweden.

Schon T, Woksepp H, Hallgren A et al (2016) Risk factors for not reaching 100% time over actual or estimated minimal inhibitor concentrations in intensive care unit patients on broad-spectrum beta-lactam antibiotics. ECCMID 2016. Abstract 1441

Serodiagnosis of acute and past Zika virus infections by ELISA

Current diagnostics are of limited value in diagnosing Zika virus infection because of high immunological cross-reactivity between flavivirus species.

Steinhagen et al (2016) used recombinant Zika virus non-structural protein 1 (NS1) in an enzyme-linked immunosorbent assay (ELISA) to assess circulating anti-Zika virus IgM and IgG antibodies.

Out of 29 Zika virus-infected patients, 28 were positive for anti-Zika virus NS1 IgM or IgG. Only one patient out of 128 infected with other flaviviruses (0.8%) showed a positive reaction for either IgM or IgG.

This ability to test for the virus' presence after the active stage could prove useful to examine the link between Zika, Guillain–Barré syndrome and microcephaly.

Steinhagen K, Probst C, Radzimski C et al (2016) Serodiagnosis of acute and past Zika virus infections without cross-reactivity to other flaviviruses by NS1-based ELISA. ECCMID 2016. Abstract 7483

Exhaled breath condensate: new non-invasive diagnostic test for invasive fungal infection?

Sue Lyon

A proof-of-concept, single-centre, prospective study suggests that exhaled breath condensate may offer a non-invasive alternative to bronchoalveolar lavage when diagnosing invasive fungal infections such as aspergillosis and candidiasis.

Presenting the study, Dr Alya Bhimji from the University of Toronto, commented: 'Diagnostic techniques for invasive fungal infection such as histopathology and culture lack sensitivity and specificity, while gold-standard methods of sample collection such as bronchoscopy may be contraindicated in seriously ill patients.'

The study compared polymerase chain reaction tests in 202 exhaled breath condensate specimens using the Luminex multiplex xTAG fungal ASR assay with conventional culture and galactomannan testing in bronchoalveolar lavage samples collected from the same lung transplant recipients as part of routine clinical practice. Using the xTAG ASR assay in exhaled breath condensate specimens and bronchoalveolar lavage fungal cultures resulted in concurrent negative results in 162 (80%) samples and positive results in 19 (9%) samples. Sensitivity, specificity, and positive and negative predictive values for the XTAG ASR assay were 82.6%, 90.5%, 52.8% and 97.6% respectively.

The xTAG ASR assay detected seventeen fungal species unidentified on bronchoalveolar lavage cultures. Four samples were culture positive for *A. fumigatus*, but negative using the xTAG ASR assay. Compared to galactomannan enzyme immunoassay, the xTAG ASR assay showed sensitivity, specificity, and positive and negative predictive values of 100%, 85.9%, 16.1% and 100% respectively.

'For the first time we have been able to detect fungal DNA in exhaled breath condensate samples. Because of the very high rate of negative concordance between exhaled breath condensate and bronchoalveolar lavage, we may be able to use exhaled breath condensate as a screening tool to rule out invasive fungal infection,' concluded Dr Bhimji.

Bhimji A (2016) Feasibility of detecting fungal DNA is exhaled breath condensate by the Luminex Multiplex xTAG fungal PCR assay in lung transplant recipients. ECCMID 2016. Abstract O133