# The Big Four Bulletin
# 2 January 2019 No. 618

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The BMJ has produces no new content this week.

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**JAMA: Journal of the American Medical Association** (25 December 2018, Vol. 320, No. 24)

**Association of the Hospital Readmissions Reduction Program With Mortality Among Medicare Beneficiaries Hospitalized for Heart Failure, Acute Myocardial Infarction, and Pneumonia**

Rishi K. Wadhera, Karen E. Joynt Maddox, Jason H. Wasfy, et al
JAMA. 2018; 320 (24): 2542-2552.
https://jamanetwork.com/journals/jama/fullarticle/2719307

**Abstract**

**Importance** The Hospital Readmissions Reduction Program (HRRP) has been associated with a reduction in readmission rates for heart failure (HF), acute myocardial infarction (AMI), and pneumonia. It is unclear whether the HRRP has been associated with change in patient mortality.

**Objective** To determine whether the HRRP was associated with a change in patient mortality.

**Design, Setting, and Participants** Retrospective cohort study of hospitalizations for HF, AMI, and pneumonia among Medicare fee-for-service beneficiaries aged at least 65 years across 4 periods from April 1, 2005, to March 31, 2015. Period 1 and period 2 occurred before the HRRP to establish baseline trends (April 2005-September 2007 and October 2007-March 2010). Period 3 and period 4 were after HRRP announcement (April 2010 to September 2012) and HRRP implementation (October 2012 to March 2015.(

**Exposures** Announcement and implementation of the HRRP.

**Main Outcomes and Measures** Inverse probability–weighted mortality within 30 days of discharge following hospitalization for HF, AMI, and pneumonia, and stratified by whether there was an associated readmission. An additional end point was mortality within 45 days of initial hospital admission for target conditions.

**Results** The study cohort included 8.3 million hospitalizations for HF, AMI, and pneumonia, among which 7.9 million (mean age, 79.6 [8.7] years; 53.4% women) were alive at discharge. There were 3.2 million hospitalizations for HF, 1.8 million for AMI, and 3.0 million for pneumonia. There were 270 517 deaths within 30 days of discharge for HF,

128 088 for AMI, and 246 154 for pneumonia. Among patients with HF, 30-day postdischarge mortality increased before the announcement of the HRRP (0.27% increase from period 1 to period 2). Compared with this baseline trend, HRRP announcement (0.49% increase from period 2 to period 3; difference in change, 0.22% ,*P* (01. = and implementation (0.52% increase from period 3 to period 4; difference in change, 0.25% , *P* (001. = were significantly associated with an increase in postdischarge mortality. Among patients with AMI, HRRP announcement was associated with a decline in postdischarge mortality (0.18% pre-HRRP increase vs 0.08% post-HRRP announcement decrease; difference in change, −0.26% ;*P* (01. = and did not significantly change after HRRP implementation. Among patients with pneumonia, postdischarge mortality was stable before HRRP (0.04% increase from period 1 to period 2), but significantly increased after HRRP announcement (0.26% post-HRRP announcement increase; difference in change, 0.22% ,*P* (01. = and implementation (0.44% post-HPPR implementation increase; difference in change, 0.40% ,*P* .(001. > The overall increase in mortality among patients with HF and pneumonia was mainly related to outcomes among patients who were not readmitted but died within 30 days of discharge. For all 3 conditions, HRRP implementation was not significantly associated with an increase in mortality within 45 days of admission, relative to pre-HRRP trends.

**Conclusions and Relevance** Among Medicare beneficiaries, the HRRP was significantly associated with an increase in 30-day postdischarge mortality after hospitalization for HF and pneumonia, but not for AMI. Given the study design and the lack of significant association of the HRRP with mortality within 45 days of admission, further research is needed to understand whether the increase in 30-day postdischarge mortality is a result of the policy.

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**Association of Genetic Variants Related to Gluteofemoral vs Abdominal Fat Distribution With Type 2 Diabetes, Coronary Disease, and Cardiovascular Risk Factors**

Luca A. Lotta, Laura B. L. Wittemans, Verena Zuber, et al

JAMA. 2018; 320 (24): 2553-2563.
https://jamanetwork.com/journals/jama/article-abstract/2719309

**Abstract**

**Importance** Body fat distribution, usually measured using waist-to-hip ratio (WHR), is an important contributor to cardiometabolic disease independent of body mass index (BMI). Whether mechanisms that increase WHR via lower gluteofemoral (hip) or via higher abdominal (waist) fat distribution affect cardiometabolic risk is unknown.

**Objective** To identify genetic variants associated with higher WHR specifically via lower gluteofemoral or higher abdominal fat distribution and estimate their association with cardiometabolic risk.

**Design, Setting, and Participants** Genome-wide association studies (GWAS) for WHR combined data from the UK Biobank cohort and summary statistics from previous GWAS (data collection: 2006-2018). Specific polygenic scores for higher WHR via lower gluteofemoral or via higher abdominal fat distribution were derived using WHR-associated genetic variants showing specific association with hip or waist circumference. Associations of polygenic scores with outcomes were estimated in 3 population-based cohorts, a case-cohort study, and summary statistics from 6 GWAS (data collection: 1991-2018).

**Exposures** More than 2.4 million common genetic variants (GWAS); polygenic scores for higher WHR (follow-up analyses).

**Main Outcomes and Measures** BMI-adjusted WHR and unadjusted WHR (GWAS); compartmental fat mass measured by dual-energy x-ray absorptiometry, systolic and diastolic blood pressure, low-density lipoprotein cholesterol, triglycerides, fasting glucose, fasting insulin, type 2 diabetes, and coronary disease risk (follow-up analyses).
**Results** Among 452 302 UK Biobank participants of European ancestry, the mean (SD) age was 57 (8) years and the mean (SD) WHR was 0.87 (0.09). In genome-wide analyses, 202 independent genetic variants were associated with higher BMI-adjusted WHR (n = 660 648) and unadjusted WHR (n = 663 598). In dual-energy x-ray absorptiometry analyses (n = 18 330), the hip- and waist-specific polygenic scores for higher WHR were specifically associated with lower gluteofemoral and higher abdominal fat, respectively. In follow-up analyses (n = 636 607), both polygenic scores were associated with higher blood pressure and triglyceride levels and higher risk of diabetes (waist-specific score: odds ratio [OR], 1.57 [95% CI, 1.34-1.83], absolute risk increase per 1000 participant-years [ARI], 4.4 [95% CI, 2.7-6.5], $P < .001$; hip-specific score: OR, 2.54 [95% CI, 2.17-2.96], ARI, 12.0 [95% CI, 9.1-15.3], $P < .001$) and coronary disease (waist-specific score: OR, 1.60 [95% CI, 1.39-1.84], ARI, 2.3 [95% CI, 1.5-3.3], $P < .001$; hip-specific score: OR, 1.76 [95% CI, 1.53-2.02], ARI, 3.0 [95% CI, 2.1-4.0], $P < .001$), per 1-SD increase in BMI-adjusted WHR.
**Conclusions and Relevance** Distinct genetic mechanisms may be linked to gluteofemoral and abdominal fat distribution that are the basis for the calculation of the WHR. These findings may improve risk assessment and treatment of diabetes and coronary disease.

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**Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis**
Dario Gregori, Giampaolo Giacovelli, Clara Minto, et al
JAMA. 2018; 320 (24): 2564-2579.
https://jamanetwork.com/journals/jama/article-abstract/2719308

**Abstract**
**Importance** Even though osteoarthritis is a chronic and progressive disease, pharmacological agents are mainly studied over short-term periods, resulting in unclear recommendations for long-term disease management.
**Objective** To search, review, and analyze long-term (≥12 months) outcomes (symptoms, joint structure) from randomized clinical trials (RCTs) of medications for knee osteoarthritis.
**Data Sources and Study Selection** The databases of MEDLINE, Scopus, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials were searched until June 30, 2018 (MEDLINE alerts through August 31, 2018) for RCTs of patients with knee osteoarthritis that had treatment and follow-up lasting 1 year or longer.
**Data Extraction and Synthesis** Data at baseline and at the longest available treatment and follow-up of 12 months' duration or longer (or the change from baseline) were extracted. A Bayesian random-effects network meta-analysis was performed.
**Main Outcomes and Measures** The primary outcome was the mean change from baseline in knee pain. Secondary outcomes were physical function and joint structure (the latter was measured radiologically as joint space narrowing). Standardized mean differences (SMDs) and mean differences with 95% credibility intervals (95% CrIs) were calculated. Findings were interpreted as associations when the 95% CrIs excluded the null value.
**Results** Forty-seven RCTs (22 037 patients; mean age range, mostly 55-70 years; and a higher mean proportion of women than men, around 70%) included the following medication categories: analgesics; antioxidants; bone-acting agents such as

bisphosphonates and strontium ranelate; nonsteroidal anti-inflammatory drugs; intra-articular injection medications such as hyaluronic acid and corticosteroids; symptomatic slow-acting drugs in osteoarthritis such as glucosamine and chondroitin sulfate; and putative disease-modifying agents such as cindunistat and sprifermin. Thirty-one interventions were studied for pain, 13 for physical function, and 16 for joint structure. Trial duration ranged from 1 to 4 years. Associations with decreases in pain were found for the nonsteroidal anti-inflammatory drug celecoxib (SMD, −0.18 [95% CrI, −0.35 to −0.01]) and the symptomatic slow-acting drug in osteoarthritis glucosamine sulfate (SMD, −0.29 [95% CrI, −0.49 to −0.09]), but there was large uncertainty for all estimates vs placebo. The association with pain improvement remained significant only for glucosamine sulfate when data were analyzed using the mean difference on a scale from 0 to 100 and when trials at high risk of bias were excluded. Associations with improvement in joint space narrowing were found for glucosamine sulfate (SMD, −0.42 [95% CrI, −0.65 to −0.19]), chondroitin sulfate (SMD, −0.20 [95% CrI, −0.31 to −0.07]), and strontium ranelate (SMD, −0.20 [95% CrI, −0.36 to −0.05]).

**Conclusions and Relevance** In this systematic review and network meta-analysis of studies of patients with knee osteoarthritis and at least 12 months of follow-up, there was uncertainty around the estimates of effect size for change in pain for all comparisons with placebo. Larger RCTs are needed to resolve the uncertainty around efficacy of medications for knee osteoarthritis.

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**The Lancet** (22 December 2018, Vol. 392, No. 10165)

**Livebirth after uterus transplantation from a deceased donor in a recipient with uterine infertility**

Dani Ejzenberg, Wellington Andraus, Luana Regina Baratelli Carelli Mendes, et al.

The Lancet: Volume 392, ISSUE 10165, P2697-2704, December 22, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31766-5/fulltext

**Summary**

**Background**

Uterus transplantation from live donors became a reality to treat infertility following a successful Swedish 2014 series, inspiring uterus transplantation centres and programmes worldwide. However, no case of livebirth via deceased donor uterus has, to our knowledge, been successfully achieved, raising doubts about its feasibility and viability, including whether the womb remains viable after prolonged ischaemia.

**Methods**

In September, 2016, a 32-year-old woman with congenital uterine absence (Mayer-Rokitansky-Küster-Hauser [MRKH] syndrome) underwent uterine transplantation in Hospital das Clínicas, University of São Paulo, Brazil, from a donor who died of subarachnoid haemorrhage. The donor was 45 years old and had three previous vaginal deliveries. The recipient had one in-vitro fertilisation cycle 4 months before transplant, which yielded eight cryopreserved blastocysts.

**Findings**

The recipient showed satisfactory postoperative recovery and was discharged after 8 days' observation in hospital. Immunosuppression was induced with prednisolone and thymoglobulin and continued via tacrolimus and mycophenalate mofetil (MMF), until 5 months post-transplantation, at which time azathioprine replaced MMF. First menstruation

occurred 37 days post-transplantation, and regularly (every 26–32 days) thereafter. Pregnancy occurred after the first single embryo transfer 7 months post-transplantation. No blood flow velocity waveform abnormalities were detected by Doppler ultrasound of uterine arteries, fetal umbilical, or middle cerebral arteries, nor any fetal growth impairments during pregnancy. No rejection episodes occurred after transplantation or during gestation. Caesarean delivery occurred on Dec 15, 2017, near gestational week 36. The female baby weighed 2550 g at birth, appropriate for gestational age, with Apgar scores of 9 at 1 min, 10 at 5 min, and 10 at 10 min, and along with the mother remains healthy and developing normally 7 months post partum. The uterus was removed in the same surgical procedure as the livebirth and immunosuppressive therapy was suspended.

**Interpretation**

We describe, to our knowledge, the first case worldwide of livebirth following uterine transplantation from a deceased donor in a patient with MRKH syndrome. The results establish proof-of-concept for treating uterine infertility by transplantation from a deceased donor, opening a path to healthy pregnancy for all women with uterine factor infertility, without need of living donors or live donor surgery.

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**Pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analogue, in patients with non-alcoholic steatohepatitis: A randomised, double-blind, placebo-controlled, phase 2a trial**

Arun Sanyal, Edgar D Charles, Brent A Neuschwander-Tetri, et al.

The Lancet: Volume 392, ISSUE 10165, P2705-2717, December 22, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31785-9/fulltext

**Summary**

**Background**

Pegbelfermin (BMS-986036), a PEGylated human fibroblast growth factor 21 (FGF21) analogue, has previously been shown to improve markers of metabolism and liver fibrosis in obese patients with type 2 diabetes. In this phase 2a study, we aimed to evaluate the safety and efficacy of pegbelfermin in patients with non-alcoholic steatohepatitis.

**Methods**

In this multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 2a study, we recruited adults (aged 21–75 years) with a body-mass index of at least 25 kg/m $^2$, biopsy-confirmed non-alcoholic steatohepatitis (fibrosis stage 1–3), and a hepatic fat fraction of at least 10% when assessed by magnetic resonance imaging-proton density fat fraction. These patients were enrolled at 17 medical centres in the USA. Eligible patients were stratified by type 2 diabetes status and they were randomly assigned (1:1:1) by a computer-based system to receive subcutaneous injections of placebo once a day, 10 mg pegbelfermin once a day, or 20 mg pegbelfermin once a week, all for 16 weeks. Participants, the study team administering treatment, and investigators analysing outcomes (who were independent of the study team and had no further involvement) were masked to treatment groups. The primary outcomes were safety and the absolute change in hepatic fat fraction after 16 weeks of treatment. All patients who were randomly assigned to groups and received the study drug or placebo were included in the primary analyses. This trial was registered with ClinicalTrials.gov, number NCT02413372.

**Findings**

Between May 12, 2015, and Aug 4, 2016, 184 overweight or obese patients with non-alcoholic steatohepatitis were screened for study inclusion. Of these, 95 (52%) patients were excluded because they no longer met study criteria and 80 (43%) patients entered the placebo lead-in phase. After further exclusions, 75 (94%) patients were randomly

assigned to groups, received at least one dose of treatment (25 patients to receive 10 mg pegbelfermin once a day; 24 patients to receive 20 mg pegbelfermin once a week, and 26 patients to receive placebo), and were included in the primary analysis. A prespecified interim analysis at week 8 showed a greater than expected change in the primary outcome and supported early closing of patient enrolment, since this analysis indicated that the full planned sample size was not needed. We observed a significant decrease in absolute hepatic fat fraction in the group receiving 10 mg pegbelfermin daily (−6·8% *vs* −1·3%; p=0·0004) and in the group receiving 20 mg pegbelfermin weekly (−5·2% *vs* −1·3%; p=0·008) compared with the placebo group. Most adverse events were mild; the most common events were diarrhoea in eight (16%) of 49 patients treated with pegbelfermin and two (8%) of 26 patients treated with placebo and nausea in seven (14%) patients treated with pegbelfermin and two (8%) patients treated with placebo. There were no deaths, discontinuations due to adverse events, or treatment-related serious adverse events.

**Interpretation**

Treatment with subcutaneously administered pegbelfermin for 16 weeks was generally well tolerated and significantly reduced hepatic fat fraction in patients with non-alcoholic steatohepatitis. Further study of pegbelfermin is warranted in patients with non-alcoholic steatohepatitis. Additional studies that use liver biopsies would allow for the assessment of pegbelfermin's effects on liver histology. Moreover, further studies should allow assessments of the safety and effectiveness of pegbelfermin in a larger number of patients.

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**Immunogenicity, safety, and tolerability of the measles-vectored chikungunya virus vaccine MV-CHIK: A double-blind, randomised, placebo-controlled and active-controlled phase 2 trial**

Emil C Reisinger, Roland Tschismarov, Eckhard Beubler, et al.

The Lancet: Volume 392, ISSUE 10165, P2718-2727, December 22, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32488-7/fulltext

**Summary**

**Background**

Chikungunya fever is an emerging viral disease and substantial threat to public health. We aimed to assess the safety, tolerability, and immunogenicity of a live-attenuated, measles-vectored chikungunya vaccine (MV-CHIK).

**Methods**

In this double-blind, randomised, placebo-controlled and active-controlled phase 2 trial, we enrolled healthy volunteers aged 18–55 years at four study sites in Austria and Germany. Participants were randomly assigned to receive intramuscular injections with MV-CHIK ($5 \times 10^4$ or $5 \times 10^5$ 50% tissue culture infectious dose), control vaccine, or measles prime and MV-CHIK, in two different administration regimens. Randomisation was done by use of three-digit randomisation codes in envelopes provided by a data management service. The participants and investigators were masked to treatment assignment, which was maintained by use of sterile saline as a placebo injection. The primary endpoint was immunogenicity, defined as the presence of neutralising antibodies against chikungunya virus, at day 56, which is 28 days after one or two immunisations. The primary endpoint was assessed in all participants who completed the study without major protocol deviations (per-protocol population) and in all randomised participants who received at least one study treatment (modified intention-to-treat population). The safety analysis

included all participants who received at least one study treatment. This trial is registered with ClinicalTrials.gov ( NCT02861586) and EudraCT (2015-004037-26) and is completed.

**Findings**

Between Aug 17, 2016, and May 31, 2017, we randomly assigned 263 participants to receive control vaccine (n=34), MV-CHIK (n=195), or measles prime and MV-CHIK (n=34). 247 participants were included in the per-protocol population. Neutralising antibodies against chikungunya virus were detected in all MV-CHIK treatment groups after one or two immunisations, with geometric mean titres ranging from 12·87 (95% CI 8·75–18·93) to 174·80 (119·10–256·50) and seroconversion rates ranging from 50·0% to 95·9% depending on the dose and administration schedule. Adverse events were similar between groups, with solicited adverse events reported in 168 (73%) of 229 participants assigned to MV-CHIK and 24 (71%) of 34 assigned to control vaccine (p=0·84) and unsolicited adverse events in 116 (51%) participants assigned to MV-CHIK and 17 (50%) assigned to control vaccine (p=1·00). No serious adverse events related to the vaccine were reported.

**Interpretation**

MV-CHIK showed excellent safety and tolerability and good immunogenicity, independent of pre-existing immunity against the vector. MV-CHIK is a promising candidate vaccine for the prevention of chikungunya fever, an emerging disease of global concern.

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**The New England Journal of Medicine** (27 December 2019, Vol. 379, No. 26)

**Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer**

Kathleen Moore, Nicoletta Colombo, Giovanni Scambia, et al.

N Engl J Med 2018; 379:2495-2505 December 27, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1810858

**Abstract**

**Background**

Most women with newly diagnosed advanced ovarian cancer have a relapse within 3 years after standard treatment with surgery and platinum-based chemotherapy. The benefit of the oral poly(adenosine diphosphate–ribose) polymerase inhibitor olaparib in relapsed disease has been well established, but the benefit of olaparib as maintenance therapy in newly diagnosed disease is uncertain.

**Methods**

We conducted an international, randomized, double-blind, phase 3 trial to evaluate the efficacy of olaparib as maintenance therapy in patients with newly diagnosed advanced (International Federation of Gynecology and Obstetrics stage III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof) with a mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete or partial clinical response after platinum-based chemotherapy. The patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or placebo. The primary end point was progression-free survival.

**Results**

Of the 391 patients who underwent randomization, 260 were assigned to receive olaparib and 131 to receive placebo. A total of 388 patients had a centrally confirmed germline BRCA1/2 mutation, and 2 patients had a centrally confirmed somatic BRCA1/2 mutation. After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with olaparib than with placebo (Kaplan–Meier estimate of the rate of freedom from disease progression and from death at 3 years, 60% vs. 27%; hazard ratio for disease

progression or death, 0.30; 95% confidence interval, 0.23 to 0.41; P<0.001). Adverse events were consistent with the known toxic effects of olaparib.

**Conclusions**

The use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo.

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**Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness**

Timothy D. Girard, Matthew C. Exline, Shannon S. Carson, et al. for the MIND-USA Investigators

N Engl J Med 2018; 379:2506-2516 December 27, 2018

https://www.nejm.org/doi/full/10.1056/NEJMoa1808217


**Abstract**

**Background**

There are conflicting data on the effects of antipsychotic medications on delirium in patients in the intensive care unit (ICU).

**Methods**

In a randomized, double-blind, placebo-controlled trial, we assigned patients with acute respiratory failure or shock and hypoactive or hyperactive delirium to receive intravenous boluses of haloperidol (maximum dose, 20 mg daily), ziprasidone (maximum dose, 40 mg daily), or placebo. The volume and dose of a trial drug or placebo was halved or doubled at 12-hour intervals on the basis of the presence or absence of delirium, as detected with the use of the Confusion Assessment Method for the ICU, and of side effects of the intervention. The primary end point was the number of days alive without delirium or coma during the 14-day intervention period. Secondary end points included 30-day and 90-day survival, time to freedom from mechanical ventilation, and time to ICU and hospital discharge. Safety end points included extrapyramidal symptoms and excessive sedation.

**Results**

Written informed consent was obtained from 1183 patients or their authorized representatives. Delirium developed in 566 patients (48%), of whom 89% had hypoactive delirium and 11% had hyperactive delirium. Of the 566 patients, 184 were randomly assigned to receive placebo, 192 to receive haloperidol, and 190 to receive ziprasidone. The median duration of exposure to a trial drug or placebo was 4 days (interquartile range, 3 to 7). The median number of days alive without delirium or coma was 8.5 (95% confidence interval [CI], 5.6 to 9.9) in the placebo group, 7.9 (95% CI, 4.4 to 9.6) in the haloperidol group, and 8.7 (95% CI, 5.9 to 10.0) in the ziprasidone group (P=0.26 for overall effect across trial groups). The use of haloperidol or ziprasidone, as compared with placebo, had no significant effect on the primary end point (odds ratios, 0.88 [95% CI, 0.64 to 1.21] and 1.04 [95% CI, 0.73 to 1.48], respectively). There were no significant between-group differences with respect to the secondary end points or the frequency of extrapyramidal symptoms.

**Conclusions**

The use of haloperidol or ziprasidone, as compared with placebo, in patients with acute respiratory failure or shock and hypoactive or hyperactive delirium in the ICU did not significantly alter the duration of delirium.


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**Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL**

Jennifer A. Woyach, Amy S. Ruppert, Nyla A. Heerema, et al.

N Engl J Med 2018; 379:2517-2528 December 27, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1812836

**Abstract**

**Background**

Ibrutinib has been approved by the Food and Drug Administration for the treatment of patients with untreated chronic lymphocytic leukemia (CLL) since 2016 but has not been compared with chemoimmunotherapy. We conducted a phase 3 trial to evaluate the efficacy of ibrutinib, either alone or in combination with rituximab, relative to chemoimmunotherapy.

**Methods**

Patients 65 years of age or older who had untreated CLL were randomly assigned to receive bendamustine plus rituximab, ibrutinib, or ibrutinib plus rituximab. The primary end point was progression-free survival. The Alliance Data and Safety Monitoring Board made the decision to release the data after the protocol-specified efficacy threshold had been met.

**Results**

A total of 183 patients were assigned to receive bendamustine plus rituximab, 182 to receive ibrutinib, and 182 to receive ibrutinib plus rituximab. Median progression-free survival was reached only with bendamustine plus rituximab. The estimated percentage of patients with progression-free survival at 2 years was 74% with bendamustine plus rituximab and was higher with ibrutinib alone (87%; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.26 to 0.58; P<0.001) and with ibrutinib plus rituximab (88%; hazard ratio, 0.38; 95% CI, 0.25 to 0.59; P<0.001). There was no significant difference between the ibrutinib-plus-rituximab group and the ibrutinib group with regard to progression-free survival (hazard ratio, 1.00; 95% CI, 0.62 to 1.62; P=0.49). With a median follow-up of 38 months, there was no significant difference among the three treatment groups with regard to overall survival. The rate of grade 3, 4, or 5 hematologic adverse events was higher with bendamustine plus rituximab (61%) than with ibrutinib or ibrutinib plus rituximab (41% and 39%, respectively), whereas the rate of grade 3, 4, or 5 nonhematologic adverse events was lower with bendamustine plus rituximab (63%) than with the ibrutinib-containing regimens (74% with each regimen).

**Conclusions**

Among older patients with untreated CLL, treatment with ibrutinib was superior to treatment with bendamustine plus rituximab with regard to progression-free survival. There was no significant difference between ibrutinib and ibrutinib plus rituximab with regard to progression-free survival.

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**Investigation of a Cluster of Sphingomonas koreensis Infections**

Ryan C. Johnson, Clay Deming, Sean Conlan, et al.

N Engl J Med 2018; 379: 2529-2539 December 27, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1803238

**Abstract**

**Background**

Plumbing systems are an infrequent but known reservoir for opportunistic microbial pathogens that can infect hospitalized patients. In 2016, a cluster of clinical sphingomonas infections prompted an investigation.

**Methods**

We performed whole-genome DNA sequencing on clinical isolates of multidrug-resistant Sphingomonas koreensis identified from 2006 through 2016 at the National Institutes of Health (NIH) Clinical Center. We cultured S. koreensis from the sinks in patient rooms and performed both whole-genome and shotgun metagenomic sequencing to identify a reservoir within the infrastructure of the hospital. These isolates were compared with clinical and environmental S. koreensis isolates obtained from other institutions.

**Results**

The investigation showed that two isolates of S. koreensis obtained from the six patients identified in the 2016 cluster were unrelated, but four isolates shared more than 99.92% genetic similarity and were resistant to multiple antibiotic agents. Retrospective analysis of banked clinical isolates of sphingomonas from the NIH Clinical Center revealed the intermittent recovery of a clonal strain over the past decade. Unique single-nucleotide variants identified in strains of S. koreensis elucidated the existence of a reservoir in the hospital plumbing. Clinical S. koreensis isolates from other facilities were genetically distinct from the NIH isolates. Hospital remediation strategies were guided by results of microbiologic culturing and fine-scale genomic analyses.

**Conclusions**

This genomic and epidemiologic investigation suggests that S. koreensis is an opportunistic human pathogen that both persisted in the NIH Clinical Center infrastructure across time and space and caused health care–associated infections.

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**Brief Report**

**Tofacitinib Treatment and Molecular Analysis of Cutaneous Sarcoidosis**

William Damsky, Durga Thakral, Nkiruka Emeagwali, et al.
N Engl J Med 2018; 379: 2540-2546 December 27, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1805958

**Summary**

There is evidence that Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling plays a role in the pathogenesis of sarcoidosis. We treated a patient with cutaneous sarcoidosis with the JAK inhibitor tofacitinib; the patient had not previously had a response to medications and had not received systemic glucocorticoids. This treatment resulted in clinical and histologic remission of her skin disease. Sequencing of RNA and immunohistochemical examination of skin-lesion samples obtained from the patient before and during therapy and immunohistochemical testing of lesion samples obtained from other patients with cutaneous sarcoidosis support a role for JAK-STAT signaling in cutaneous sarcoidosis.

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**Sources**

| | |
|---|---|
| BMJ: British Medical Journal | http://www.bmj.com/theBMJ |
| JAMA: The Journal of the American Medical | http://jama.ama-assn.org/ |

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|---|---|
| Association | |
| The Lancet | www.thelancet.com |
| The New England Journal of Medicine | http://content.nejm.org/ |
| The British Medical Journal (BMJ), JAMA and the New England Journal of Medicine (NEJM) can be accessed in full-text through your NHS Athens account. Unfortunately the national subscription to The Lancet has been cancelled. | https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases<br><br>or http://www.openathens.net/ |
| If you have not already registered for an NHS Athens Account, please register at:<br><br>NB: It is recommended that you register on a Trust (NHS) PC for speedy confirmation of your username and password. Once registered, your account can be accessed from any device with online access. | https://openathens.nice.org.uk/ |

## Library News

# New Year, New Logo!

Following the merger of our two libraries, we now have new branding. We hope you like it.

# ClinicalKey

**ClinicalKey** is a **clinical** search engine that makes it easier for clinicians and other healthcare professionals to find and apply relevant knowledge to help them make better decisions – anywhere, anytime, in any patient scenario.

Includes full-text journals, book chapters, images, graphs, monographs, videos and much more. Many available for download.

**Access it via our website:** http://www.uhdblibrary.co.uk/e-resources

# KnowledgeShare

## Having trouble keeping up to date?

**KnowledgeShare** is a web-based current awareness system that provides a personalised current awareness service, direct to your inbox.

**How it works:** Let us know your areas of interest (e.g. physical conditions, professional interests such as mentoring, providing education) and we will set you up with an account. You will then receive regular emails targeted to your interests.

**OpenAthens:** You will need to have an NHS OpenAthens account registered with us, prior to setting up a **KnowledgeShare** account. To register for an Athens account, please go to: https://openathens.nice.org.uk

Further information can be found via this link:
http://www.uhdblibrary.co.uk/current-awareness

# New e-learning modules

Struggling to search published literature effectively? Knowledge for Healthcare (KfH) and Health Education England have published a suite of e-learning modules. More information can be found on our website: http://www.uhdblibrary.co.uk/e-learning

# BMJ Case Reports

The Library and Knowledge Service now has full-text access to *BMJ Case Reports*. *"Case Reports is a unique & growing repository for all healthcare professionals & researchers to submit, search & view case reports in all disciplines."*

BMJ Case Reports can be access here: http://casereports.bmj.com. Click on Login via OpenAthens on the right hand side to log in.

Guidance for authors can be found at:
http://casereports.bmj.com/site/about/guidelines.xhtml

If you wish to submit a case report, the institutional fellowship code is 4315973. An additional fee needs to be paid by the author if s/he wishes to make their submission open access. Details can be found within the guidance.

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