On-scene resuscitation beats hospital transfer

If you have a cardiac arrest in the street, your chances of survival are substantially better if resuscitation is continued on the scene rather than while you are transported to hospital, according to this Canadian cohort study. However, given the observational study design, there is potential for confounding factors. Ideally, a trial that randomises people to on-scene resuscitation or transport to hospital at a prespecified time would offer stronger evidence. But it’s notable that the intra-arrest group tended to have more favourable characteristics but still fared worse than the group treated on the scene. And most survivors who did undergo intra-arrest transport had already been stabilised (measured by return of spontaneous circulation) before they arrived in hospital.

Fitbits and sleep

Sleep duration and patterns are highly variable, and people with a high body mass index (>30) tend to sleep for a slightly shorter time than non-obese people (6.62 v 6.87 hours) and show more variability in their sleep patterns, according to this research letter, which analysed anonymised data from 200,000 Fitbit wearers. This sort of study clearly cannot determine whether being obese interferes with your sleep and/or poor sleep makes you obese. The sleep measures were estimated from accelerometers/optical sensors rather than gold standard polysomnography (although other validation studies suggest that Fitbits are likely to be accurate in measuring total sleep time). People who use wearable devices are generally richer, younger, and healthier than the population at large. The measurements of body mass index are based on self-reported height and weight measurements. And there’s no information about daytime naps or about other comorbidities. We already know that poor sleep is associated with obesity and poor health outcomes. I’m not sure that this study adds anything to lose sleep over.

The genetics of stillbirth

Most cases of stillbirth remain unexplained even after extensive investigation. Around 10-20% are attributed to chromosomal abnormalities, but the precise cause is rarely found. This study used exome sequencing (a genomic technique to sequence all of the protein-coding regions of genes in a genome) in 246 stillbirths (gestation >20 weeks) and found a molecular diagnosis in 6%. Identifying a monogenic disorder helps calculate recurrence risk, plan the management of future pregnancies, and identify novel targets for treatment. Around half of the stillbirths attributable to genetic causes were due to pathogenic variants known to cause disorders in infants and adults, and a similar number were due to loss of function variants critical to in utero survival but not previously known to cause stillbirth or postnatal disease. Larger studies and more widespread use of exome sequencing are needed to improve understanding and prevention of this devastating event.

Vaccinating premature babies

Is the standard schedule of infant immunisations suitable for very preterm babies? This prospective observational study found that preterm infants given the (Dutch) routine schedule developed lower IgG levels than those born at full term, but that 95% or more still achieved protective cover against diphtheria, tetanus, pertussis, pneumococcus, and hepatitis B. The exception was Haemophilus influenzae type b (Hib); only 40.6% developed protective levels of IgG after the primary immunisation schedule and 88.1% after a booster dose. Findings from this Dutch study may not apply to other countries with different vaccines and vaccine schedules for preterm infants, but the finding about Hib certainly bears further investigation.
Remdesivir for severe covid-19: a clinical practice guideline

Bram Rochwerg, Arnav Agarwal, Linan Zeng, Yee-Sin Leo, John Adabie Appiah, Thomas Agoritsas, Jessica Bartoszko, Romina Brignardello-Petersen, Begum Ergan, Long Ge, Heike Geduld, Hayley B Gershengorn, Hela Manai, Minhua Huang, François Lamontagne, Seema Kanda, Leticia Kawano-Dourado, Linda Kurian, Arthur Kwizera, Srinivas Murthy, Nida Qadir, Reed Siemieniuk, Maria Asuncion Silvestre, Per Olav Vandvik, Zhikang Ye, Dena Zeraatkar, Gordon Guyatt

Clinical question What is the role of remdesivir in the treatment of severe covid-19? This guideline was triggered by the ACTT-1 trial published in the New England Journal of Medicine on 22 May 2020.

Recommendations The guideline panel makes a weak recommendation for the use of remdesivir in severe covid-19 while recommending continuation of active enrolment of patients into ongoing randomised controlled trials examining remdesivir.

The evidence The linked systematic review (published 31 Jul 2020) identified two randomised trials with 1300 participants, showing low certainty evidence that remdesivir may be effective in reducing time to clinical improvement and may decrease mortality in patients with severe covid-19. Remdesivir probably has no important effect on need for invasive mechanical ventilation. Remdesivir may have little or no effect on hospital length of stay.

Understanding the recommendation Most patients with severe covid-19 would likely choose treatment with remdesivir given the potential reduction in time to clinical improvement. However, given the low certainty evidence for critical outcomes and the fact that different perspectives, values, and preferences may alter decisions regarding remdesivir, the panel issued a weak recommendation with strong support for continued recruitment in randomised trials.

Readers’ note This is version 1 of the guideline, published online on 30 July (BMJ 2020;370:m2924).
The evidence

To date, two RCTs have evaluated remdesivir versus placebo in severe covid-19.4,11 The study by Wang et al enrolled 237 patients in China, all with severe disease, of whom 16.1% were critically ill at baseline.12 The ACTT-1 trial enrolled 1063 patients across 13 countries including those in North America, Europe, and Asia.4 Most of these patients experienced severe disease, but the trial also included some (11.9%) with mild/moderate disease. Both trials evaluated remdesivir given intravenously at a dose of 100 mg per day for 10 days. Gilead Sciences, the manufacturer of remdesivir, provided the drug free for both trials and was involved in protocol development in the ACTT trial. Patients in both trials were randomised approximately 9-11 days after initial symptom onset and were predominantly men (60-65%) with a mean age between 58 and 65 years old. These two trials together addressed the critical outcomes for treatment of covid-19 as defined by the panel, including mortality, mechanical ventilation, time to clinical improvement, duration of hospitalisation, and adverse events related to drug administration.

We included data from both trials in the network meta-analysis10 to generate pooled estimates of effect (see main infographic for summary of findings). For outcomes in which the networks were too sparse to generate trustworthy effect estimates (need for and duration of mechanical ventilation, time to clinical improvement), we generated pooled estimates based on direct pairwise meta-analysis. We used the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) dataset,15 prospectively collected data from over 15 000 hospitalised patients with covid-19 from 36 countries, to calculate the baseline risk of outcomes of mortality (37%) and mechanical ventilation (11.6%). The baseline risk from the ISARIC data was then used, along with the pooled relative risk from the network meta-analysis, to calculate the absolute effect estimates presented in our evidence summaries. We generated baseline risk for the other outcomes of interest based on the control arms of the two included trials.

Remdesivir may decrease mortality (network meta-analysis odds ratio 0.66 (95% confidence interval (CI) 0.40 to 1.14), absolute effect estimate 8.5% reduction (95% CI 16.5% reduction to 3.0% increase)), but this is based on low certainty evidence with very serious imprecision.

Remdesivir may reduce time to clinical improvement (mean difference 3.04 days fewer (0.89 to 5.19 days fewer), mean in supportive care group 19 days, mean in remdesivir group 16 days); this result also has low certainty due to imprecision and indirectness. Clinical improvement was measured using an ordinal scale, in which the importance of individual components varies. In general, both studies used similar definitions and ones that would probably be consistent with what patients or clinicians would expect (that is, no longer requiring life support, no longer requiring oxygen therapy, no longer requiring hospitalisation). However, we did still lower the certainty in this outcome for indirectness, as not all aspects of clinical improvement (such as symptom resolution and functional status) were considered. The panel concluded that a three day reduction in time to clinical improvement would likely be important to most individuals; however, as the clinical importance of the individual components of the scale vary, the overall interpretation of this outcome remains somewhat uncertain.16-17

Remdesivir may have little to no effect on risk for mechanical ventilation (network meta-analysis odds ratio 1.03 (0.50 to 2.13), absolute effect estimate 0.3% more (5.4% fewer to 10.2% more), low certainty), or duration of hospitalisation (mean difference 0 days fewer (4 days fewer to 4 days more), low certainty). Decisions regarding discharge may not track closely with clinical improvement: Wang et al reported no difference in the duration of hospitalisation,11 and the ACTT-1 trial did not report hospital duration.

Remdesivir may increase the risk of serious adverse events leading to drug discontinuation (network meta-analysis odds ratio 1.26 (0.52 to 3.94), absolute effect estimate 1.9% more (3.7% fewer to 17.5% more), low certainty).

Understanding the recommendations

Recommendation No 1—We suggest remdesivir rather than no remdesivir for the treatment of patients with severe covid-19 infection (weak recommendation).

– The panel made its recommendation on the basis of the low certainty evidence of a modest reduction in time to clinical improvement and no effect on duration of hospitalisation. We made this recommendation despite an uncertain impact on survival. A weak recommendation implies that most patients with severe covid-19 infection would choose to take remdesivir; a minority will, depending on individual shared decision making, decline.

– The panel was reassured that the risk for adverse effects with remdesivir seems minimal, although a full safety analysis will require documentation of adverse effects in much larger numbers of patients.18

– Potential adverse events associated with remdesivir include hyperglycaemia, liver dysfunction, and renal failure. Administration of remdesivir should always be in addition to, and not instead of, routine supportive therapy.
We suggest remdesivir rather than no remdesivir in patients with severe covid-19.

**Evidence profile**

<table>
<thead>
<tr>
<th>Event</th>
<th>Usual supportive care</th>
<th>Remdesivir</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>330</td>
<td>245</td>
<td>LOW</td>
</tr>
<tr>
<td>Mechanical ventilation risk</td>
<td>116</td>
<td>119</td>
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<tr>
<td>Serious adverse events</td>
<td>80</td>
<td>99</td>
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<tr>
<td>Median days</td>
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<td></td>
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<tr>
<td>Mean days</td>
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<td>16</td>
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</tr>
<tr>
<td>Time to clinical improvement</td>
<td>19</td>
<td>16</td>
<td>LOW</td>
</tr>
<tr>
<td>Length of stay in intensive care</td>
<td>Not measured</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Recommendation 2**

Randomised controlled trials examining remdesivir in patients with covid-19 should continue pending further data.

Further information is necessary to raise the quality of evidence for all outcomes. Further information is required to identify subgroups of covid-19 patients that are more or less likely to benefit from therapy.

Disclaimer: This infographic is not a validated clinical decision aid. This information is provided without any representations, conditions, or warranties that it is accurate or up to date. BMJ and its licensors assume no responsibility for any aspect of treatment administered with the aid of this information. Any reliance placed on this information is strictly at the user’s own risk. For the full disclaimer wording see BMJ’s terms and conditions: http://www.bmj.com/company/legal-information/
**Recommendation No 2**—Randomised controlled trials examining remdesivir in patients with covid-19 should continue.

− Although the panel made a weak recommendation for remdesivir, uncertainty regarding any mortality benefit, possible reduction in hospitalisation, and the magnitude of any benefit in time to clinical improvement can only be resolved by continuing enrolment in RCTs examining remdesivir in comparison with placebo or usual care for patients with severe covid-19. Clarification of the benefits and harms of remdesivir is even more important in economically constrained hospital systems.

**Who does it apply to?**

Recommendation 1 applies to all adult patients with severe confirmed covid-19. As criteria for hospitalisation vary among jurisdictions, we anchored our definition of severe infection to the initial WHO criteria, which specifies one or more of respiratory rate >30 breaths per minute, respiratory distress, or SpO₂ <94% on room air. In most treatment centres, need for hospitalisation or oxygen therapy are reasonable surrogates for severe covid-19. However, as some centres have admitted less sick patients with covid-19 (even those not requiring oxygen therapy) or don’t have the ability to provide oxygen therapy, the panel was more comfortable using objective clinical criteria in order to maximise applicability.

The panel’s plan to address several subgroups— including (a) critically ill versus non-critically ill, (b) early initiation of remdesivir versus later initiation, and (c) patients with evidence of pneumonia not requiring oxygen versus those requiring supplemental oxygen—proved unfeasible because of lack of informative data. The subgroup findings from the two trials were deemed of very low credibility, and the panel based recommendations on the entire population with severe covid-19.

**Values and preferences**

We did not perform a systematic review of patient values and preferences for this guideline and therefore views expressed are those of the panel members, which included covid-19 survivors and patient partners. As with other Rapid Recommendations, the panel took an individual patient perspective to values and preferences. The panel felt that uncertainty remains regarding the extent to which patients would find a three day reduction in time to clinical improvement, in the absence of reduction in hospital stay, important. This anticipated variability in patients’ values and preferences, combined with the low certainty evidence for most outcomes, resulted in a weak recommendation to offer remdesivir to patients.

**Resource considerations**

The panel also considered the impact of resource allocation in economically constrained health systems when generating this recommendation, a perspective in which widespread provision of novel therapies for covid-19 may require higher quality evidence of important benefits. Resource constrained environments exist in low and middle income countries, as well as, to varying degrees, in high income countries. In such environments, opportunity costs—that is, drawing resources away from alternative, perhaps more worthwhile, expenditures—become a particularly salient concern. This is especially relevant in covid-19, as even centres in high resource settings may experience resource constraints with diversion of time, funds, attention, and workforce during a pandemic surge.

**Practicalities**

Some practicalities in the administration of remdesivir may limit its use. To date, it can only be administered intravenously, and it is relatively costly with, at least for now, limited availability. Remdesivir is contraindicated in patients with liver dysfunction (alanine aminotransferase >5 × normal at baseline) or renal dysfunction (estimated glomerular filtration rate <30 mL/minute).

**Ongoing uncertainty**

Important uncertainties remain, including:

− The impact of remdesivir on mortality
− The effect of remdesivir on time to clinical improvement, duration of hospitalisation, and long term morbidity
− The effect of remdesivir in combination with other agents
− The optimal timing of drug initiation, dose, and duration of remdesivir. A recently completed RCT compared a 10 day course versus a five day course of remdesivir and found no difference in patient-important outcomes, but the trial had important methodological limitations

− Whether there are specific subgroups of patients with covid-19 who may benefit more or less from remdesivir
− Generalisability of study results to other regions and populations
− The long term safety of remdesivir

− The impact of remdesivir on patient-reported outcomes such as symptom burden.

We anticipate more evidence on the effect of remdesivir from RCTs and on long term safety from observational studies with sufficient length of follow-up. The largest ongoing trials examining remdesivir include WHO SOLIDARITY, DISCOVERY (NCT04315948), and SIMPLE (NCT04292899). The living network meta-analysis associated with this guideline will incorporate new data as the evidence base increases and allow for analysis of many different interventions within the same analytic model.

**Competing interests** See bmj.com.

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Painful perianal ulcers with nicorandil

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This is one of a series of occasional articles to help doctors prevent, diagnose, and respond to adverse drug reactions that may be serious if not recognised. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and City Hospital Birmingham, and Patricia McGettigan, reader in clinical pharmacology and medical education, Queen Mary University of London.

A 73 year old man presents with painful ulcers around his anus that have worsened, despite his use of a barrier cream. His bowel habit is unchanged, his weight is stable, he is not anaemic, and he has experienced no rectal bleeding. He has ischaemic heart disease for which he takes aspirin, atorvastatin, bisoprolol, diltiazem, nicorandil, and ramipril. You find extensive perianal ulceration. Rectal examination is painful, but no masses are evident. Since clinical findings do not suggest cancer or inflammatory bowel disease, you consider if this might represent an adverse reaction to nicorandil, recalling a photograph you had seen (figure).

Nicorandil, a drug occasionally used to treat symptoms of angina, can cause a rare but serious adverse reaction of painful, non-healing ulcers that affect the skin and mucosa.1 Failure to recognise this adverse drug reaction can result in serious harm to some patients.2-5 The danger is increased because nicorandil treatment is usually initiated by cardiologists, but this rare adverse reaction usually presents to others, including general practitioners, surgeons, dentists, ophthalmologists, and dermatologists.

What is nicorandil?

Nicorandil is a nicotinamide ester that dilates arteries and veins, reducing after-load and pre-load on the heart.1 Guidelines from the European Society of Cardiology and National Institute for Health and Care Excellence recommend nicorandil as second line treatment in the management of stable angina that is inadequately controlled by first line agents such as β blockers and calcium antagonists or where these agents are not tolerated.1,2 The box shows licensing and safety warnings by drug regulatory bodies. Nicorandil is not indicated for the prevention of cardiovascular events. In the 12 months to 30 June 2019, nearly 1.5 million prescriptions for nicorandil were issued in primary care in England, (www.openprescribing.com), but information on hospital prescribing is unavailable.

How do patients with this adverse reaction present?

Patients may present with ulcers, which are usually painful, in the mouth, around the anus, or on the cornea, skin, or genitalia.2-17 Those with ulcers in the bowel may present with gastrointestinal haemorrhage. Perianal ulcers can be particularly problematic owing to complications that include infection, bleeding, and fistula formation.5-18 Nicorandil has also been associated with non-healing surgical wounds and ulceration at stoma sites.3 Ulcers develop in some patients shortly after starting nicorandil treatment, and in others after years of uneventful use.

Perianal ulceration, reproduced from Kulakov E, Baron S. BMJ 2013;346:f3686

WHAT YOU NEED TO KNOW

- Nicorandil, a second line treatment for angina, may cause severe, painful ulcers that affect the skin and mucosa.1 Failure to recognise this adverse drug reaction can result in serious harm to some patients.2-5 The danger is increased because nicorandil treatment is usually initiated by cardiologists, but this rare adverse reaction usually presents to others, including general practitioners, surgeons, dentists, ophthalmologists, and dermatologists.

Regulatory approval and warnings

Nicorandil was developed as an anti-anginal treatment by the Chugai Pharmaceutical Company of Japan. It is licensed in Europe (Austria, Denmark, France, Ireland, the Netherlands, Portugal, UK) and elsewhere for this indication. It is not approved for marketing in the US.1,8 Reports of ulceration in patients began to appear during the 1990s.3 Since then, medicines regulators including the Medicines and Healthcare Products Regulatory Agency in the UK, the New Zealand Medicines Safety Agency, and the Therapeutic Goods Authority in Australia have issued warnings that nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers, which may progress to perforation, haemorrhage, fistula, or abscess.9-12 These warnings have been reiterated by the World Health Organization.13 A European Medicines Agency review of nicorandil harmonised product information EU-wide and the changes became legally binding in 2015 (https://www.ema.europa.eu/en/medicines/human/referrals/ikorel-dancor).
How common are these reactions?

The Europe-wide EudraVigilance database of suspected adverse drug reaction reports includes 1785 unclassified reports for nicorandil up to June 2020. The Summary of Product Characteristics states that rectal bleeding is common with nicorandil (frequency ≥1/100, <1/10). Gastrointestinal ulceration at any site (mouth, small/large intestine, anus) is rare, (≥1/10 000, <1/1000). Skin, perianal, genital, para-stomal, and perianal ulcers are very rare (<1/10 000). In a small UK based surgical study of 30 patients with nicorandil associated anal ulceration, the incidence of anal ulcers was 4/1000 in patients treated with nicorandil.

People with diverticular disease may be at increased risk of developing gastrointestinal ulcers. Gastrointestinal ulceration and bleeding risks are increased when nicorandil is taken with other medicines associated with these problems, such as non-steroidal anti-inflammatory drugs and aspirin.

What is the evidence?

Various mechanisms for nicorandil-associated ulceration have been proposed, but none has been validated. Many case reports describe nicorandil-associated ulcers; however, few studies have evaluated risks at the population level. A nationwide epidemiological study from Taiwan found that 25.8% (183/710) of nicorandil users developed gastrointestinal ulceration compared with 9.3% (61 281/659 081) of a cohort of non-users from the general population (adjusted hazard ratio (aHR) 1.43; 95% confidence interval, 1.23 to 1.65; 6848 excess cases per 100 000 patient years of use). The study also reported gastrointestinal perforation rates of 1.6% versus 0.3%, respectively (aHR 1.60, 95% confidence interval 1.03 to 2.51; 315 excess cases per 100 000 person years).

Despite the paucity of studies, the association is strong owing to the consistent pattern of healing reported when nicorandil is withdrawn, and of relapse on re-commencing nicorandil.

Some studies have reported greater risk at doses at or above 30 mg/day than at lower doses, but severe tongue ulceration has been reported with a dose of 10 mg/day.

How is it managed?

Among patients taking nicorandil and who develop ulcers at any site, recognise this as a possible adverse drug reaction. The ulcers are refractory to treatment other than withdrawal of the drug. Failure to suspect this association has led to catastrophic outcomes for some patients, including fistula formation, unnecessary surgical resections and colostomies, and life threatening bleeding.

The single effective treatment for the ulcers is to stop the nicorandil. General practitioners may be reluctant to stop or change nicorandil for fear of harming the patient. This “no-touch” approach is reasonable for some specialty drugs but not for nicorandil owing to the patient harm caused. Stopping nicorandil treatment is unlikely to increase the risk of cardiovascular events, although it may exacerbate anginal symptoms. Discuss substituting or increasing the dose of another anti-anginal drug for symptomatic relief if the patient experiences symptoms on stopping nicorandil. Explain to the patient that nicorandil is a possible cause for the painful ulcers even though the drug has been taken for some time. Discuss substituting another anti-anginal drug or stopping altogether. Assess anginal symptoms and if the patient is still in cardiology care, keep the cardiologist informed.

Depending on the severity of the ulcer and any complications, healing is reported within 2–4 months after cessation, longer for more severe ulcers. Medical and surgical treatments, including ulcer excision, resection, skin grafts, dressings, and topical medications are ineffective, delaying both healing and pain relief. Monitor pain control and ulcer healing; if the ulcers heal, this is circumstantial evidence implicating nicorandil. If they are not healing or worsening despite ceasing the nicorandil, other causes need to be considered and a surgical opinion may be helpful.

How can the risk of harm be minimised?

Well informed and vigilant patients (or carers) represent the first line of protection. Make sure patients are aware of this adverse effect of nicorandil. Discuss potential benefits and harms of nicorandil treatment, and the risk of ulceration. Ask them to report gastrointestinal symptoms, eye problems, and ulcers anywhere on the body. Ask about ulceration every time the patient renews a nicorandil prescription.

In patients who develop an ulcer, avoid nicorandil in the future. Add it as a drug to be avoided on the patient’s medical record. Make sure the patient knows this too. Notify the relevant authorities (in the UK this is a Yellow Card report at https://yellowcard.mhra.gov.uk/).

Competing interests None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.m3351

In creating the article, our patients were not directly involved in creating the article. The case reports referenced are based on patient accounts and our patient example is a compilation from these.

Educational practice

• What would you discuss with your patient when re-commencing nicorandil or renewing a prescription for it?
• How many patients are on nicorandil at your practice?
• Are they aware of this adverse drug reaction, and have any patients experienced this?
Malignant causes of nasal obstruction

This picture shows an extranodal natural killer/T cell lymphoma, nasal type in a man in his 30s. He was referred with a two month history of a painless obstructive mass and yellow exudates in the right anterior nares, with the columella shifted to the left, after unsuccessful treatment for rhinitis (this diagnosis was suspected because of a lack of pain and bleeding).

Histopathology showed abundant lymphoid cells infiltrating the subepithelial region of the mucosa, and whole body positron emission tomography with computed tomography showed a concentration of radioactivity in the mass. These findings confirmed the diagnosis. Extranodal natural killer/T cell lymphoma, nasal type is a rare subtype of non-Hodgkin’s lymphoma. It has a poor prognosis and, in the early stages, is often assumed to be sinusitis or nasal polyps. Consider malignancy when nasal obstruction is not alleviated with medical treatment.

If you would like to write a Minerva picture case, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

Implant survival after total hip replacement

An analysis of a database of hip replacements in England and Wales finds variation between hospitals in the longevity of the implant. One of the hospitals with the highest implant survival rates used a single type of hip replacement for all patients. When analyses were restricted to patients who received this implant, differences between hospitals disappeared, which suggests that the predominant influence on implant survival isn’t the skill of the surgeon or the quality of care provided by the hospital, but the choice of prosthesis (PLoS Med doi:10.1371/journal.pmed.1003291).

Iron deficiency after surgery for weight loss

Bariatric surgery carries a serious long term risk of iron deficiency and anaemia, according to a retrospective study of nearly 400 people who underwent Roux-en-Y gastric bypass or sleeve gastrectomy at a single centre in Canada (Blood Adv doi:10.1182/bloodadvances.2020001880). Over a mean follow-up of 30 months, the cumulative incidence of iron deficiency and iron deficiency anaemia reached 43% and 16%, respectively.

Sarcoidosis

Sarcoidosis is characterised by the formation of non-caseating granulomas in various tissues, most commonly the lungs and intrathoracic lymph nodes. The cause is a mystery but a large case-control study from Sweden reports that the prevalence of occupational silica exposure was higher among cases than controls (BMJ Open doi:10.1136/bmjopen-2020-038926). Even so, only about one in seven cases had been exposed, so it’s unlikely that silica can account for more than a small proportion of the disease.

Childhood deaths from infection

Roughly 5000 children died of infection in England and Wales between 2013 and 2015. This represents a fall of around 30% when compared with infectious disease deaths during a similar period a decade earlier. Most infection-related deaths were bacterial in origin and an underlying comorbidity was present in more than half of the children who died (Arch Dis Child doi:10.1136/archdischild-2019-318001). Although this downward trend is encouraging, infection continues to contribute to one in five childhood deaths.

Loneliness, social isolation, and cardiovascular events

Data from the English Longitudinal Study of Ageing flags up loneliness as a risk factor for cardiovascular disease. After adjusting for other cardiovascular risk factors, people with high scores on a scale of loneliness were one third more likely to develop cardiovascular disease (Heart doi:10.1136/heartjnl-2020-316614). Surprisingly perhaps, living alone correlated poorly with loneliness. While a subjective perception of loneliness seemed to be harmful for cardiovascular health, social isolation did not.

Recurrent muscle strain

Having had the disease before is a strong predictor of many medical conditions. Someone who has had an attack of gout for example, is more likely to experience another than someone who has never had gout. An analysis of data from players in the Australian Football league shows that the same is true for muscle strain (Br J Sport Med doi:10.1136/bjsports-2019-100755). The strongest risk factor for a major muscle strain, whether affecting hamstring, quadriceps, calf, or groin, was having had a similar injury fairly recently. The increased risk persisted for 15 weeks after return to play.

Patient consent obtained.

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