The importance of TIAs
Are transient ischaemic attacks (TIAs) a warning shot for impending stroke? Lioutas and colleagues examined the incidence of stroke in people who had had a TIA compared with age and sex matched controls who had not had a TIA in a large retrospective cohort study (the Framingham Heart Study). They found that almost 30% of those who had a TIA went on to have a stroke. A fifth of the strokes happened within seven days of the TIA, and two fifths of the strokes had happened by 90 days. Half the strokes happened more than a year later. Matched control participants who had not had a TIA had much lower stroke rates. The close temporal relation between the TIAs and strokes suggests we should consider TIAs as a pre-stroke phenomenon. These data are helpful for being able to quantify risk, with the caveat that our patients may be quite different from the Framingham population.


Still active
Older adults do quite a lot even when they have dementia, disability, or depression—according to this survey of US adults aged over 65 years living in the community and participating in the National Health and Aging Trends Study between 2011 and 2015. The researchers focused on “meaningful activity”—defined as “self-reported participation in a favorite activity that enhanced cognitive engagement (eg, reading), social connectedness (eg, socializing with others), or physical aptitude (eg, walking/jogging).” In all, 84% of people without dementia, disability, or depression did meaningful activity compared with 74% of those with dementia alone, 56% of those with disability alone, and 68% of those with depression alone. Rates of meaningful activity were much lower if participants had more than one of these conditions. However, the assessment was based on self-reporting, which could be biased.


Aspirin to reduce pregnancy loss
We rely on the intention-to-treat analysis of randomised controlled trials because per protocol analysis can negate the bias resistance that randomisation provides. Yet it’s very tempting to rely on the effect seen in those who actually took the treatment. Naimi and colleagues present a per protocol analysis of a previously published study of aspirin initiated before conception for improving pregnancy outcomes. This study did not show a positive effect, and that was attributed to non-adherence. In this post hoc analysis, taking aspirin more than four days a week improved pregnancy outcomes. The authors rightly acknowledge that “trial data for this study were analyzed as observational data, thus are subject to the limitations of prospective observational studies.” The positive effects reported here are therefore food for thought but insufficient for recommending aspirin for people with one or two pregnancy losses who are attempting pregnancy.

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Morbid but important
When life sustaining measures are withdrawn, it’s important to know when death (that is, cessation of cardiac activity) has occurred for the purpose of organ donation. Dhanani and colleagues systematically studied 631 adults in three countries, but primarily Canada, in whom withdrawal of life sustaining measures without cardiopulmonary resuscitation and imminent death was anticipated. Monitoring included blood pressure, electrocardiography, and oxygen saturations for 15 minutes after withdrawal and for 30 minutes after death. Retrospective analysis identified 67 (14%) instances of one or more cardiac cycles. Only 1% of patients were recognised to have this at the time. The latest time these occurred after pulselessness was within 4 minutes and 20 seconds. Is this a big enough cohort to trust that 5 minutes is long enough? Possibly, but there were limitations—such as large numbers of excluded patients owing to incomplete data for waveform analysis, and patients who proceeded to organ recovery so the observation ended at 5 minutes.


Useful coil trial
Turok and colleagues randomised women to receive either the copper intrauterine device (IUD) or a levonorgestrel IUD (which provides local progestogen hormone) for emergency contraception after unprotected sex in the preceding five days and who agreed to implantation. If only 2.5% more pregnancies occurred in the levonorgestrel IUD group, it would be considered non-inferior. This sounds pretty generous to me given the nature of the outcome (an unwanted pregnancy). Fortunately, the difference between the two groups was 0.3%, so it does seem that the levonorgestrel IUD does seem non-inferior to the traditional copper coil. This is good news because the former is better tolerated than the copper coil as a form of long term contraception.


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Decoding the unknowns in long covid

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Relatively few peer reviewed papers have documented the disease features of “long covid,” but patient groups report several months of sequelae. These can be varying, relapsing, and remitting, and may include respiratory, cardiovascular, urological, neurological, and/or gastrointestinal symptoms in unpredictable combinations. We do not know whether long covid will come to be seen as a condition that typically lasts months, years, or is life long.

Many of the risk factors for severity of acute covid-19, such as age, male sex, obesity, and ethnicity do not appear explicitly to enhance the chance of long covid. Also, there seems no clear correlation between severity of the acute disease and long term sequelae. Indeed, many patients come from that large, hidden group who self-isolated when they were unwell at home, did not access a polymerase chain reaction test, and so have no formal health record of covid-19. These points highlight an uncharted pathophysiology, and demand a better answer than “post-viral syndrome” or the notion that people are bound to “feel a bit rough” coming out of hospital.

Starting points

At least 10% of people with acute covid-19 are estimated to have symptoms that do not resolve over the subsequent months. 1 2 Extrapolated to the current global burden of covid-19, this suggests potentially more than five million current “long haulers.” Biomedical research is needed to tackle the many challenges imposed by these estimates: formal assessment of the epidemiology, risk factors, symptoms, and pathology. We need recognised criteria for a working diagnosis, not least to facilitate access to appropriate services and allow healthcare provision planning. But we must also move beyond the observational to the interventional. Achieving this will need some hard thinking to decode aetiological mechanisms in a confounding condition that seems to move around the body and between systems and, thus, in healthcare management, between distinct clinical specialties and treatment pathways. What should our starting points be in decoding the unknowns?

Infection with covid-19 can leave a lingering trail of changes on computed tomography scans of the lungs. 3 ACE-2 positive cells within the lung, heart, kidney, and elsewhere are susceptible to direct infection with SARS-CoV-2, which can lead to fibrosis. Initial reporting of the COVERSCAN magnetic resonance imaging study of more than 200 individuals with long covid at around four months after infection shows multi-organ involvement, especially the heart and lungs. 4

Conceptual models

The notion of long term virus persistence has not previously been considered for coronaviruses, yet gastrointestinal biopsies taken four months after acute covid-19 show persistent live virus in about a third of individuals. 5 Nonetheless, presence of the virus would not be a prerequisite to account for persistent disease. Several acute viral infections are known to induce immune and inflammatory responses and lead to long term sequelae. Autoimmune/inflammatory conditions can persist for years after Ebolavirus or Chikungunya virus, and profound immune subset perturbations can be provoked by Epstein-Barr virus (EBV) in infectious mononucleosis. Furthermore, the status of EBV in aetiological risk of multiple sclerosis exemplifies the potential roles of viral infection in triggering autoimmunity.

The mechanisms underlying autoimmune diseases may offer some conceptual models relevant to symptom patterns in long covid. Cyclical relapsing and remitting disease is a key feature of multiple sclerosis. This is often taken to reflect fluxes of immune effector and regulatory cellular subsets, though consensus is lacking. Lupus, which is the result of an autoantibody driven disease process, can variably affect many organs, so that a patient may need to see a rheumatologist, nephrologist, neurologist, or immunologist in different care pathways. It is a disease of a single system—the immune system—yet it affects diverse organs at different times. Chikungunya virus—a mosquito-borne virus causing acute fever, headache, and myalgia, sometimes with neurological involvement—can cause a substantial minority of patients to later develop severe arthralgia, which can persist for years.

In Brazil, which has a high Chikungunya case burden, it is this aftermath of disease which has been the most devastating with respect to individuals’ employment, quality of life, mental health, and long term unforeseen demand on national health provision. In the UK, the Royal College of General Practitioners is already predicting a significantly increased workload owing to long covid.

Long covid patients need insights into the nature of their condition, how long it’s likely to go on for, what can be done about it, and through which clinical specialties.

Potentially, more than five million people are covid-19 “long haulers”
Managing the long term effects of covid-19: rapid guideline from NICE, SIGN, RCGP

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For a proportion of people covid-19 leads to long term effects that can have a significant impact on quality of life. According to the Office for National Statistics, around one in five people testing positive for covid-19 exhibit symptoms for a period of five weeks or more.1 This presents challenges for determining best-practice standards of care. As yet, no commonly agreed clinical definition of long term covid-19 exists, nor a clear definition of treatment pathway. To assist clinicians, the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) have developed the “COVID-19 rapid guideline: managing the long term effects of COVID-19.”2 It covers care for people with signs and symptoms that continue for more than four weeks, and which developed during or after an infection consistent with covid-19, and which are not explained by alternative diagnoses.

The guideline provides clinical definitions of the effects of covid-19 at different times and provides advice on diagnosis and management based on the best available evidence and the knowledge and experience of the expert panel. It will be subject to a “living” approach, which means that targeted areas of the guideline will be reviewed weekly and updated in response to emerging evidence and evolving expert experience. This article summarises the guideline recommendations as published on 18 December 2020, with particular emphasis on primary care. Updates are available on the NICE website.2

Recommendations

The guideline is part of a series of rapid guidelines on covid-19.1 Available evidence was of poor quality, unsurprisingly given the novel nature of this condition, and recommendations were made mainly based on expert opinion.

Definitions

The guideline defines acute covid-19, ongoing symptomatic covid-19, and post-covid-19 syndrome, according to duration of symptoms. The guideline acknowledges common usage of “long covid,” but the panel felt discrete, time-bound terms would better facilitate access to support, provide the basis for service planning, and enable clinical datasets to be established for monitoring and research. The box gives definitions.

Identifying people with ongoing symptomatic covid-19 or post-covid-19 syndrome

The guideline makes recommendations for healthcare professionals caring for people who have had suspected or confirmed acute covid-19 and present to any healthcare setting, irrespective of whether they were hospitalised or had a positive or negative SARS-CoV-2 test (polymerase chain reaction, antigen, or antibody). The guideline emphasises providing information to empower people to understand their symptoms, and to recognise when to seek help.

• Give people who have had suspected or confirmed acute covid-19 (and their families or carers, as appropriate) advice and written information on
  – the most common new or ongoing symptoms after acute covid-19
  – what they might expect during their recovery, including:
    • recovery time is different for everyone, but for many people symptoms will resolve by 12 weeks
    • the likelihood of developing ongoing symptomatic covid-19 or post-covid-19 syndrome is not thought to be linked to the severity of their acute covid-19 (including whether they were in hospital)
    • if new or ongoing symptoms occur they can change unpredictably, affecting people in different ways at different times
  – how to self-manage ongoing symptomatic covid-19 or post-covid-19 syndrome
  – symptoms to look out for that mean they should contact their healthcare professional
  – who to contact if they are worried about new, ongoing, or worsening symptoms, especially if they have them more than four weeks after the start of acute covid-19.

WHAT YOU NEED TO KNOW

• The likelihood of developing long term effects of covid-19 is not thought to be related to the severity of the acute infection
• The most common symptoms of long term covid-19 are fatigue and breathlessness. Symptoms may be singular, multiple, constant, transient, or fluctuating, and can change in nature over time
• Offer a chest radiograph by 12 weeks after acute covid-19 if the person has not had one already and has continuing respiratory symptoms
• For people who are concerned about new or ongoing symptoms four weeks or more after acute covid-19, offer an initial consultation and use shared decision making to discuss and agree with the person whether the meeting should be by video, phone, or in person.

Support people in underserved or vulnerable groups to access assessment and care by (for example) raising awareness about the long term effects of covid-19, and providing extra time or additional support (such as an interpreter or advocate) during consultations. Consider follow-up for people in vulnerable groups who have self-managed in the community after suspected or confirmed acute covid-19.

Assessing people with new or ongoing symptoms after acute covid-19

The most common symptoms are fatigue and breathlessness. Other possible symptoms are listed in box 2 (bmj.com). Symptoms may be singular, multiple, constant, transient, or fluctuating, and can change in nature over time. Assessment should include physical, cognitive, psychological, and psychiatric symptoms, as well as functional abilities.

• Include in the comprehensive clinical history:
  – history of suspected or confirmed acute covid-19
  – the nature and severity of previous and current symptoms
  – timing and duration of symptoms since the start of acute covid-19
  – history of other health conditions.

• Discuss how the person’s life and activities, for example their work or education, mobility, and independence, have been affected by ongoing symptomatic covid-19 or suspected post-covid-19 syndrome.

• Discuss the person’s experience of their symptoms and ask about any feelings of worry or distress. Listen to their concerns with empathy and acknowledge the impact of the illness on their day-to-day life, for example, activities of daily living, feelings of social isolation, work and education, and wellbeing.

Covid-19 definitions

Acute covid-19 infection—Signs and symptoms of covid-19 for up to four weeks

Ongoing symptomatic covid-19—Signs and symptoms of covid-19 present from four weeks and up to 12 weeks

Post-covid-19 syndrome—Signs and symptoms that develop during or after an infection consistent with covid-19, present for more than 12 weeks and are not attributable to alternative diagnoses

• Do not predict whether a person is likely to develop post-covid-19 syndrome based on whether they had certain symptoms (or clusters of symptoms) or were in hospital during acute covid-19.

• When investigating possible causes of a gradual decline, deconditioning, worsening frailty or dementia, or loss of interest in eating and drinking in older people, bear in mind that these can be signs of ongoing symptomatic covid-19 or suspected post-covid-19 syndrome.

Investigation and referral

Covid-19 may cause complications such as myocarditis and postural hypotension. However, not all symptoms will be related to covid-19. Investigations serve to rule out serious or urgent complications, evaluate symptoms secondary to ongoing symptomatic covid-19 or post-covid-19 syndrome, or to look for new, unrelated diagnoses. No one set of investigations and tests would be suitable for everyone because of the wide range of symptoms and severity.

• Offer blood tests, which may include a full blood count, kidney and liver function, C reactive protein, ferritin, B-type natriuretic peptide, and thyroid function.

• Offer a chest radiograph by 12 weeks after acute covid-19 if the person has not had one already and has continuing respiratory symptoms. Chest radiography appearances alone should not determine the need for referral for further care. Be aware that a plain chest radiograph may not be sufficient to rule out lung disease.

• If appropriate, offer an exercise tolerance test suited to the person’s ability (for example the 1 minute sit-to-stand test). During the exercise test, record level of breathlessness, heart rate, and oxygen saturation. Follow an appropriate protocol to carry out the test safely.

• For people with postural symptoms, for example palpitations or dizziness on standing, carry out lying and standing blood pressure and heart rate recordings (3 minute active stand test, or 10 minutes if you suspect postural tachycardia syndrome, or other forms of autonomic dysfunction).

• Refer people with ongoing symptomatic covid-19 or suspected post-covid-19 syndrome urgently to the relevant acute services if they have signs or symptoms that could be caused by an acute or life threatening complication, including (but not limited to):
  – severe hypoxaemia or oxygen desaturation on exercise
  – signs of severe lung disease
  – cardiac chest pain
  – multisystem inflammatory syndrome (in children).
This should include:
- ways to self-manage their symptoms, such as setting realistic goals
- who to contact if they are worried about their symptoms or they need support with self-management
- sources of advice and support, including support groups, social prescribing, online forums, and apps
- how to get support from other services, including social care, housing, and employment, and advice about financial support
- information about new or continuing symptoms of covid-19 that the person can share with their family, carers, and friends.

Support people in discussions with their employer, school, or college about returning to work or education, for example by having a phased return. Based on their experience, the guideline panel agreed that symptom diaries and symptom tracking apps can be helpful for self-monitoring. The evidence for different symptom tracking apps was not reviewed, so the panel could not recommend a specific product. The NHS website “Your COVID Recovery” was highlighted as a potential source of reliable, up-to-date information and support.

Follow-up and monitoring
- Agree with the person how often follow-up and monitoring are needed and which healthcare professionals should be involved.
- Using shared decision making, offer people the option of monitoring in person or remotely depending on availability, the person’s preference, and whether it is clinically suitable for them.
- Tailor monitoring to the person’s symptoms and discuss any changes, including new or worsening symptoms and the effects of these on the person’s life and wellbeing.

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Hypertension and stroke are associated with long-term use of topical corticosteroids—is greater than 4%.

be attributed to exposure to topical fractures in the population that can is to say the proportion of osteoporotic the population attributable risk—that because these drugs are widely used, the absolute risk is small. However, because these drugs are widely used, the population attributable risk—that is to say the proportion of osteoporotic fractures in the population that can be attributed to exposure to topical corticosteroids—is greater than 4%.

Fracture risk of topical corticosteroids

Exposure to potent and very potent topical corticosteroids carries an increased risk for osteoporosis and major fracture, according to a nationwide registry study from Denmark (JAMA Dermatol doi:10.1001/jamadermatol.2020.4968). For an individual using these medications, the absolute risk is small. However, because these drugs are widely used, the population attributable risk—that is to say the proportion of osteoporotic fractures in the population that can be attributed to exposure to topical corticosteroids—is greater than 4%.

Mental health outcomes after breast cancer

A primary care database study of the mental health of 60,000 women finds that a diagnosis of breast cancer is associated with raised risks of anxiety, depression, fatigue, sleep disorders, pain, and sexual dysfunction (PLoS Med doi:10.1371/journal.pmed.1003504). Risks were highest around the time of diagnosis and during initial treatment and tended to decrease over time. Even so, rates of anxiety and depression were still raised several years later.

Adolescents’ low intake of fruit and vegetables

Eating fruit and vegetables lowers risk for cardiovascular disease, type 2 diabetes, some cancers, and obesity. If healthy dietary habits are established during early life, they are likely to continue into adulthood, which makes it important that young people eat well. A survey from the US finds that those eating a fully vegan diet had high serum folate levels but worryingly low levels of vitamin D and vitamin A. Vitamin B12, zinc, iron, and iodine levels were normal. No differences were seen between vegan children and those in other dietary groups in z-scores for height, body mass index, or mid-upper arm circumference (EMBO Mol Med doi:10.15252/emmm.202013492).

Obesity policies

Over the past 30 years, successive UK governments have struggled to tackle the problem of obesity. None of the many interventions that have been tried has been successful. Currently, a quarter of children aged 2 to 15 are overweight or obese and the gap between the least and most deprived children is growing. A critical review identifies problems with implementation, failure to learn from past mistakes, and a focus on persuading individuals to change their behaviour instead of tackling unhealthy environments (Milbank Quarterly doi:10.1111/1468-0009.12498).

Adherence to pandemic social distancing guidelines

The best predictor of someone’s compliance with restrictions imposed during the covid-19 pandemic is the behaviour of their friends and family, according to an international survey (Br J Psychol doi:10.1111/bjop.12491). People distanced themselves most conscientiously when they believed that their close social circle did the same. This social influence had a stronger effect than their own views about whether distancing was an effective strategy.

Vegan diet in children

On the subject of diet, a small cross sectional study among children aged 3 to 4 at Finnish daycare centres reports that those eating a fully vegan diet had high serum folate levels but worryingly low levels of vitamin D and vitamin A. Vitamin B12, zinc, iron, and iodine levels were normal. No differences were seen between vegan children and those in other dietary groups in z-scores for height, body mass index, or mid-upper arm circumference (EMBO Mol Med doi:10.15252/emmm.202013492).

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