education

FROM THE JOURNALS Edited highlights of weekly research reviews

Checkpoint inhibition: hopeful in lung cancer…

Extensive stage small cell lung cancer (SCLC) that has spread throughout one or both lungs, or to distant sites, has a terrible prognosis with five year survival rates of only 2-3%. Standard treatment is with chemotherapy using platinum-etoposide combinations. Serplulimab acts as a checkpoint inhibitor by blocking programmed cell death-1 protein (PD-1), which tries to stop the body's immune system from attacking cancer cells.

In this randomised trial of 585 patients with extensive stage SCLC who had never had any systemic therapy, serplulimab plus chemotherapy was more effective than chemotherapy alone in prolonging survival (15.4 months *v* 10.9 months). Secondary outcomes—including progression-free survival, objective response rate, and duration of response—all seemed to be better in the serplulimab group, and the rate of adverse events was similar in both groups. We still need to know how serplulimab compares with other immunotherapy drugs such as atezolizumab or durvalumab and whether serplulimab remains effective and safe in the longer term.

JAMA doi:10.1001/jama.2022.16464

…disappointing in kidney cancer

Surgery (partial or radical nephrectomy) can be curative in renal cell carcinoma (RCC), but the cancer recurs in 20-40% of cases, and then options include immunotherapy drugs such as atezolizumab, a checkpoint inhibitor that binds to programmed cell death-ligand 1 (PD-L1). However, results were disappointing in a multicentre study of adjuvant immunotherapy for RCC in people at increased risk of recurrence. There was no evidence of clinical benefit in disease-free survival (57 *v* 49 months) or overall survival at 3 years (around 90% in both groups) with adjuvant atezolizumab compared with placebo in patients with high-risk localised or fully resected RCC.

Lancet doi:10.1016/S0140-6736(22)01658-0

A time to die

This may seem macabre, but it would be helpful for many patients and families to know how long they've got left to live. I'd certainly welcome an informed prediction before I draft an advanced care plan, decide whether to attend cancer screening, or start medication to prevent long term complications that I may not live long enough to develop.

This US study used two cohorts of people with probable dementia who were living in the community (1998-2016 and 2011-19) to develop and externally validate a mortality prediction model using clinical predictors such as demographics, health factors, functional measures, and chronic conditions. The participants' mean age was 82 years, and 81% had died by the end of the four year follow-up period. The model provided accurate mortality risk predictions across a 10 year time frame. The diagnosis and classification of dementia in this study were uneven, but the model seemed to perform well compared with previous models.

JAMA Intern Med doi:10.1001/jamainternmed.2022.4326

Smokers past and present still get puffed

Around a quarter of people who have ever smoked, including those who have quit, say that they get breathless on exertion despite normal lung function tests. It's tempting to prescribe bronchodilators in these cases, but this randomised study of 535 former or current smokers with normal lung function tests on spirometry found that dual long-acting bronchodilators didn't help respiratory symptoms compared with placebo (mean change in predicted FEV_1 2.48 *v* −0.09 percentage points). A significant flaw in the study is that participants may have had coughs, wheeze, or breathlessness due to non-respiratory problems such as heart disease, and their inclusion may have led to an underestimate of the bronchodilator effect. It's also possible that inhaled glucocorticoids, azithromycin, or pulmonary rehabilitation may help respiratory symptoms in this group.

N Engl J Med doi:10.1056/NEJMoa2204752

Monkeypox vaccine highly effective

There have been nearly 60 000 recorded cases of monkeypox (MPX) worldwide in the current outbreak. The MVA-BN vaccine, developed as a smallpox vaccine, is licensed for MPX prevention, and the immunogenicity data look great, with 100% response rate at two weeks after two doses.

This small, single centre study of people who tested positive for MPX at least one day after getting the vaccine found that most (69/90) did so within the first two weeks of the vaccine, before it was likely to have become fully effective. Some of these people may have been incubating the virus before they got the vaccine as the incubation period is 3-17 days. There were also two breakthrough cases more than three weeks after the second dose.

Over a third of the post-vaccination cases were among men living with HIV, although the vast majority were virologically suppressed. The trial results need to be treated with caution because of the small numbers, single test site, and inconsistent follow-up.

JAMA doi:10.1001/jama.2022.18320

Ann Robinson, NHS GP and health writer and broadcaster

Cite this as: *BMJ* 2022;378:o2381

STATE OF THE ART REVIEW

Vaping and respiratory health

Andrea Jonas

Division of Pulmonary, Allergy, and Critical Care, Department of Medicine, Stanford University, Stanford

Correspondence to: A Jonas andreajonas@stanford.edu

This is a summary of a State of the Art Review *Impact of vaping on respiratory health*, published on bmj.com in July 2022

The full article is available at www.bmj.com/content/378/bmj-2021-065997

CPD READING

0.5 HOURS

Since the advent of vape pens in the mid 2000s, vaping has seen a steady uptake among young, never smokers.[4-6] Vaping is now the preferred modality of nicotine consumption among young people,[7] and 2020 surveys indicate that one in five US high school students currently vapes.[8] These trends are reflected internationally, where the prevalence of vape products has grown in China and the UK.[9] Relatively little is known, however, about the health consequences of chronic vape pen use.[10 11] Although vaping was initially heralded as a safer alternative to cigarette smoking,[12 13] the toxic substances found in vape aerosols have raised new questions about the long term safety of vaping.[14-17]

Vaping as harm reduction

An NHS report determined that vaping nicotine is "around 95% less harmful than cigarettes,"[62] and a 2020 Cochrane review found that vaping nicotine assisted with smoking cessation over placebo.[63] However, the public health benefit of vaping for smoking cessation is counterbalanced by vaping uptake among never smokers,[2 54] and questions surround the safety of chronic vaping.[10 11 42 69] Studies have shown airborne particulate matter in the proximity of active vapers,[70] and concern remains that secondhand exposure to vaped aerosols may cause adverse effects.[71 72]

Studies of vape aerosols suggest multiple pro-inflammatory effects on the respiratory system. These include increased airway resistance,[130] impaired response to infection,[131] and impaired mucociliary clearance.[132] Vape aerosols have further been found to induce oxidative stress in lung epithelial cells,[133] and to induce DNA damage and impair DNA repair.

Vaping lung injury—clinical presentations

The potential health effects of vape pen use are varied and centred on injury to the airways and lung parenchyma.

The first known case was reported in 2012, when a patient presented with cough, diffuse ground glass opacities, and lipid laden macrophages (LLM) on bronchoalveolar lavage (BAL) return in the context of vape pen use.[76] Over the following seven years, an additional 15 cases of vaping related acute lung injury were reported, and included cases of eosinophilic pneumonia,[77-79] hypersensitivity pneumonitis,[80] organising pneumonia,[81 82] diffuse alveolar haemorrhage,[83 84] and giant cell foreign body reaction.[85] Parenchymal lung injury is most commonly reported, but additional cases describe episodes of status asthmaticus[86] and pneumothoraces[87] attributed to vaping. Non-respiratory vape pen injury has also been described, including cases of nicotine toxicity from vape solution ingestion,[88 89] and injuries sustained owing to vape pen device explosions.[90]

The 2019 EVALI outbreak

In summer 2019, 2807 cases of idiopathic acute lung injury were recorded in predominantly young, healthy individuals, and resulted in 68 deaths.[19 91] Epidemiological work to uncover the cause of the outbreak identified an association with vaping, particularly the use of THC-containing products, and hereafter was referred to as e-cigarette or vaping use-associated lung injury (EVALI). Criteria defined by the US Centers for Disease Control and Prevention (CDC) for EVALI are outlined in box 1.

Clinical, radiographical, and pathological features of EVALI

Patients with EVALI fit a pattern of diffuse, acute lung injury in the context of vape pen exposure. A systematic review of 200 reported cases of EVALI showed that those affected were predominantly men in their teens to early 30s, and most (80%) had been using THC-containing products.[100] Symptoms were respiratory (95%), constitutional (87%), and gastrointestinal (73%). Radiological studies mostly featured diffuse ground glass opacities bilaterally. Lung biopsy was not required to achieve diagnosis; however, of 33 cases that underwent tissue biopsy, common features included organising pneumonia, inflammation, foamy macrophages, and fibrinous exudates.

Box 1 | CDC criteria for establishing EVALI diagnosis

CDC lung injury surveillance
Primary case definitions
Confirmed case

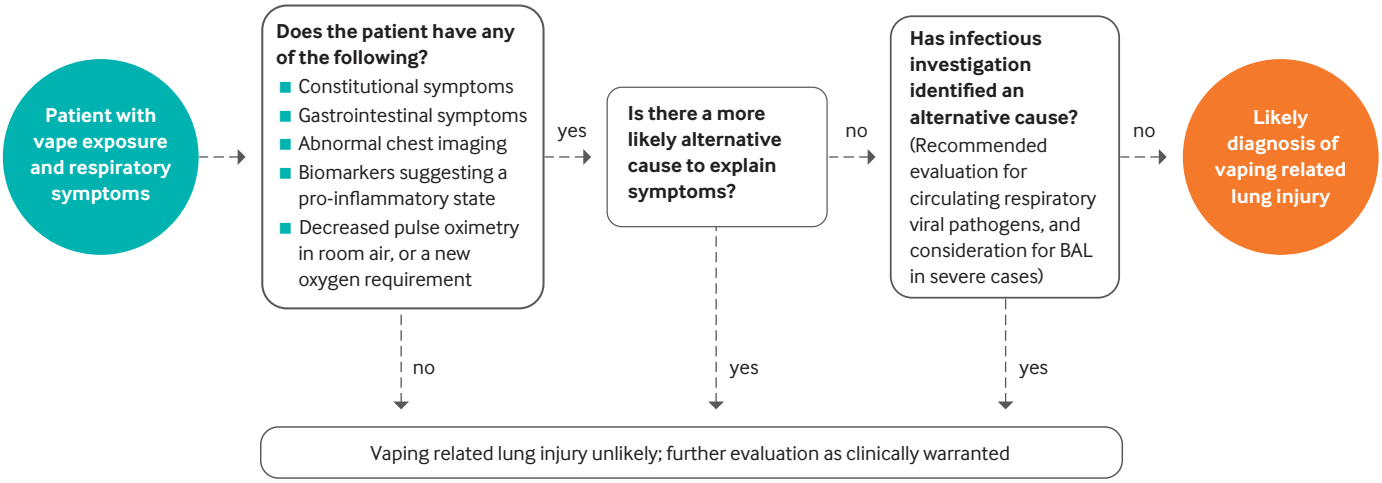
- Vape use* in 90 days prior to symptom onset; and
- Pulmonary infiltrate on chest radiograph or ground glass opacities on chest computed tomography (CT) scan; and
- Absence of pulmonary infection on initial investigation†; and
- Absence of alternative plausible diagnosis (eg, cardiac, rheumatological, or neoplastic process).

Probable case

- Vape use* in 90 days prior to symptom onset; and
- Pulmonary infiltrate on chest radiograph or ground glass opacities on chest CT; and
- Infection has been identified; however, is not thought to represent the sole cause of lung injury OR minimum criteria† to exclude infection
- Absence of alternative plausible diagnosis (eg, cardiac, rheumatological, or neoplastic process).

*Use of e-cigarette, vape pen, or dabbing

†Minimum criteria for absence of pulmonary infection: negative respiratory viral panel, negative influenza testing (if supported by local epidemiological data), and all other clinically indicated infectious respiratory disease testing is negative



Flowchart outlining the procedure for diagnosing a vaping related lung injury

VAPE TECHNOLOGY AND INGREDIENTS

A conventional vape pen is a battery operated handheld device that contains a storage chamber for the vape solution and an internal element for generating the characteristic vape aerosol. Aerosol generation entails a heating coil that atomises the vape solution. Most solutions contain an active ingredient, commonly nicotine[42]; however, alternative agents include tetrahydrocannabinol (THC) or cannabidiol (CBD). Vape solutions are typically composed of a combination of a flavourant, nicotine, and a carrier (commonly propylene glycol or vegetable glycerin) that generates the characteristic smoke appearance of vape aerosols.

Box 2 | Practical guide to collecting a vaping history

Ask with empathy

Young adults may be reluctant to share a history of vaping use. Familiarity with vaping terminology, asking in a non-judgmental manner, and asking in a confidential space may help.

Ask what they are vaping

Vape products—Vape pens commonly contain nicotine or an alternative active ingredient, such as THC or CBD. Clinicians may also inquire about flavourants, or other vape solution additives, that their patient is consuming, particularly if vaping related lung injury is suspected.

Source—Ask where they source their product from. Sources may include commercially available products, third party distributors, or friends or local contacts.

Ask how they are vaping

Device—What style of device are they using?

Frequency—How many times a day do they use their vape pen (with frequent use considered >5 times a day)? Alternatively, clinicians may inquire how long it takes to deplete a vape solution cartridge (with use of one or more pods a day considered heavy use).

Nicotine concentration—For individuals consuming nicotine-containing products, clinicians may inquire about concentration and frequency of use, as this may allow for development of a nicotine replacement therapy plan.

Ask about other inhaled products

Clinicians should ask patients who vape about use of other inhaled products, particularly cigarettes. Further, clinicians may ask about use of water pipes, heat-not-burn devices, THC-containing products, or dabbing.

A systematic review of identified cases found that most patients with confirmed disease required admission to hospital (94%), and a quarter were intubated.[100] Mortality among EVALI patients was low (2-3%)[101-103] and was associated with age over 35 and underlying asthma, cardiac disease, or mental health conditions.[103]

Clinical aspects of vaping related lung injury

Diagnosis

A general approach to diagnosing vaping related lung injury is shown in the figure. Clinicians may consider the diagnosis when faced with a patient with new respiratory symptoms in the context of vape pen use, without an alternative cause to account for their symptoms. Suspicion should be especially high if respiratory complaints are coupled with constitutional and gastrointestinal symptoms. Patients may present with non-specific markers indicative of an ongoing inflammatory process: fevers, leukocytosis, elevated C reactive protein, or elevated erythrocyte sedimentation rate.[19]

Vaping related lung injury is a diagnosis of exclusion. Chest imaging via radiograph or computed tomography (CT) may identify a variety of patterns, although diffuse ground glass opacities remain the most common radiographical finding. Generally, patients with an abnormal chest radiograph should undergo chest CT imaging for further investigation.

Exclude infectious causes, such as bacterial and viral causes of pneumonia, as deemed appropriate by clinical judgment and epidemiological data. Exclusion of common viral causes of pneumonia is imperative, particularly influenza and SARS-CoV-2. Bronchoscopy with BAL should be considered on a case-by-case basis for those with more severe disease and may be helpful to identify patients with vaping mediated eosinophilic lung injury. Lung biopsy may be beneficial to exclude alternative causes of lung injury in severe cases.[92]

Summary of clinical guidelines

Source	Reference	Date published	Imaging	Infectious investigation	Further diagnostic investigation	Empiric antibiotics	Steroid administration	Follow-up testing
J Thorac Oncol	Rice, 2020	November 2020	Outpatients: chest radiograph Inpatients: chest radiograph or CT scan	Outpatients: influenza testing Inpatients: infectious testing including covid-19	BAL or lung biopsy for admitted patients	Empiric antibiotics for inpatients "as the condition warrants"	Systemic steroids "as the condition warrants"	No recommendation
J Thorac Dis	Hage, 2020	July 2020	Chest CT preferable. Any patient with an abnormal chest radiograph should undergo chest CT	Blood cultures, sputum culture, and Gram staining, urine *Legionella* and *Pneumococcus* antigen, respiratory viral panel	BAL for patients with abnormal radiology; consider staining for lipids. Arterial blood gas, urine toxicology, spirometry	Antibiotic and/or antiviral therapy should be considered	High dose systemic corticosteroids associated with improvement	Pulse oximetry, chest radiograph, spirometry with CO diffusion
CDC	MMWR 68;919-927	October 2019	Chest radiograph on all patients. Consider chest CT on a case-by-case basis	Respiratory viral panel, additional testing per guidelines for evaluation of community acquired pneumonia	BAL on a case-by-case basis, including staining for lipids	Outpatients: consider empiric antibiotics or antivirals Inpatients: strongly consider empiric antibiotics and/or antivirals for severe illness	Systemic corticosteroids might be helpful; empiric trial warranted in severe illness	Pulse oximetry, chest radiograph, spirometry with CO diffusion

Treatment

No definitive therapy has been identified to treat vaping related lung injury, and data are limited to case reports and public health guidance on the topic. CDC guidance encourages consideration of systemic corticosteroids for patients requiring admission to hospital, or those with higher risk factors for adverse outcomes, including age over 50, immunosuppressed status, or underlying cardiopulmonary disease.[100] Steroids are recommended in patients who have undergone a confirmatory BAL, given case reports of vaping mediated acute eosinophilic pneumonia.[77 79]

Additional therapeutic options include empiric antibiotics and/or antivirals, depending on the clinical scenario. For patients requiring admission to hospital, prompt subspecialty consultation with a respiratory specialist can help guide management. Outpatient follow-up with chest imaging and spirometry is recommended, and counselling for vaping cessation is a core component in post-discharge care. Interventions specific to vaping cessation are under investigation.[66]

Health outcomes among vape pen users

No large scale prospective cohort studies exist to establish a causal link between vape use and adverse respiratory outcomes, although early work suggests a correlation between vape pen use and poorer cardiopulmonary outcomes. Survey studies of teens who regularly vape found increased frequencies of respiratory symptoms, including productive cough, that were independent of smoking status.[160 161] Studies among adults have shown a similar pattern, with increased prevalence of chronic respiratory conditions (ie, asthma or chronic obstructive pulmonary disease) among vape pen users,[165 166] and higher risk of myocardial infarction and stroke, but lower risk of diabetes.[167]

Covid-19 and vaping

Studies investigating the role of vaping in covid-19 prevalence and outcomes have been limited by the small size of the populations studied and results have been inconsistent. Early work noted a geographical association in the US between vaping prevalence and covid-19 cases,[173] and a subsequent survey study found that a covid-19 diagnosis was five times more likely among teens who had ever vaped.[174] In contrast, a UK survey study found no association between vaping status and covid-19 infection rates, although it captured a much smaller population of vape pen users.[175] Reports of nicotine use upregulating the angiotensin converting enzyme 2 (ACE-2) receptor,[176] which serves as the binding site for SARS-CoV-2 entry, raised the possibility of increased susceptibility to covid-19 among chronic nicotine vape pen users.[177 178] Further, vape use associated with sharing devices and frequent touching of the mouth and face were posited as potential confounders contributing to increased prevalence of covid-19 in this population.[179]

Studies of teens who regularly vape found increased frequencies of respiratory symptoms, including productive cough

Collecting and recording a vaping history

Gathering a vaping history is not dissimilar to asking about smoking and use of other tobacco products (box 2).

Collecting a partial history is preferable to no history at all, and simply recording whether a patient is vaping or not adds valuable information to the medical record. Unlike cigarette use, vape pen use is not built into most electronic medical record systems.[187]

Guidelines

Guidelines on management of vaping related lung injury are summarised in the table.[194-196] These recommendations reflect best practices and expert opinion, and most focus on the diagnosis and management of EVALI. No guidelines exist to date for managing vaping related lung injury more generally.

Competing interests: AJ receives consulting fees from DawnLight Inc for work unrelated to this piece

Cite this as: *BMJ* 2022;378:e065997

Find the full version with references at doi: 10.1136/bmj-2021-065997

RAPID RECOMMENDATIONS

A living WHO guideline on drugs for covid-19

Full author details on bmj.com

Correspondence for this iteration to:
François Lamontagne francois.lamontagne@usherbrooke.ca;
Miriam Stegemann miriam.stegemann@charite.de

CPD READING
0.5 HOURS

Updates

This is the twelfth version (eleventh update) of the living guideline, replacing earlier versions (available as data supplements).

Clinical question

What is the role of drugs in the treatment of patients with covid-19?

New or updated recommendations

- Remdesivir: a conditional recommendation for its use in patients with severe covid-19; and a conditional recommendation against its use in patients with critical covid-19.
- Concomitant use of IL-6 receptor blockers (tocilizumab or sarilumab) and the JAK inhibitor baricitinib: these drugs may now be combined, in addition to corticosteroids, in patients with severe or critical covid-19.
- Sotrovimab and casirivimab-imdevimab: strong recommendations against their use in patients with covid-19, replacing the previous conditional recommendations for their use.

Understanding the new recommendations

For remdesivir, new trial data provided sufficiently trustworthy evidence to demonstrate benefits in patients with severe covid-19, but not critical covid-19. The Guideline Development Group (GDG) considered benefits of remdesivir to be modest and of moderate certainty for key outcomes such as mortality and mechanical ventilation, resulting in a conditional recommendation. For baricitinib, the GDG considered clinical trial evidence (RECOVERY) demonstrating reduced risk of death in patients already receiving corticosteroids and IL-6 receptor blockers. The GDG acknowledged that the clinical trials were not representative of the world population and that the risk-benefit balance may be less advantageous. The panel anticipated that there would be situations where clinicians may opt for less aggressive immunosuppressive therapy or to combine medications in a stepwise fashion in patients who are deteriorating. When making a strong recommendation against the use of monoclonal antibodies for patients with covid-19, the GDG considered in vitro neutralisation data demonstrating that sotrovimab and casirivimab-imdevimab evaluated in clinical trials have meaningfully reduced neutralisation activity of the currently circulating variants of SARS-CoV-2. There was consensus that the absence of in vitro neutralisation activity strongly suggests absence of clinical effectiveness of these monoclonal antibodies.

The recommendations

Remdesivir (Update 11, published 16 September 2022)

Overview

Remdesivir is a nucleoside analogue which interacts with the SARS-CoV-2 polymerase to elicit delayed chain termination during RNA genome synthesis. An initial conditional (weak) recommendation was made not to use remdesivir for patients with covid-19 regardless of illness severity. In the tenth iteration of the guideline, a new recommendation was made for the use of remdesivir for patients with non-severe illness. In this twelfth iteration of the guideline, new recommendations for patients with severe or critical covid-19 are provided, given new trial data providing sufficiently trustworthy evidence for a subgroup effect demonstrating modest benefit in patients with severe, but not critical, covid-19.

Evidence-The clinical evidence underpinning the recommendations (focused on the benefits and short term harms from trial data) is outlined in the box.

Recommendation 1: For patients with severe covid-19, we suggest treatment with remdesivir (weak or conditional recommendation).

When moving from evidence to the conditional recommendation to use remdesivir in patients with severe covid-19, the GDG emphasised the benefits on survival and reduction in need for invasive mechanical ventilation, and the likelihood of little or no serious adverse events attributable to the drug. Of note, although the GDG has recommended for other antiviral drugs in patients with non-severe illness, remdesivir is the only one with a recommendation for use in patients with severe covid-19.

The GDG did not anticipate important variability in patient values and preferences, although the low certainty of evidence and ongoing uncertainty in effect contributed to the conditional recommendation. There was insufficient trial level data to examine subgroups based on age or to consider patients requiring non-invasive ventilation.

When making the recommendation for treatment with remdesivir, the GDG carefully considered the credibility of subgroup findings based on severity of disease, where remdesivir demonstrated a possible survival benefit in patients with severe covid-19, while possibly having no impact on mortality in patients with critical covid-19. The GDG ultimately decided the credibility of the observed subgroup finding based on severity of illness was moderate, therefore warranting separate recommendations for each.

Applicability—Insufficient evidence exists to inform a recommendation around use in children. Decisions regarding its use in pregnant or breastfeeding women should, in the absence of trials enrolling such participants, be made between the pregnant person and their healthcare provider.

Remdesivir data for severe or critical covid-19

The living network meta-analysis for remdesivir was informed by five trials, which enrolled 7643 patients with severe or critical covid-19. All trials were published in peer-reviewed journals, and none included children or pregnant women. See more trial details in appendix 12 on bmj.com.

For patients with severe covid-19, remdesivir possibly reduces mortality (odds ratio (OR) 0.89 (95% confidence interval (CI) 0.78 to 1.02); absolute difference 13 fewer deaths per 1000 patients (95% CI 26 fewer to 2 more); low certainty), probably reduces the need for mechanical ventilation (OR 0.87 (0.77 to 0.99); absolute difference 14 fewer per 1000 patients (24 fewer to 1 fewer); moderate certainty), and probably has little or no impact on time to symptom improvement (absolute difference 0.7 fewer days (1.8 fewer to 0.6 more); moderate certainty).

For patients with critical covid-19, remdesivir possibly has little or no effect on mortality (OR 1.15 (0.89 to 1.51); absolute difference 34 more deaths per 1000 patients (27 fewer to 101 more); low certainty) and need for mechanical ventilation (OR 0.97 (0.61 to 1.54); absolute difference 7 fewer per 1000 patients (96 fewer to 100 more); low certainty), and has an uncertain effect on time to symptom improvement (absolute difference 0.4 more days (4.3 fewer to 8.7 more); very low certainty). Overall, the drug was well tolerated, and adverse events were rare.

Practical issues—Remdesivir is administered as one intravenous infusion daily over 10 consecutive days. The recommended dose is 200 mg intravenously on day 1, followed by 100 mg intravenously on days 2 to 10. Shorter regimens of five days are described in the smaller trials, and local practices may vary. Administration should be as early as possible in the time course of the disease. Patients with severe liver or kidney disease warrant additional caution.

Resource implications, acceptability, feasibility, equity, and human rights—Given the intravenous administration of remdesivir daily over 10 days, this is more easily done for hospitalised patients with severe disease, as opposed to the outpatient setting. Obstacles to access in low and middle income countries due to cost, feasibility, and availability are of concern.

Recommendation 2: For patients with critical covid-19, we suggest not to use remdesivir (weak or conditional recommendation).

When moving from evidence to the conditional recommendation not to use remdesivir in patients with critical covid-19, the GDG emphasised the lack of benefit on survival or other patient-important outcomes as demonstrated in the subgroup analysis judged to be of moderate credibility.

The GDG did not anticipate important variability in patient values and preferences, although the low certainty of evidence and ongoing uncertainty in effect contributed to the conditional recommendation. There was insufficient trial level data to examine subgroups based on age, or to consider patients requiring non-invasive ventilation.

RECOVERY has provided evidence demonstrating that combining corticosteroids, IL-6 receptor blockers, and baricitinib provides incremental survival benefit

Janus kinase (JAK) inhibitors (Update 11, published 16 September 2022)

Overview

JAK inhibitors inhibit intracellular signalling in response to numerous interleukins, interferons, colony stimulating factors, and hormones. They interfere with many cellular responses, including antiviral responses, angiotensin-converting enzyme 2 (ACE2) expression, T cell function and differentiation, and macrophage activation. Baricitinib, ruxolitinib, and tofacitinib are three of at least nine JAK inhibitors. Their inherent differences, as well as variation in dosing and administration and pharmacokinetics, limit class-wide recommendations, and the GDG decided to make separate recommendations for individual drugs.

Update—The existing strong recommendation concerning baricitinib for patients with severe or critical covid-19 was updated by the GDG in this 12th version of the living guideline. This follows the availability of new clinical trial evidence for baricitinib administered in combination with corticosteroids and IL-6 receptor blockers suggesting that the incremental survival benefit afforded by baricitinib exists even among patients also treated with corticosteroids and IL-6 receptor blockers.[10]

Evidence—For patients with covid-19, data were derived from four trials that enrolled 10 815 inpatients for baricitinib, two trials that enrolled 475 inpatients for ruxolitinib, and one trial that enrolled 289 inpatients for tofacitinib.

Recommendation 1: We recommend treatment with baricitinib for patients with severe or critical covid-19 (strong recommendation).

Understanding the recommendation—In this update, the GDG confirmed the existing strong recommendation to use baricitinib in patients with severe or critical covid-19. This update was based on additional data from 8156 patients enrolled in the RECOVERY trial, which confirmed a survival benefit (now high certainty evidence) and other benefits, with little or no serious adverse events, of a drug that may be administered easily.[10]

The GDG had previously made a strong recommendation for use of IL-6 receptor blockers (tocilizumab and sarilumab) or baricitinib as alternative agents administered in addition to corticosteroids for patients with severe or critical covid-19. The GDG had elected to refrain from recommending the combination of these three immunosuppressive drugs until clear evidence of incremental benefit emerged. The RECOVERY trial has now provided this evidence, demonstrating that combining corticosteroids, IL-6 receptor blockers, and baricitinib provides incremental survival benefit.[10] In RECOVERY, 2659 patients received baricitinib along with corticosteroids and IL-6 receptor blockers. The effect of baricitinib in this subgroup was consistent with the beneficial effect of baricitinib in patients who were not treated with IL-6 receptor blockers.[10]

Although these three immunosuppressive drugs are recommended and may be administered jointly, the panel anticipated that there would be situations where clinicians may opt for less aggressive immunosuppressive therapy or choose to combine medications in a stepwise fashion in

patients who are deteriorating. Since the drugs have not undergone direct comparisons, the GDG felt that clinicians should choose between baricitinib and IL-6 receptor blockers on the basis of experience and comfort using the drugs, local institutional policies, route of administration (baricitinib is oral; IL-6 receptor blockers are intravenous), and cost.

Applicability—None of the included randomised controlled trials for baricitinib enrolled children, or pregnant or lactating women; therefore, the applicability of this recommendation to these groups remains uncertain.

Practical issues—Baricitinib is administered orally once daily as tablets; it can be crushed, dispersed in water, or given via a nasogastric tube. Based on trials informing the recommendation, the recommended dose is 4 mg daily orally in adults with normal renal function for a duration of 14 days or until hospital discharge, whichever is first. The optimal duration of treatment is unknown.

Dose adjustments may be needed for patients with leucopenia, renal impairment, or hepatic impairment, all of which should be monitored during treatment, and for patients taking strong organic anion transporter 3 (OAT3) inhibitors such as probenecid, where drug interactions warrant dose reductions.

Baricitinib, like IL-6 receptor blockers, should be initiated at the same time as systemic corticosteroids; there are currently no data to suggest that specific timing during hospitalisation or the course of illness is beneficial.

Resource implications, feasibility, equity, and human rights—Compared with some other candidate treatments for covid-19, baricitinib is expensive. The recommendation does not take into account cost effectiveness. As baricitinib is administered orally once daily, hospitalised patients should find it easy to accept this treatment.

Recommendation 2: We suggest not to use ruxolitinib or tofacitinib for patients with severe or critical covid-19 (conditional or weak recommendation).
Low to very low certainty evidence for mortality and duration of mechanical ventilation and a possible increase in serious adverse events, particularly for tofacitinib, drove the weak recommendation not to use ruxolitinib or tofacitinib in patients with severe or critical covid-19. Clinicians should consider using ruxolitinib or tofacitinib only if neither baricitinib nor IL-6 receptor blockers (tocilizumab or sarilumab) are available.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The GDG included four patients who previously had covid-19. Their perspectives were crucial in considering the values and preferences associated with the various treatments.

Sotrovimab (Update 11, published 16 September 2022)
Overview
Sotrovimab is a single human monoclonal antibody that binds to a highly conserved epitope in the SARS-CoV-2 spike protein, preventing the virus from entering cells.

Update—Previously, a conditional recommendation was provided for patients with non-severe covid-19 at highest risk of hospitalisation. Following the emergence of the currently circulating SARS-CoV-2 variants and subvariants (such as omicron) now dominating covid-19 worldwide, and availability of evidence showing sotrovimab lacks related in vitro neutralisation activity, the GDG made a strong recommendation against the use of sotrovimab.

Recommendation: We recommend not to use sotrovimab for patients with non-severe covid-19 (strong recommendation).
Although previous clinical trial evidence available via the LNMA remains accurate,[7] the panel concluded that it is no longer applicable to covid-19 caused by the SARS-CoV-2 variants that are currently circulating globally. The panel surmised that the likelihood of covid-19 caused by former variants was extremely low and that, accordingly, evidence of sotrovimab's clinical effectiveness for covid-19 was inexistent.

Casirivimab-imdevimab (neutralising monoclonal antibodies) (Update 11, published 16 September 2022)
Overview
Casirivimab and imdevimab are two fully human antibodies that bind to the SARS-CoV-2 spike protein and have demonstrated antiviral activity in animal models. It has been postulated that administration of a combination of casirivimab and imdevimab might have differential effects in patients who have produced their own anti-SARS-CoV-2 spike protein antibodies compared with those who have not; it was hypothesised that effects might be larger for, or restricted to, individuals who have not yet mounted an effective natural antibody response.

Update—Previously, a conditional recommendation was provided for patients with non-severe covid-19 at highest risk of hospitalisation, and for patients with severe or critical illness with seronegative status. Following the emergence of the currently circulating SARS-CoV-2 variants and subvariants (such as omicron) now dominating worldwide, and availability of in vitro data showing lack of neutralisation activity, the GDG made a strong recommendation against the use of casirivimab-imdevimab for all patients with covid-19.

Recommendation: We recommend not to use casirivimab-imdevimab for patients with covid-19, regardless of illness severity (strong recommendation).
Although previous clinical trial evidence available via the LNMA remains accurate,[7] the GDG concluded that it is no longer applicable to covid-19 caused by the SARS-CoV-2 variants that are currently circulating globally. The panel surmised that the likelihood of covid-19 caused by former variants was extremely low and that, accordingly, evidence of casirivimab-imdevimab clinical effectiveness for covid-19 was inexistent.

Competing interests: See bmj.com.
Cite this as: *BMJ* 2020;370:m3379
Find the full version with references at http://dx.doi.org/10.1136/bmj.m3379

the bmj Visual summary

Treatments for covid-19

Overview of rapid recommendations

See an interactive version of this graphic online
https://bit.ly/BMJrrcovid

Population

This recommendation applies only to people with these characteristics:

Interventions

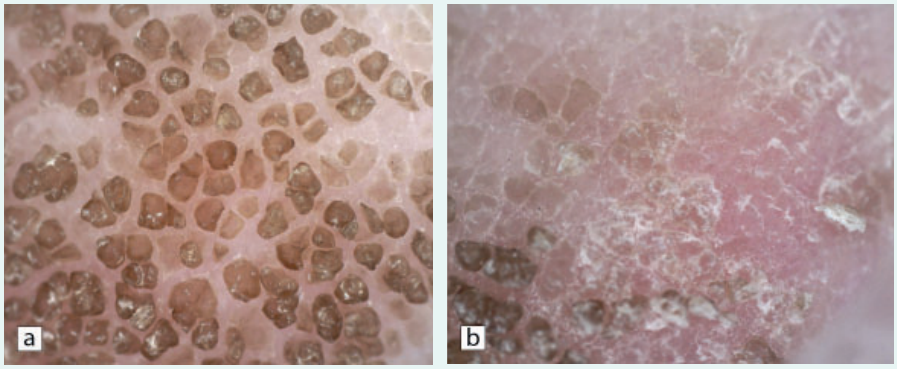
Disease severity

	Non-severe	Severe	Critical
	Absence of signs of severe or critical disease	Oxygen saturation <90% on room air Signs of pneumonia Signs of severe respiratory distress	Requires life sustaining treatment Acute respiratory distress syndrome Sepsis Septic shock
Strong recommendations in favour		Corticosteroids IL-6 receptor blockers Baricitinib All three may be combined UPDATE	
For those with highest risk of hospital admission	Nirmatrelvir and ritonavir		
Weak or conditional recommendations in favour	Molnupiravir Requires mitigation strategies to reduce potential harms Remdesivir	Remdesivir UPDATE	
Weak or conditional recommendations against	Corticosteroids Fluvoxamine Only in research settings	Ruxolitinib and tofacitinib Should be considered only if neither baricitinib nor IL-6 receptor blockers are available Convalescent plasma Only in research settings	Ivermectin Only in research settings Remdesivir UPDATE
Strong recommendations against	Colchicine Convalescent plasma Hydroxychloroquine Lopinavir-ritonavir Casirivimab and imdevimab Sotrovimab UPDATE		

CASE REVIEW

Cobblestone-like rashes on the penis

A young boy presented to the dermatology clinic with asymptomatic papillomatous brown plaques on his penis that had appeared two weeks previously. He denied itching, pain, or other physical complaints. There was no previous inflammation and trauma at the same site. A fungal direct microscopic examination was negative. Dermoscopy revealed multiple brown polygonal granules with a cobblestone pattern (fig 1a). The plaques were partially removed with a 75% ethyl alcohol swab (fig 1b) but had no response to cleaning with soap and water.



Dermoscopy showing (a) multiple brown polygonal granules with a cobblestone pattern, and (b) the granules after rubbing with a 75% ethyl alcohol swab

1 What is the most likely diagnosis?
2 What are the differential diagnoses?
3 How would you treat this condition?

Submitted by Li-Wen Zhang, Wen-Ju Wang, and Tao Chenk
Parental consent obtained

Cite this as: *BMJ* 2022;378:e070996

answers

CASE REVIEW **Cobblestone-like rashes on the penis**

1 What is the most likely diagnosis?

Terra firma-forme dermatosis (TFFD). TFFD is a keratin retention disorder favoured by constitutional or acquired factors. This is an acquired cutaneous pigmentation disorder characterised by brown to black patches or plaques with a dirt-like appearance. The term "terra firma" comes from Latin, meaning "dry land," due to the mosaic or cobblestone-like appearance. A retrospective study found a 2.19% prevalence in a group of 869 outpatients. Another systematic review included 256 patients with TFFD presenting at a mean age of 18 years and a ratio of male to female of 1:1.37. TFFD has a possible link with atopy (atopic dermatitis, asthma, and allergic rhinitis). It preferentially involves the trunk, extremities, and skin folds (neck, axilla, inguinal region, umbilical fold).

2 What are the differential diagnoses?

Differential diagnoses include dermatosis neglecta, acanthosis nigricans, verrucous naevi, ichthyosis, seborrhoeic keratosis, pityriasis versicolor, dirty neck syndrome, and confluent and reticulated papillomatosis.

Dermatosis neglecta results from the accumulation of sebum, sweat, keratin, and other forms of dirt, and can be washed off with soapy water. It occurs due to the unconscious neglect of self cleaning. Most patients with TFFD have good hygiene, and the rashes are not removed with soap and water. Dermoscopy and histopathology are useful to confirm the clinical diagnosis. The dermoscopic clue of TFFD is polygonal brown clods or plate-like scales with a mosaic pattern distribution. Pathologically, TFFD usually presents lamellar hyperkeratosis with compact orthokeratotic whorls and globules in the stratum corneum without parakeratosis.

3 How would you treat this condition?

Isopropyl alcohol can clear the rash by dissolving the keratin deposited on the skin in TFFD. Topical salicylic acid or urea-based exfoliants, retinoids, and other keratolytic agents are also effective treatment options.

LEARNING POINTS

- TFFD is a common and easily underestimated cutaneous disorder. Diagnosis is mainly based on a distinct clinical presentation and positive response to the alcohol swab test.
- Dermoscopy is a useful non-invasive diagnostic tool.

PATIENT OUTCOME

The rash was eliminated one week after treatment with topical 75% ethyl alcohol, and no recurrence occurred over a six month follow-up.

CPD READING
0.5 HOURS

You can record CPD points for reading any article. We suggest half an hour to read and reflect on each

LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at learning.bmj.com.

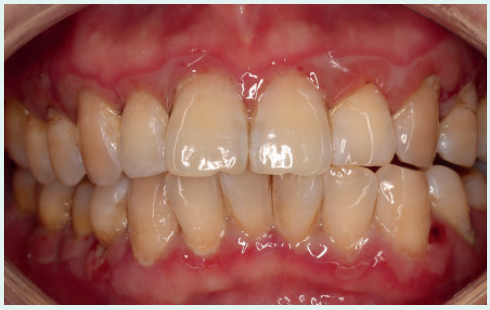
Erythema and erosion on the gingiva

This is pemphigoid on the gingiva of a woman in her 50s.

The patient presented with a one year history of pain while eating that had worsened acutely over the previous two weeks. She did not smoke, and her fasting blood glucose level was 6.5 mmol/L.

Given the duration and severity of symptoms a gingival biopsy sample was taken. Pathology showed severe inflammation and erosions of the gingival mucosa and a large number of plasma cell infiltrates. Direct immunofluorescence of the specimen showed a linear deposition of IgG on the basement membrane. An IgG autoantibody level of 90 U/mL (normal value <20 U/mL) against anti-bullous pemphigoid 180 (anti-BP180) was found on enzyme linked immunosorbent assay, consistent with a diagnosis of pemphigoid. Pemphigoid is a multisystem autoimmune disease that produces autoantibodies at the junction of the mucosal epithelium and subepithelial connective tissue. Although pemphigoid commonly affects the oral mucosa, it can affect the ocular mucosa, skin, genital mucosa, oesophagus, and throat. Gingival pemphigoid usually manifests as diffuse gingival erythema, blisters, and erosions.

Early recognition and treatment of pemphigoid is necessary to prevent damage to organs such as the eyes and larynx.



Jianqiu Jin, Chinese Academy of Medical Sciences, Beijing, China; Xiaobo Chen (bdcxb@163.com), Hospital of Tsinghua University, Beijing, 100084, China

Patient consent obtained

Cite this as: *BMJ* 2022;379:e071812

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

Survival after bariatric surgery

Around 60 000 people living in Sweden and Finland underwent a surgical procedure for obesity in the period 2007 to 2020. Most were treated with a gastric bypass but 16% had a sleeve gastrectomy. Over seven years of follow-up, all-cause mortality was under 3% after both procedures. People with diabetes experienced higher mortality after sleeve gastrectomy than after gastric bypass, but this observation is hard to interpret because the procedures weren't allocated randomly (*Diabetes Care* doi:10.2337/dc22-0485).

Vertebral fractures

Among 2500 people aged 55 and over who took part in a longitudinal survey in Norway, 14% had one or more vertebral fractures when investigated by dual energy x ray absorptiometry. A weak, statistically non-significant association was seen between vertebral fracture status and mortality during 11 years of follow-up. Only in people with three or more vertebral fractures or at least one severe vertebral fracture was mortality increased compared with those with no vertebral fractures (*Am J Epidemiol* doi:10.1093/aje/kwac161).

Methotrexate and melanoma

The immunosuppressive and photosensitising properties of methotrexate—which is widely used to treat psoriasis, rheumatoid arthritis, and other inflammatory disorders—have prompted concern that taking the drug might contribute to developing melanoma. A systematic review reckons that any increase in risk is negligible. The absolute risk, of course, will depend on background rates of melanoma, but even in places such as Australia, where the incidence is high, the calculated number needed to harm was greater than 18 000. (*JAMA Dermatol* doi:10.1001/jamadermatol.2022.3337).

Better together

The usual story about it being the fastest, strongest, and fittest spermatozoan that wins the race and fertilises the egg may be wrong. Recent experiments show that, in many mammalian species, spermatozoa team up to navigate the female reproductive tract. Clustering together seems to help sperm swim straighter—rather like a shoal of fish moving upstream or a peloton of cyclists in a road race (*Front Cell Dev Biol* doi:10.3389/fcell.2022.961623/full).

Avoiding dementia

Between 2006 and 2010, the UK biobank study recruited 500 000 middle aged participants who were free from dementia. During the next eight to 10 years, individuals whose habits included frequent leisure time exercise, housework related activity, and visits to friends and family were least likely to develop dementia. The findings applied to both vascular dementia and Alzheimer's disease and were independent of disease susceptibility evaluated by polygenic risk score, apolipoprotein E genotype, and presence of a family history of dementia (*Neurology* doi:10.1212/WNL.0000000000200701).

Sniffing out the diagnosis

Twenty years ago, the *BMJ* published an investigation that showed dogs could be trained to recognise patients with bladder cancer from samples of their urine (*BMJ* doi:10.1136/bmj.329.7468.712). A recent study from four centres in China claims that sniffer dogs can identify patients with Parkinson's disease with a high degree of accuracy (*Mov Disord* doi:10.1002/mds.29180). Minerva was rather taken with the idea that neurology clinics should have a dog in residence.

Non-pharmaceutical interventions against SARS-CoV-2

Which of the various restrictions imposed by governments on their populations was most successful in slowing the spread of SARS-CoV-2? An analysis of data from 79 countries concludes (with provisos about high levels of uncertainty and local variations) that banning small gatherings and closing businesses and schools had the greatest effect. Land border restrictions and stay-at-home orders also made a difference. Less intrusive measures such as providing support for vulnerable people, educating the public, and clear communication were probably important too (www.nature.com/articles/d41586-022-02823-4).

Cite this as: *BMJ* 2022;379:o2343