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Recommendations for the recognition, diagnosis, and management of patients with Post Covid-19 Condition ("long covid"): A Delphi study

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ABSTRACT

Background: The present work aims to provide a rapid expert guide for Post Covid-19 Condition ("long covid") clinical services. In the absence of research into mechanisms, therapies and care pathways, yet faced with an urgent need, guidance based on "emerging experience" is required.

Methods: The authors generated 33 recommendations pertaining to the recognition, investigation, and management of long covid. These were distributed online to a Delphi panel of UK doctors (any specialty) with an interest in, lived experience of, and/or experience treating long covid. Over two rounds of Delphi testing, panellists indicated their agreement with each recommendation (a 5-point Likert scale) and gave comments. Recommendations eliciting a response of "strongly agree", "agree", or "neither agree nor disagree" from ≥90% of respondents were taken as showing consensus.

Findings: Thirty-three UK-based clinicians representing 14 specialties completed both rounds of the Delphi. Twenty-nine (88%) had lived experience of long covid and five (15%) were clinicians developing services for long covid. Of the 33 recommendations presented in Round 1, 18 were incorporated into the final list, 13 were amended to reflect respondents' feedback, and two were excluded. Of the 19 presented in Round 2, 17 were added to the final list and two were excluded. The final list thus comprised 35 recommendations: six pertaining to clinic organisation, 13 to diagnosis of the underlying disorder, and 16 to management.

Interpretation: Long covid clinics need to operate not in isolation but in the context of rapidly evolving practice amongst both GPs and specialists. Care pathways in holistic care, investigation of specific complications, management of potential symptom clusters in cardiac disease, dysautonomia and mast cell disorder, and individualised rehabilitation are needed.

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RESEARCH IN CONTEXT

Evidence before this study:

- Long covid is thought to affect 10% of those diagnosed with covid-19 and consists of a wide range of symptoms affecting many systems including cardiac, respiratory, neurocognitive, and immune function.
- Although research is starting, there is an urgent need to devise clinical pathways and guidance for clinics.

Added value of this study:

- In the absence of conclusive research to inform clinical practice, "expert physician-patients" (i.e., doctors with long covid and those involved in nascent clinics) are a source of professional expertise.
- Using robust consensus methodology, we have derived 35 clear and practical recommendations to assist in the organisation of clinics and the diagnosis and management of patients with long covid.

Implications of all the available evidence:

- Medically-led multidisciplinary clinics are required as serious sequelae such as thromboembolism and myocarditis can present with only non-specific symptoms of fatigue and breathlessness.
- Clusters of symptoms in respiratory, neurocognitive, cardiac, and immune systems deserve particular research to identify suitable treatments.

INTRODUCTION

Post Covid-19 Condition is an umbrella term for a complex, multi-system illness that follows on from an acute covid-19 infection, irrespective of severity, either immediately or sometime after apparent recovery. The terms "long covid" (UK) and "long-haulers" (US) were adopted by patient groups as people came together to compare their experiences.[1] Much of the publicity and campaigning has been around the term "long covid", however WHO and SNOMED International have adopted the term "Post Covid-19 Condition" for classification. We will use the term "long covid" in this article but accept that medical terminology may continue with "Post Covid-19 Condition" or "Post-Acute Sequelae of SARS-CoV-2" in the USA. The term does not refer solely to patients that are recovering after an ICU admission with covid-19. Associated conditions have yet to be fully delineated, but examples are included Box 1.[2] The illness commonly has an unpredictable, relapsing-remitting pattern with significant associated conditions often appearing weeks to months into the disease course. Therefore, a high index of suspicion and a low threshold for referral to secondary care specialists or doctor-led long covid clinics with diagnostic capabilities, as per local availability, is advised.

Box 1: Known examples of conditions associated with long covid.

- Myocarditis or pericarditis
- Microvascular angina
- Cardiac arrhythmias, including inappropriate sinus tachycardia, atrial flutter, atrial fibrillation, and high burden of ventricular ectopics
- Dysautonomia, including postural (orthostatic) tachycardia syndrome (PoTS)
- Mast cell activation, including urticaria, angioedema, and histamine intolerance
- Interstitial lung disease
- Thromboembolic disease (e.g. pulmonary emboli, microthrombi, or cerebral venous thrombosis)
- Myelopathy, neuropathy, and neurocognitive disorders
- Renal impairment
- New-onset diabetes and thyroiditis

In December 2020, the UK National Institute for Health and Care Excellence (NICE) produced a "rapid guideline",[3] alongside the launch of both community-based and specialist clinics for long covid. Discussion amongst an online community of doctors with long covid quickly identified that there was a practical gap between best consensus practice in clinical care and the cautious, evidenced-based approach adopted by NICE (itself limited by the paucity of evidence concerning investigation and treatment of this new condition).[4] This paper aims to fill that gap by using robust consensus-based methods to delineate current best practice in the recognition, investigation, and management of long covid. These recommendations are intended to guide generalist doctors providing medical supervision of a community-based long covid clinic with access to specialist referrals if required.

METHOD

Panel selection

A Delphi panel should consist of experts in the area of interest. In long covid, there is developing expertise through experience. Research studies have only recently begun to receive funding, but doctors with long covid have over the past year carried out a dynamic discussion on social media, highlighting new case reports,

important studies, and potential clinical advances. Many of these doctors are involved in research and/or publishing articles. At this point in our knowledge, a pool of doctors with lived experience of long covid, combined with UK-based clinicians (of varying specialities) involved in service provision for long covid, form a suitable expert group.[5]

A call for panellists was placed on the "UK doctors #longcovid" support group, hosted by the social media platform Facebook. This is a closed group, exclusive to UK doctors with an interest in long covid, many of whom are seeing patients with long covid and/or have lived experience of the condition themselves (currently, approximately 1,100 members). Doctors interested in joining the panel were asked to provide their e-mail address by direct message. To ensure representation of all relevant specialties, specialist experts known to the authors were approached directly (via e-mail) and invited to join the panel.

The Delphi process

The present Delphi study comprised three stages, described below.

Initial identification of items

Following the publication of the NICE rapid guideline[3] and a "living review" by the UK National Institute of Health Research (NIHR),[6] the named authors generated a list of potential recommendations ("items") to cover common clinical problems that were not fully addressed in the review. These were refined in a series of Zoom meetings to create 33 statements. Panellists had all seen the NIHR review and NICE guidance, had been following the research literature, and more importantly in this case, following evolving clinical experience.

Round 1

Panellists were e-mailed a link to an online questionnaire (hosted by Qualtrics) with a request to respond within four days. Upon clicking the link, they gave demographic information (name, e-mail address, specialty, year of qualification) and informed consent. Thereafter, they read a brief introduction to the study (aim and remit) and a definition of long covid (with examples).[2] They then indicated the degree to which they agreed with each of the 33 initial items (presented sequentially) on a 5-point Likert scale (1="strongly disagree", 2="disagree", 3="neither agree nor disagree", 4="agree", 5="strongly agree"). They were also encouraged to comment on each item in a free-text box, particularly if they disagreed with the item.

Items eliciting a response of "strongly agree", "agree", or "neither agree nor disagree" from ≥90% of panellists were taken as showing consensus. Items with consensus were subject to minor amendment for sense only. If more substantial amendments were needed, the item was reworked on the basis of panel comments and retested in Round 2, alongside items that did not obtain consensus initially.

Round 2

Respondents that took part in Round 1 were e-mailed a link to a second Qualtrics questionnaire (Round 2), with a request to respond within five days. As in Round 1, they indicated their level of agreement with sequentially-presented items (either amended from Round 1 or newly-added to Round 2) using the 5-point Likert scale and gave comments. Items that achieved consensus were included in the final list of recommendations (with minor amendments as before to reflect participants' feedback). Items that failed to achieve consensus were not included in the final list.

Ethical approval

As this is considered service development, ethical approval was not required for this study. Delphi participants gave informed consent before taking part. All aspects of the study were conducted in the UK in January-March 2021.

Role of the funding source

No sponsors or funders had any role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

RESULTS

Panel characteristics

Thirty-seven doctors responded to the Facebook call and were e-mailed a link to Round 1; of these, 29 (78%) completed it. A further eight clinicians involved in service provision for long covid (known to the research team) were e-mailed a link to Round 1; of these, four (50%) completed it and four (50%) were too busy with acute covid work. All of the doctors that completed Round 1 also completed Round 2 (i.e., no doctors lost to follow up).

The panel therefore comprised 33 UK-based clinicians, representing a wide range of specialties (Fig. 1). The median number of years since qualification was 21 (range 0-41). Twenty-nine (88%) were recruited via social media and four (12%) via direct e-mail.

Twenty-nine (88%) had lived experience of long covid and five (15%) were clinicians developing services for long covid.

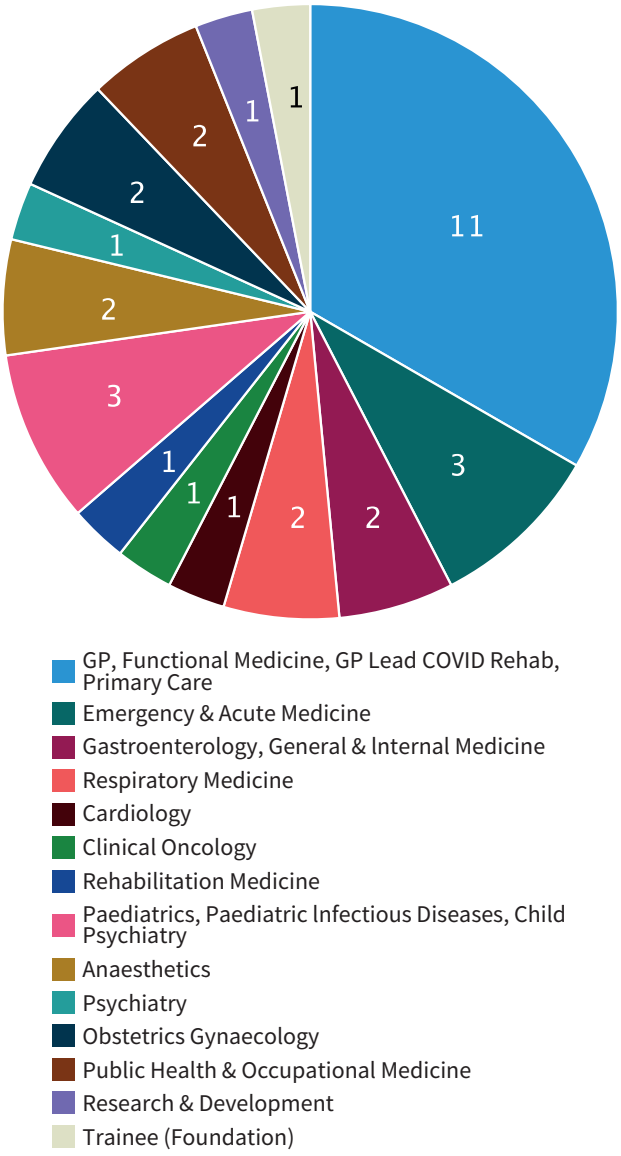

Figure 1. Number of panellists per specialty.

Round 1

Data collection took place over a nine-day period (24 Jan-1 Feb 2021). All 33 items obtained consensus. Of these, 18 required no/minor changes and were incorporated into the final list of recommendations (Appendix A: Round 1, blue text). The remaining 15 required more substantial work: 13 were amended to reflect panellists' feedback (Appendix A: Round 1, green text) and two were excluded (Appendix A: Round 1, red text). One of the excluded items was deemed self-evident (item 38), the other was strongly opposed by a relevant (respiratory) specialist (item 39).

Round 2

Round 2 data were collected over a six-day period (11 Feb-16 Feb 2021). Of the 19 items presented, 13 were amended from Round 1 and six were newly-added (usually to disentangle diagnosis and treatment when a Round 1 statement had addressed both). Eighteen items achieved consensus; of these, 17 were added to the final list of recommendations (Appendix A: Round 2, blue text) and one was excluded (Appendix A: Round 2, item 36): it was superfluous to another item that had obtained better agreement (agreement for item 36=97% vs. agreement for item 20=100%). One item did not obtain consensus (item 37, agreement=64%) and we did not feel that there would be a route to achieving this; therefore, this item was also excluded. Fig. 2 displays the results of the Delphi process graphically.

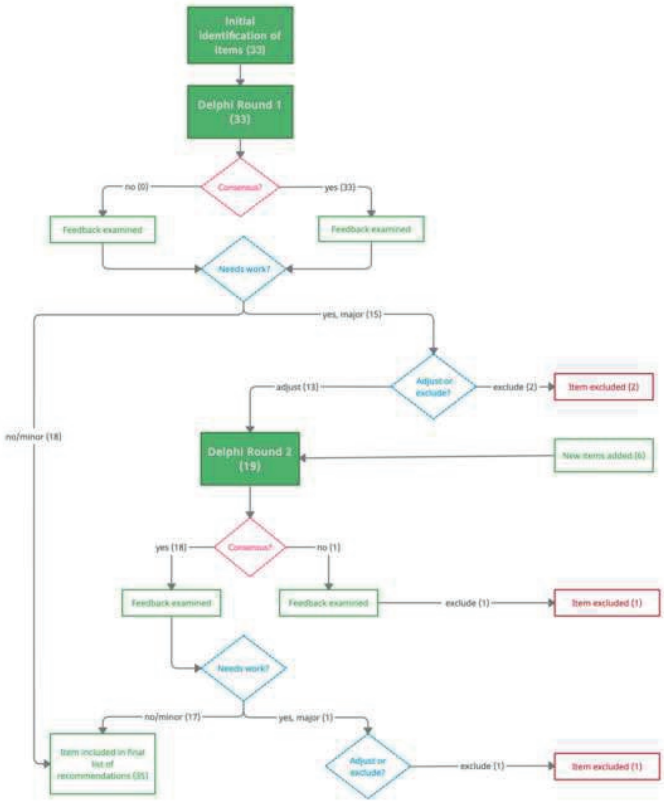

Figure 2. Flowchart of the Delphi procedure and results.

Final list of recommendations

The final list comprises 35 recommendations: six pertaining to clinic organisation (Box 2), 13 to diagnosis of the underlying disorder (Box 3), and 16 to management (Box 4). For a full and printable list of the recommendations, see Appendix B.

Box 2: Recommendations pertaining to clinic organisation.

1) **Consider long covid in patients with a clinical diagnosis of covid-19 as per WHO criteria7 or test-positive history with new or fluctuating symptoms including but not limited to breathlessness, chest pain, palpitations, inappropriate tachycardia, wheeze, stridor, urticaria, abdominal pain, diarrhoea, arthralgia, neuralgia, dysphonia, fatigue including neurocognitive fatigue, cognitive impairment, prolonged pyrexia, and neuropathy occurring beyond four weeks of initial covid-19** (strongly agree=19, 58%; agree=11, 33%; neither agree nor disagree=0, 0%; disagree=2, 6%; strongly disagree=1, 3%).

2) **Multispecialty long covid clinics should be led by a doctor with crossspecialty knowledge and experience of managing this condition** (strongly agree=29, 88%; agree=2, 6%; neither agree nor disagree=1, 3%; disagree=0, 0%; strongly disagree=1, 3%).

3) **Consider individualised investigations, management, and rehabilitation planning via a multispecialty long covid assessment service as local services allow. Prioritise physician-led medical assessments and diagnostics initially, and consider allied health professionals including physiotherapy and OT input as adjuncts** (strongly agree=23, 70%; agree=8, 24%; neither agree nor disagree=1, 3%; disagree=1, 3%; strongly disagree=0, 0%).

4) **It is inappropriate for long covid clinics to be led by mental health specialists e.g., IAPT, clinical or health psychologist. They may be useful in supporting the multispecialty team but do not have the expertise to investigate and manage potential organ damage** (strongly agree=27, 82%; agree=5, 15%; neither agree nor disagree=1, 3%; disagree=0, 0%; strongly disagree=0, 0%).

5) **All under-18-year-olds need access to similar services run by paediatric specialists with knowledge of how presentations and treatments differ to adults and with close liaison with school** (strongly agree=26, 79%; agree=7, 21%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=0, 0%).

6) **Patients with comorbid mental health difficulties should have equal access to medical care as a patient without mental health difficulties and should not be triaged away from services** (strongly agree=28, 85%; agree=5, 15%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=0, 0%).

As covid-19 is a new condition with both lasting organ damage and excess deaths reported,[8] it cannot be assumed that patients are suffering "merely from post-viral fatigue" and that rehabilitation is sufficient, or indeed that viral persistence has been excluded. However, input from expert physiotherapists and occupational therapists who are familiar with the condition is an important aspect of caring for long covid patients.[9,10] Patients require a holistic clinical approach that prioritises investigation of potential physical pathology.[2,11] The lead clinician should be a doctor, "well versed in multisystem disorders", working across disciplines, and able to refer to specialists. A respondent who runs a long covid clinic noted the importance of "easy access to multispeciality input without multiple onward referrals (e.g., via multi-speciality post covid MDT)" and another that "isolated consultant clinics (without full MDT) will not work." Long covid is not a primary mental health problem, but mental health specialists such as neuropsychiatrists can offer a supporting role to the multidisciplinary team. Psychological aspects of disease should be managed as part of the recovery process, but not seen as the primary treatment focus.[2,3] Panellists were clear that no discrimination should exist in the treatment of patients with pre-existing mental health difficulties with regard to equal access to care for their long covid, and appropriate investigations for organ damage.[11] Regarding children, a Consultant Paediatrician should lead the service.2 NICE guidelines recommend considering referral from four weeks for specialist advice for children with ongoing symptomatic covid-19 or long covid.[3]

Box 3: Recommendations pertaining to diagnosis of underlying disorder.

<u>GENERAL APPROACH:</u>

7) **In someone with long covid, symptoms of possible non-covid-19 related issues should be investigated and referred as per local guidelines. Long covid alone is not a sufficient diagnosis unless other causes have been excluded** (strongly agree=21, 64%; agree=8, 24%; neither agree nor disagree=2, 6%; disagree=1, 3%; strongly disagree=1, 3%).

8) **Carry out a face-to-face assessment including a thorough history and examination, consider other non-covid-19 related diagnoses, and measure FBC, renal function, CRP, LFT, thyroid function, HbA1c, Vitamin D, Magnesium,* B12, folate, ferritin, and bone studies** (strongly agree=24, 73%; agree=9, 27%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=0, 0%).

<u>RESPIRATORY:</u>

9) **In those with respiratory symptoms, consider CXR at an early stage. Be aware that a normal appearance does not exclude respiratory pathology** (stronglyagree=27, 82%; agree=4, 12%; neither agree nor disagree=1, 3%; disagree=1, 3%; strongly disagree=0, 0%).

10) **Be aware that simple spirometry may be normal but patients may have diffusion defects indicative of scarring, chronic PEs, or microthrombi. Consider referral to respiratory for full lung function testing** (strongly agree=23, 70%; agree=10, 30%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=0, 0%).

* Magnesium level may not be available in general practice

11) Measure oxygen saturation at rest and after an age-appropriate brief exercise test in people with breathlessness and refer for investigation if hypoxaemic or if any desaturation on exercise (strongly agree=17, 52%; agree=14, 42%; neither agree nor disagree=2, 6%; disagree=0, 0%; strongly disagree=0, 0%).

CARDIAC:

12) Consider the possibility of a cardiac cause of breathlessness (strongly agree=27, 82%; agree=5, 15%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=1, 3%).

13) Be aware that a normal D-dimer may not exclude thromboembolism, especially in a chronic setting, and referral for investigation is therefore indicated if there is a clinical suspicion of pulmonary emboli. Additionally, be mindful that thromboembolism may occur at any stage during the disease course (strongly agree=26, 79%; agree=6, 18%; neither agree nor disagree=1, 3%; disagree=0, 0%; strongly disagree=0, 0%).

14) In patients with inappropriate tachycardia and/or chest pain, carry out ECG, troponin, Holter monitoring, and echocardiography. Be aware that myocarditis and pericarditis cannot be excluded on echocardiography alone (strongly agree=22, 67%; agree=8, 24%; neither agree nor disagree=2, 6%; disagree=1, 3%; strongly disagree=0, 0%).

15) In patients with chest pain consider a referral to cardiology as cardiac MRI may be indicated in a normal echo to rule out myopericarditis and microvascular angina (strongly agree=25, 76%; agree=6, 18%; neither agree nor disagree=1, 3%; disagree=1, 3%; strongly disagree=0, 0%).

16) In patients with palpitations and/or tachycardia, consider autonomic dysfunction (strongly agree=25, 76%; agree=7, 21%; neither agree nor disagree=0,0%; disagree=0, 0%; strongly disagree=1, 3%).

OTHERS:

17) In patients with urticaria, conjunctivitis, wheeze, inappropriate tachycardia, palpitations, shortness of breath, heartburn, abdominal cramps or bloating, diarrhoea, sleep disturbance, or neurocognitive fatigue,[12] consider mast cell disorder (strongly agree=15, 46%; agree=14, 42%; neither agree nor disagree=4, 12%; disagree=0, 0%; strongly disagree=0, 0%)

18) In patients with cognitive difficulties sufficient to interfere with work or social functioning, consider neurocognitive assessment (strongly agree=23, 70%; agree=9, 27%; neither agree nor disagree=0, 0%; disagree=1, 3%; strongly disagree=0, 0%).

19) In patients with joint swelling and arthralgia, consider a diagnosis of reactive arthritis or new connective tissue disease and investigate and refer as appropriate (strongly agree=20, 61%; agree=12, 36%; neither agree nor disagree=1, 3%; disagree=0, 0%; strongly disagree=0, 0%).

At present there is a considerable risk to patient safety if appropriate investigation of common symptoms of long covid (such as chest pain, breathlessness, palpitations, abdominal pain, fatigue) which have wide differential diagnoses is not undertaken. Serious conditions, related to SARS-CoV-2 infection or not, must be adequately excluded[13] and investigations should be appropriately guided by the history. Long covidspecific examination (e.g., for PoTS) or tests such as ECG are best conducted in person, and chest x-ray (CXR) may be appropriate. CXR may exclude relevant pathology such as Tuberculosis but is less relevant in investigating cardiac, pulmonary vascular, or autonomic causes for breathlessness where Computed Tomography or Ventilation/Perfusion (V/Q) scans are more likely to be indicated.[14] In keeping with NICE guidance on asthma management,[15] the panel agreed that spirometry with beta-agonist reversibility could be used to diagnose airway hyper-reactivity. Studies on venous thromboembolic disease are limited to patients with acute covid-19,[16] severe disease,[17,18] or based on expert opinion, but are an important diagnosis to consider.[19] Oxygen desaturation on exertion occurs in both acute and long covid and should form part of baseline assessment. Precise definitions of hypoxaemia and desaturation pertain to severity of acute covid-19 illness[20,21] and no specific data are available in long covid. Doctors working in existing clinics indicated that assessments like 1-minute sit-to-stand tests[22] and 6-minute walk tests[23] do or should form part of the assessment in community or specialist clinics. The exertional test chosen should take account of any pre-covid-19 limitations and should include heart rate (HR) as this may help to assess autonomic function. Referral for more detailed assessment is required in the following scenarios: desaturation with or without overt/reported dyspnoea; nocturnal desaturation; extreme fatigue; behavioural change in those who struggle with verbal communication; patient reports significant post exercise malaise after such testing (lasting beyond the next day); severe tachycardia; postural blood pressure drop.

There is increasing evidence of cardiovascular complications with covid-19.[24-31] Patients with long covid (of all ages) have been diagnosed with arrhythmias, autonomic dysfunction, myocarditis, pericarditis, and microvascular ischaemia.[32] The latter three may only be seen on Cardiac Magnetic Resonance (CMR) scans (gadoliniumenhanced; stress). Rapid Access Chest Pain Clinics may be suitable for some patients. Echocardiography has a low diagnostic yield for myocarditis in long covid,[32,33] but diagnosis is important as people experience significant improvement in daily function through heart rate control, anti-anginals and colchicine. Pulmonary embolism

appears to be rare more than six weeks after the acute illness and there are feasibility concerns about a potential surge of investigations for long covid. Usual risk scoring calculators were not valid in this context[34] and research is needed. Autonomic dysfunction, especially manifesting as Postural Orthostatic Tachycardia Syndrome (PoTS), occurs commonly post covid-19. [35] There is a need to consider a differential for tachycardia and palpitations which, in long covid, includes pulmonary embolus, cardiac and respiratory causes. It was noted that autonomic dysfunction should also be suspected in patients with light-headedness, chest pain, and nausea, and the association of autonomic dysfunction with mast cell disorders considered.

As there are no accepted UK criteria for the diagnosis of "Mast Cell Activation Syndrome" and it remains an area of controversy, we used the term "mast cell disorder" to describe patients who present with a range of features listed in recommendation 17.[36] The list is not exhaustive and other serious disorders need to be excluded. This area is an important target of mechanistic and potential therapeutic studies in long covid. Neurocognitive testing is a particularly scarce resource[3] and neurology review and brain MRI may be more helpful early in the illness. The benefits of testing would support the need for rehabilitation from OT or a neuropsychologist.[3,37] NICE guidelines on long covid advise considering neuro-psychometric testing after six months if no improvement/worsening of cognitive function, as many will resolve.[38] At present, evidence related to joint swelling and arthralgia consists of only case reports, but clinicians should include long covid in a differential diagnosis of arthritis once other known autoimmune causes have been excluded.[39]

Box 4: Recommendations pertaining to management.

GENERAL APPROACH:

20) **For patients with fatigue and worsening symptoms hours to days following an activity, emphasise the importance of an initial phase of convalescence followed by careful pacing and rest** (strongly agree=27, 82%; agree=6, 18%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=0, 0%).

21) **Support patients in shifting their mental timeline of recovery to reflect thelikely prolonged course, with a possibly long phased return to work** (strongly agree=24, 73%; agree=9, 27%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=0, 0%).

22) **Further support patients with signposting to patient resources. Applicable resources may include: management of post-exertional symptom exacerbation, activity pacing, acupuncture, diagnosis-specific management as relevant** (strongly agree=14, 42%; agree=16, 49%; neither agree nor disagree=1, 3%; disagree=2, 6%; strongly disagree=0, 0%).

23) **Provide patients with signposting to social prescribing, sickness certification, and financial advice. Discuss with the patient whether sickness certification will state long covid as diagnosis** (strongly agree=26, 79%; agree=6, 18%; neither agree nor disagree=1, 3%; disagree=0, 0%; strongly disagree=0, 0%).

24) **Clinicians should ensure that the occupational status of patients with long covid is recorded (in/out of work, part/full time, student)** (strongly agree=25, 76%; agree=8, 24%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=0, 0%).

25) **Follow patients up regularly to monitor progress from a full biopsychosocial and occupational perspective** (strongly agree=19, 58%; agree=13, 39%; neither agree nor disagree=1, 3%; disagree=0, 0%; strongly disagree=0, 0%).

26) **Encourage reporting of new symptoms (expected) and expectation of waxingwaning course** (strongly agree=25, 76%; agree=8, 24%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=0, 0%).

27) **Consider contributing patient data to research on long covid, using the WHO Case Report Form or similar**[40] (strongly agree=22, 67%; agree=9, 27%; neither agree nor disagree=2, 6%; disagree=0, 0%; strongly disagree=0, 0%).

MANAGEMENT OF SPECIFIC CONDITIONS:

28) **Patients with cardiac symptoms should be advised to limit their HR to 60% of maximum (usually around 100-110bpm) and investigated with at least ECG and echocardiogram before taking up exercise. Supervised exercise testing should be considered for this patient group as they may have perimyocarditis and exercise carries risk of arrhythmia and worsening cardiac function**[41] (strongly agree=16, 49%; agree=14, 42%; neither agree nor disagree=2, 6%; disagree=1, 3%; strongly disagree=0, 0%).

29) **For autonomic dysfunction including PoTS (Postural Orthostatic Tachycardia Syndrome), consider first increased fluids, salts, compression hosiery, and specific rehabilitation**[35] (strongly agree=18, 55%; agree=13, 39%; neither agree nor disagree=2, 6%; disagree=0, 0%; strongly disagree=0, 0%).

30) **If PoTS and no or inadequate response to non-pharmacological therapy consider beta blocker, Ivabradine, or Fludrocortisone (with BP and response monitoring)** (strongly agree=18, 55%; agree=13, 39%; neither agree nor disagree=1, 3%; disagree=1, 3%; strongly disagree=0, 0%).

31) **In patients with possible mast cell disorder, consider a one-month trial of initial medical treatment and dietary advice. Higher than standard dose of antihistamines are commonly used for this indication. If partial effect consider adding second level treatment such as Montelukast, as well as referral to allergy or immunology specialists**[42,43] (strongly agree=17, 52%; agree=14, 42%; neither agree nor disagree=2, 6%; disagree=0, 0%; strongly disagree=0, 0%).

32) **Be aware that adverse drug reactions are more**

common in patients with mast cell disorder, for example to beta lactam antibiotics, NSAIDs, codeine, morphine, or buprenorphine (strongly agree=17, 52%; agree=13, 39%; neither agree nor disagree=3, 9%; disagree=0, 0%; strongly disagree=0, 0%).

33) For breathing pattern disorder, consider specialist physiotherapy and/or using alternative therapies such as pranayama breathing and meditation (strongly agree=12, 36%; agree=14, 42%; neither agree nor disagree=4, 12%; disagree=3, 9%; strongly disagree=0, 0%).

34) In patients expressing distress, significant low mood, anxiety, or symptoms of PTSD, consider mental health assessment (strongly agree=20, 61%; agree=13, 39%; neither agree nor disagree=0, 0%; disagree=0, 0%; strongly disagree=0, 0%).

35) Over the counter supplementation is common, including vitamin C, D, niacin (nicotinic acid), and quercetin. Be aware of significant drug interactions, such as with niacin or quercetin (strongly agree=21, 64%; agree=10, 30%; neither agree nor disagree=1, 3%; disagree=0, 0%; strongly disagree=1, 3%).

The experience of many patients is of post-exertional ymptom relapse. Physical or cognitive workload beyond the patient's "energy envelope" may cause an exacerbation of symptoms including fatigue, fever, myalgia, and breathlessness.[44] Exacerbations may manifest immediately or after a delay of 24-48 hours and may last days or months. As the threshold for this effect varies not only by patient but over time, pacing needs to be flexible and careful. Doctors play a key role in supporting patients through the complexity of specialist investigations and differential diagnoses, and considering symptomatic treatments. In addition, occupational health service referrals and medical reports supporting the return-to-work process are needed. Employers should discuss with their employee suitable adjustments to aid a return to work, and both parties should be provided with written advice such as the leaflet "covid-19 return to work guide for recovering workers" by the Society of Occupational Medicine.[45] The relapsing-remitting nature of the illness needs to be emphasised as employer pressure may result in patients returning to work too soon. The onus is on the doctor with current clinical responsibility for the patient to complete the fit note; this includes secondary care doctors.[46] The content of the fit note should be agreed between the patient and doctor, including a "medically-recognised diagnosis". For NHS staff to receive "covid pay" during absence, the fit note must mention covid.[47] The ability to return to work after illness is a marker of recovery and clinicians must, therefore, record work status in the clinical notes in situations of chronic ill-health.[48,49] From a public health perspective, counting days lost to sickness and lost income on account of long covid is essential.

Long covid, like all long-term conditions, impacts on many aspects of life and is best managed holistically with physical, psychological, and social factors addressed.[50] Prolonged illness following SARS-CoV-2 infection is characterised by the development of new symptoms at different timepoints.[51] Clinicians need to provide patient "safetynetting" advice and guidance on expected patterns of illness. Although NICE guidance states that new symptoms after three months are unlikely to be due to covid,[3] this is not borne out by research[52] or patient and specialist experience. The importance of research into long covid was emphasised by many, which should include quantification of the burden of disease. To this end, one panellist advised that case reporting should be mandatory. The length of the WHO case report form was noted, however, and flagged as a potential barrier to case reporting in practice. Patients should be made aware of research studies: participation could add meaning to what is often a very negative experience.

ECG and echocardiogram do not reliably exclude myocarditis. Therefore, ongoing exertional chest pain may warrant referral to a Rapid Access Chest Pain Clinic and/or cardiac MRI.[53] Exercise to 60% maximum heart rate can be advised but patients need to work out their own limits, which may be lower than this. In some cases, there is a difficulty in managing tachycardia and pharmacological approaches are needed, such as beta blockers or Ivabradine. Growing expertise between long covid assessment clinics needs to be sought over the most appropriate pharmacological treatment.[8] PoTS (and other dysautonomic symptoms such as breathlessness, orthostatic intolerance, dizziness, and tremor) is an unfamiliar diagnosis for many clinicians, but seems to affect a significant subgroup of long covid patients. Whilst many would advocate specific investigation, NHS autonomic services are patchy, and if they are not to be overwhelmed, there will be significant educational needs for referring clinicians.[54] PoTS treatment can start with fluids, compression, and lifestyle adaptations (for which specific patient support materials are available),[55,56] but may need to escalate to medication if symptoms are not improved.[57,58] Midodrine may be helpful, though this is only available following secondary care initiating the prescription in many parts of the UK. There is an urgent need for research, education, and clear guidance to help GPs in managing this condition.

Similarly to treating urticaria, mast cell features require two-to-four-fold larger doses of antihistamines

to suppress them.[12] Dermatologists and GPs with an interest in mast cell disorders have experience in counselling patients about such off-label use and an individual therapeutic trial is simple to arrange. Some patients exhibit sensitivity to histamine-rich foods and prominent GI symptoms (bloating, cramping pain, diarrhoea, acid reflux). These and other known triggers of mast cell activation should be avoided; the aim is to switch off the immune overreaction.[59] Unfortunately, H2-receptor antagonists are not readily available in the UK. Further research including clinical trials are needed in this area, but the recommendations represent a simple solution to dealing with very troublesome symptoms in some long covid patients.[8] We used the term "breathing pattern disorder" to describe the subjective experience of patients which is not "breathlessness" in the strict sense of the word.[60] Its aetiology is unknown but may represent a disorder of central breathing control. Whilst specialist physiotherapy should be available to patients being seen in clinics, many patients seek help from alternative therapy, such as pranayama breathing. Meditation/mindfulness is promoted in the NHS as an effective therapy for anxiety and sensation of breathlessness.[61]

It has been long established that chronic physical diseases have an increased risk of secondary mental health problems. A meta-analysis showed that 36.6% of people with a chronic physical disease had a co-existent mental health disorder.[62] Having a mental health disorder should not preclude investigation of any organic disease and unexplained symptoms or signs, and neuropsychiatric features should always prompt exclusion of organic pathology in the first place. Addressing epistemic injustice issues in the investigation and management of long covid should be a priority for local services.[63]

Patients with long covid commonly refer to taking "the stack" or "the supplement stack", which includes high dose vitamin C and D, niacin (nicotinic acid), quercetin, zinc, selenium, and sometimes also magnesium.[64-66] Further research is needed to confirm or refute supplement impact in long covid.[67] Examples of noteworthy interactions with supplements include: niacin causing an increased risk of bleeding events when combined with SSRIs or NSAIDs, increased risk of rhabdomyolysis together with statins,[68] and quercetin causing inhibition and induction of various human cytochrome P450 enzymes.[69]

A recommendation concerning the name ("long covid") did not obtain consensus and was ultimately excluded (Appendix A: item 37). In Round 1, we suggested the term "long covid" in preference to "Post Covid-19 Syndrome" and this achieved consensus (94% agreement); in Round 2, we decided to use the recently-approved WHO term "Post Covid-19 Condition" but this did not obtain consensus (64% agreement). The naming of the condition is a subject of considerable controversy[70]: "long covid" and "long-hauler" have been adopted by patients in the UK and USA (respectively) as neutral terms that make no assumptions about aetiology, presence/absence of ongoing infection, or prognosis.[3] NICE suggested adoption of two terms: "Ongoing Symptomatic Covid-19" (4-12 weeks) and "Post Covid-19 Syndrome" (12+ weeks).[3] In the USA the term "Post-Acute Sequelae of Covid-19" (PASC) has been adopted.[71] In contrast, the WHO have adopted "Post Covid-19 Condition" for ICD 11, reflected also in SNOMED coding.[72] This enables the creation of subclassifications or SNOMED coordinated terms for any future subcategories of long covid. Given the desire for international adoption and its use in coding, we accept the use of "Post Covid-19 Condition" as another medical term to describe long covid.

DISCUSSION

Validity of study

With a novel viral pathogen giving rise to a newly-recognised condition and a worldwide pandemic, there is at present no "evidence" on which to base recommendations for clinical care. Mechanisms which aim to identify, appraise, and use evidence in guidelines cannot function effectively when there is no evidence, only hypothecated comparisons with other conditions. It is estimated that over one million people (of a population of 66 million) in the UK are currently living with long covid (prolonged symptoms at 4+ weeks).[73] No such data are available for other countries, but numbers are likely to be proportionate. This puts huge and immediate pressure on health services worldwide. In such particular circumstances, we must turn to clinical experience during 2020 as a guide for managing long covid. Clinicians with lived experience of the condition have been particularly instrumental in helping to define the problem and "expert clinician-patient" self-help groups remain a vital resource in providing advice to the wider clinical community. We therefore recruited Delphi participants from one such group, and augmented the panel with clinicians involved in newly-established long covid clinics. We ensured that a wide range of specialisms was represented in the panel, and that all panellists completed both rounds of the Delphi (no drop-outs).

In the absence of a developed research literature we chose a high threshold for agreement (90%) to ensure that the statements were strongly supported. The midpoint of the Likert scale ("neither agree nor disagree") was interpreted as "agreement", but classifying this as "disagreement" would affect only three recommendations (7, 17 and 33), whose consensus would fall below 90% but nonetheless clear a threshold of 70%.[74] A rich set of views and relevant literature surrounding the recommendations has been summarised, even when a clear consensus was present.

Limitations and Further Work

By the second round, 35 statements were agreed covering recognition, diagnosis, therapies, and wider management of long covid. The statements go further than NICE in many areas, particularly in the need to investigate potential cardiac conditions, dysautonomia, and immune dysfunction. The recently published NIHR "Living with Covid-19 – second review" echoes many of the themes explored here, including potential subgroups, need for investigation, and the relapsing-remitting nature of the condition, but offers a broad narrative rather than specific, practical statements for clinical use.75 Practical management of such issues as PoTS and mast cell dysfunction can be very helpful for many long covid patients and need to be debated and tried in therapeutic settings, ideally as part of controlled studies. However, given the benign nature of many treatments (e.g., compression stockings, fluids, and electrolytes for PoTS; over the counter antihistamines for mast cell suppression; pranayama breathing, meditation, and respiratory physiotherapy for breathing pattern disorder), it would be "nihilism-based medicine" to deny patients a trial of therapy when their lives are put on hold – unable to work or function socially on account of long covid. We hope that these statements will act as a stimulus for research, medical education, and discussions around services for long covid. Research needs to prioritise rapid learning from long covid clinics, with mixed methods improvement science, learning from best practice by sharing data and by targeted mechanistic studies leading eventually to an evidence-based guideline on patient investigation, segmentation, and specific therapies. We acknowledge that there are significant challenges in resourcing services for long covid and that strict adherence to these guidelines will not always be possible but – at the acute part of the pandemic – doing nothing is not an option. We simply cannot sit back and say to hundreds of thousands of patients "some research has started, meanwhile we don't know what to do". These statements are a carefully considered and reasonable approach to helping patients until further evidence is available, generated by a robust consensus method from a unique group of "lived experience" professionals.

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In order to maintain independence of the panel from authoring and publishing the recommendations, BD and MN did not participate in the Delphi panel.

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Author contributions:

BD devised the study and is guarantor, BD CR AF ST LJ NM MN wrote and revised the Delphi Statements and worked on the clinical content, MN managed the Qualtrics and Delphi processes and drafted the manuscript. Additional listed authors formed the rest of the Delphi panel and provided comments and references for the discussion on statements. All authors were involved in re-drafting the manuscript and approving the final draft. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests:

There are no conflicts of interest.

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