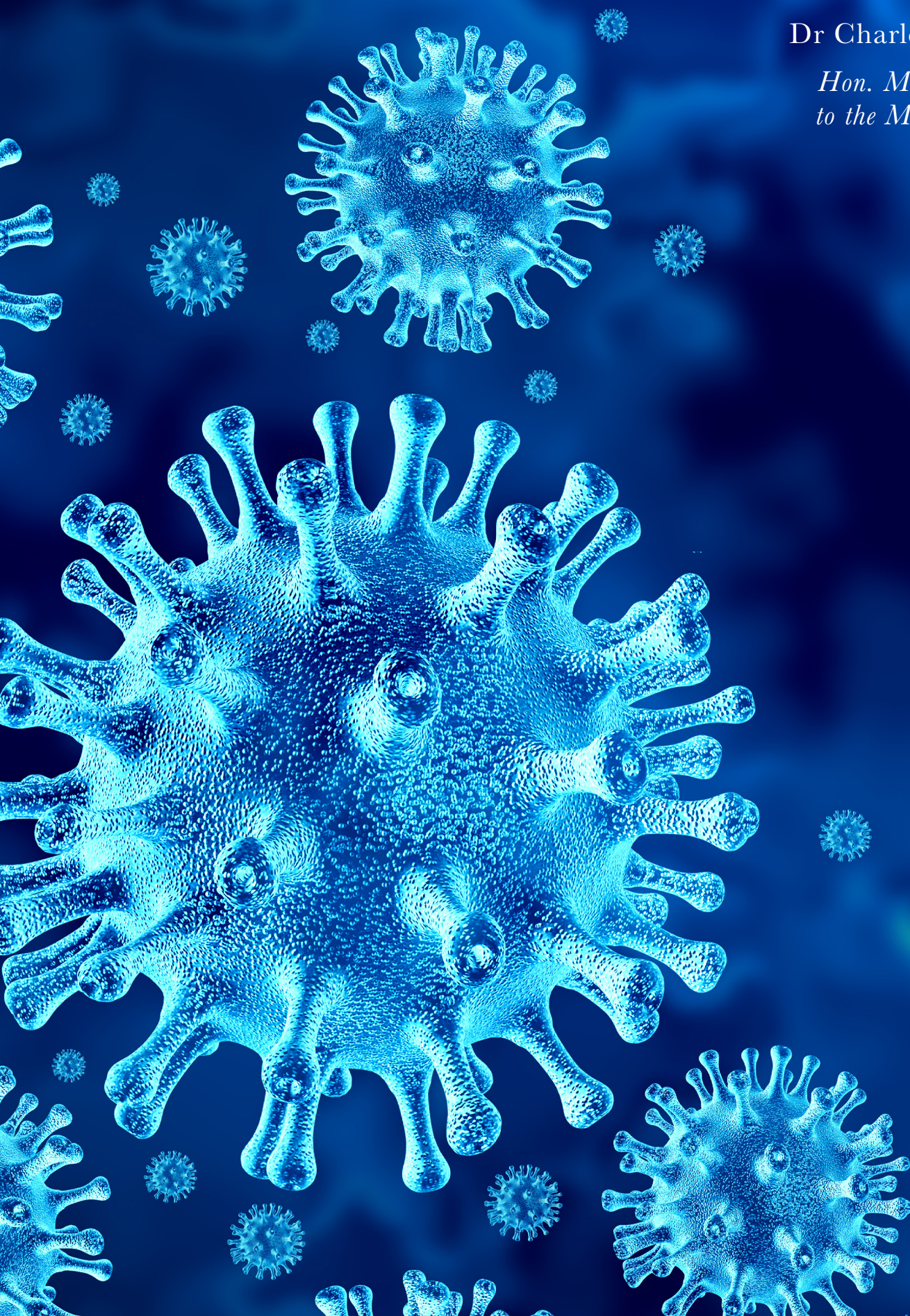


LONG COVID AND ME/CFS

Dr Charles Shepherd

*Hon. Medical Adviser
to the ME Association*



THE ME ASSOCIATION

me

APRIL 2021 UPDATE

Information and guidance from The ME Association on Post-Covid Fatigue, Post-Covid Syndromes, Long covid and the overlaps with ME/CFS.

**Prepared by Dr Charles Shepherd
Hon Medical Adviser, ME Association**

If you are in any doubt about what you should be doing, especially if you develop symptoms that you suspect might be Covid-19, please consult the Government websites:

England: <https://www.gov.uk/coronavirus>

Northern Ireland: <https://tinyurl.com/yby7h7h4>

Scotland: <https://tinyurl.com/vth7xtd>

Wales: <https://gov.wales/coronavirus>



CONTENTS

01	INTRODUCTION	<u>5</u>
1.1	How many people have a post-covid syndrome or Long covid?	<u>5</u>
1.2	Nomenclature	<u>6</u>
1.3	Key messages	<u>7</u>
02	CURRENT SITUATION	<u>8</u>
2.1	Post-covid intensive care syndrome	<u>8</u>
2.2	Post-covid fatigue	<u>8</u>
2.3	Post-covid syndromes and Long covid	<u>9</u>
2.4	Long covid and ME/CFS	<u>9</u>
2.5	Covid-19 in people who already have ME/CFS	<u>11</u>
03	PATIENT EVIDENCE – ‘CITIZEN SCIENCE’ ON LONG COVID	<u>12</u>
04	WHAT DO WE KNOW ABOUT THE POSSIBLE CAUSES AND SYMPTOMS OF POST-VIRAL FATIGUE, POST-VIRAL FATIGUE SYNDROMES AND THE DEVELOPMENT OF ME/CFS	<u>13</u>
4.1	Post-viral fatigue	<u>13</u>
4.2	What are the possible causes of post-viral fatigue and post-covid fatigue?	<u>13</u>
4.3	Post-viral fatigue syndrome (PVFS) and ME/CFS: symptoms	<u>15</u>
4.4	PVFS and the possible progression to ME/CFS	<u>17</u>
05	CLINICAL ASSESSMENT OF PEOPLE WITH POST-COVID SYNDROMES AND LONG COVID	<u>18</u>
06	MANAGEMENT OF POST-VIRAL/COVID FATIGUE AND LONG COVID SYNDROMES	<u>22</u>
6.1	Convalescence - Rest, relaxation and cautiously increasing activity levels	<u>22</u>
6.2	Four Important basics: Planning, Prioritising, Delegating and Explaining	<u>23</u>
6.3	Activity and Energy Management	<u>23</u>
6.4	Sleep	<u>25</u>
6.5	Neurological symptoms	<u>26</u>
6.6	Drug treatments and symptom relief	<u>27</u>
6.7	Mental well being and relationships	<u>28</u>
6.8	Nutrition and fluid intake	<u>28</u>
6.9	Education and Employment	<u>28</u>
6.10	Finances	<u>29</u>
07	PROGNOSIS	<u>30</u>
08	MANAGEMENT OF POST-COVID ME/CFS	<u>31</u>

CONTENTS (cont.)

09	RESEARCH INTO WHAT MAY CAUSE POST-VIRAL/COVID FATIGUE AND LONG COVID	<u>32</u>
9.1	Research into PVF and PVFS	<u>32</u>
9.2	Research into organ damage in Long covid	<u>33</u>
9.3	Other research	<u>35</u>
10	FURTHER INFORMATION	<u>36</u>
10.1	Information and guidance from NHS sources	<u>36</u>
10.2	Health professional responses	<u>36</u>
10.3	Media responses	<u>37</u>
10.4	ME Association portfolio of Covid-19 information	<u>38</u>

01

INTRODUCTION

The ME Association (MEA) has been helping people with post-viral fatigue/debility, post-viral fatigue syndromes (PVFS) and ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) for many years.

Back in April 2020 we became aware of an increasing number of people who had been ill with COVID-19 and were not improving, even after several weeks.

Almost all had been self-managed at home with an illness that mostly varied from mild to moderate in severity, but not usually requiring hospital admission.

Most had debilitating fatigue, often combined with continuing COVID-19 symptoms involving the lungs or heart in particular. Many also had symptoms that are more consistent with the sort of post-viral fatigue syndromes that may precede ME/CFS.

In April and November 2020 we produced MEA information and guidance to the management of post-covid fatigue, post-covid fatigue syndromes and the overlap between ME/CFS and Long covid. This information and guidance was based on how our knowledge and expertise about post-viral fatigue, post-viral fatigue syndromes and ME/CFS could be transferable to people who were not recovering from COVID-19, and where the symptoms were the same or very similar to ME/CFS.

This information and guidance has now been fully updated to take account of developments in our understanding of the presentations and management of post COVID-19 ill health and the how best to name the various clinical presentations.

01.1

How many people have a Post-Covid Syndrome or Long Covid?

At present, we have no firm indication as to how many people are experiencing persisting ill health following COVID-19. However, if current estimates of around 10% of people who were home-managed are remaining unwell after 3 months are accurate, this would translate into well over 100,000 people with some form of significant post-covid ill health that has persisted beyond 3 months.

The latest data (March 2021) from the Office of National Statistics (ONS) indicates that:

- One in five people were still symptomatic at 5 weeks after the start of the initial infection - approximately 1 million people
- One in seven were symptomatic at 12 weeks - approximately 700,000 people
- Around 70,000 people were still symptomatic one year on from the initial infection
- In 20% of cases this was having a significant effect on day-to-day activities

■ Post-covid ill health was more common in people working in health and social care professionals

Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK, 1st April 2021:

<https://tinyurl.com/eu3dku85>

Data from the latest (March 2021) University of Leicester/PHOSP-COVID study of people who were admitted to hospital indicates that seven out of ten people who were hospitalised with COVID-19 were still not recovered five months after discharge.

Researchers reported that each participant had an average of nine persistent symptoms. The ten most common symptoms were: muscle pain, fatigue, physical slowing down, impaired sleep quality, joint pain or swelling, limb weakness, breathlessness, pain, short-term memory loss, and slowed thinking. Around 25% also had significant anxiety or depression.

<https://tinyurl.com/ettbr9kx>

01.2 Nomenclature : Post-Covid Fatigue, Post-Covid Syndromes, Long Covid and Long Covid ME/CFS

Post-Covid Fatigue: A large number of people who have largely self-managed COVID-19 at home have failed to recover and return to normal levels of health within a period of one month from the onset of their initial symptoms – possibly around 20%.

In this case, based on our experience with other post-viral conditions, a diagnosis of **Post-Covid Fatigue/debility, or a Post-Covid Fatigue Syndrome**, may be the most suitable diagnostic label to use at this stage.

Long Covid: A smaller number, possibly around 10%, continue to remain unwell after three months – where a diagnosis of Long Covid is often being made. In some cases a diagnosis of Long or Post-Covid ME/CFS is now being made at this stage.

01.3 Key Messages

1. As with ME/CFS, there is a significant female predominance and many people with Long covid are previously fit (sometimes very fit) young adults in their 20s to early 50s. Some children and adolescents are also remaining unwell and are now being diagnosed with Long covid. By contrast, most people who develop serious complications and require hospital admission are male and over the age of 50.
2. Long Covid is not one condition. It is an umbrella term that covers a range of symptoms that relate to the parts of the body (ie lungs, heart, liver, kidneys, gastrointestinal tract, central nervous system etc) that were involved at the time of the original infection, often combined with symptoms that are characteristic of post-viral fatigue syndromes and ME/CFS.
3. Many have debilitating fatigue as the main and most debilitating symptom.
4. Some have respiratory, heart and other symptoms that are the same, or very similar, to their acute COVID-19 infection - i.e. breathlessness, dry cough, chest pains, palpitations, intermittent fevers, headaches, loss of taste or smell.
5. Others have symptoms – brain fog/cognitive dysfunction, dysautonomia – including orthostatic intolerance and PoTS, unrefreshing sleep, post-exertional malaise - that are very similar to those seen in the post-viral fatigue syndromes that can follow any infective illness and may precede ME/CFS.
6. Some have a combination of acute COVID-19 infection symptoms and post-viral fatigue syndrome or ME/CFS type symptoms.
7. In cases where symptoms have persisted for more than three months, and are consistent with those of ME/CFS, a diagnosis of Long or Post-covid ME/CFS should be considered. The diagnosis should be confirmed through the process of a careful clinical assessment.
8. Although there is no specific drug treatment for Long covid, there is a lot that can be done to help people to deal with their activity and energy management and to help them cope with the various symptoms that are often causing a significant degree of functional impairment affecting all aspects of everyday life.
9. Activity and energy management in post-viral fatigue syndromes requires a different and more flexible approach than is used in people who are having cardiorespiratory rehabilitation.
10. The outlook for people with Long covid is uncertain. Patient evidence indicates that some people are steadily improving and returning to normal or near normal health. But many are remaining unwell with what could be turning into a long-term illness that often fluctuates in symptom severity – just like ME/CFS.

02 CURRENT SITUATION

The MEA has been dealing with a growing number of people who have post-covid fatigue, a post-covid syndrome or Long covid over the past year. However, there is quite a lot of overlap and not everyone fits neatly into one of these three groups.

In most cases it seems sensible to separate this type of failure to recover from mild or moderate COVID-19 from the often complex rehabilitation problems that people who have been seriously ill in hospital are often experiencing.

02.1 Post-Covid Intensive Care Syndrome

This description defines people who have been sufficiently unwell to require hospital-based treatment. They often had significant respiratory, heart and/or blood clotting complications whilst in hospital. The initial infection may have also affected kidney, liver, gastrointestinal and neurological function. So they now have a range of health and disability problems that are frequently seen in people who have been treated in intensive care units and required ventilation.

These problems may include loss of muscle mass (people can lose around 3% of muscle mass per day whilst in intensive care), more severe cognitive dysfunction (from reduced levels of oxygen to the brain), loss of taste and smell and complications relating to ventilation tubes, catheters etc. Some have on-going and significant neurological symptoms. Not surprisingly many people in this group also have debilitating fatigue.

This group is likely to require a prolonged period of specialist rehabilitation – preferably under the care of a multidisciplinary hospital-based team that is used to dealing with respiratory, neurological and cardiovascular rehabilitation.

02.2 Post-Covid Fatigue

As happens with most other viral infections, some people continue to feel fatigued, along with some of their other symptoms relating to the original infection, for several weeks. In many cases this fatigue will gradually resolve – provided people take it easy and gradually return to their normal level of physical and mental activity by carefully pacing their activities.

02.3 Post-Covid Syndromes

Again, as with other viral illnesses, some people continue to feel fatigued, generally unwell, and develop symptoms that are consistent with a post-viral fatigue syndrome (see section 4.3) for several weeks or even months. In a post-covid syndrome this is likely to include symptoms relating to the initial infection. With good management this sort of persisting ill health can steadily improve and people are able to gradually return to normal levels of health. However, in some cases significant levels of ill health will still be present after three months. Where this occurs a diagnosis of Long covid will need to be considered and is probably more appropriate.

02.4 Long Covid

A diagnosis of Long covid should therefore be considered where symptoms have persisted for more than three months after the initial infection.

Most people with Long covid are still suffering from some or all of the initial symptoms of COVID-19. In some cases there was a return to normal, or near normal health. But in most cases their COVID-19 symptoms never went away. As people in this group are largely home -managed, many do not have a positive antibody test for COVID-19.

COVID-19 symptoms of Long Covid

- debilitating fatigue
- intermittent fevers
- breathlessness, dry cough, 'lung burn'
- palpitations or cardiac arrhythmias/heart rhythm disturbances, chest pain
- loss of smell or taste and sometimes a distorted sense of smell (parosmia)
- abdominal pain and diarrhoea
- skin rashes and 'covid toes'

In some cases, the symptoms are fairly constant. In others, the overall clinical picture fluctuates – sometimes quite dramatically. So they may have days, or parts of a day, when they feel reasonably well. The symptoms then recur – sometimes following undue exertion. Sometimes for no apparent reason. Progressive deterioration appears to be unusual but has been reported.

Many people with Long covid also have symptoms that are consistent with the sort of post-viral fatigue syndrome (PVFS) that we are used to dealing with in people who then go on to develop ME/CFS.

PVFS and ME/CFS symptoms that may accompany Long covid include

- activity-induced muscle fatigue and weakness and muscle twitching (fasciculations)
- muscle, nerve and joint pains (myalgia, neuropathic pain and arthralgia) but without joint redness or swelling
- headaches which may have a migrainous quality
- 'brain fog' or cognitive dysfunction (problems with short term/working memory, concentration, information processing, word finding ability)
- sensory disturbances – eg pins and needles/paraesthesiae, patches of numbness
- dysautonomia – problems relating to dysfunction of the autonomic nervous system. These can include increased pulse rate/sinus tachycardia, orthostatic intolerance (problems in remaining upright, feeling dizzy or faint), postural hypotension (a fall in blood pressure on standing) and postural orthostatic tachycardia syndrome/POTS (where there is a rise in pulse rate of 30 or more beats per minute in adults, or 40 beats per minute in those age 12 to 19, within 10 minutes of moving from sitting or lying to a standing position)
- unrefreshing sleep, which may include excessive sleep (hypersomnia) in the early post infection stage
- problems with temperature regulation (thermoregulation)
- post-exertional malaise (PEM) or symptom exacerbation – which is the cardinal feature of ME/CFS

While most people with ME/CFS do not have any significant symptoms relating to the specific viral illness that triggered their illness some do. The situation with Long covid is unusual but is not unique.

A large number of other symptoms have been linked to Long covid and in some cases there are symptoms and clinical features (eg Mast cell activation syndrome) that overlap with ME/CFS.

Mental health symptoms

In some cases there are significant mental health symptoms – anxiety, depression, even post-traumatic stress disorder. This aspect may dominate the clinical picture.

02.5 Long Covid and ME/CFS

Where post-covid syndrome symptoms have persisted for more than three or four months, and the symptoms are more consistent with ME/CFS symptomatology, and there are no significant COVID-19 related symptoms and no evidence of lung or heart damage, a diagnosis of a post-covid ME/CFS may be more appropriate.

02.6 COVID-19 in people who already have ME/CFS

We have also been dealing with people who already have ME/CFS and have caught COVID-19. They have, not surprisingly, had a significant exacerbation or relapse of their ME/CFS symptoms. However, it is interesting to note that we have received very few reports about people with ME/CFS being seriously ill with COVID-19 who had to be admitted to hospital. We have received very few reports about children and adolescents with ME/CFS catching COVID-19.

03

PATIENT EVIDENCE ON LONG COVID –
‘CITIZEN SCIENCE’

People with Long covid have been making some very valuable contributions to medical publications - as well as on social media forums and support groups - to aid our understanding of what is happening and how we should be managing these conditions.

These are some of the important messages from this feedback about how people with Long covid should be managed in general practice/primary care - where most people are looking for help and not always getting it:

- People need to be listened to, believed, and not have their symptoms dismissed as anxiety or depression – just because there is no objective evidence of organ damage and their blood test results are all normal.
- GPs need to provide on-going support - not just diagnose Long covid and leave it at that.
- People with respiratory or heart symptoms need to have their lungs and heart physically examined in a face-to-face consultation - this cannot be done by phone or Zoom consultation!
- Those with significant respiratory or heart symptoms need to be referred to a relevant specialist for further assessment and investigation - as there is emerging evidence to demonstrate that a significant proportion of the home-managed group have developed heart and lung problems that were not apparent at the time. See section 9.2
- There needs to be a multidisciplinary approach to management in both primary care and secondary care that brings in community physiotherapists, occupational therapists and other health professionals.

BMJ opinion article on the stigma associated with Long Covid:

<https://tinyurl.com/xves2u5m>

Lancet editorial – Long covid guidelines need to reflect lived experiences:

<https://tinyurl.com/2ytt5k7>

Video from journalist George Monbiot:

<https://tinyurl.com/2z9cmzsh>

04 WHAT DO WE KNOW ABOUT THE POSSIBLE CAUSES AND SYMPTOMS OF POST VIRAL FATIGUE, POST-VIRAL FATIGUE SYNDROMES AND THE DEVELOPMENT OF ME/CFS?

04.1 Post-Viral Fatigue

Some degree of post-viral fatigue (PVF) or debility is a fairly common occurrence after any type of viral infection.

In most cases this is short-lived and there is normally a steady return to normal health and activity levels over a period of a few weeks. However, a full return to normal health can take rather longer.

Additional symptoms may also develop, where the term post-viral fatigue syndrome (PVFS) becomes a more appropriate diagnosis.

04.2 What are the possible causes Post-Viral Fatigue and Post-Covid Fatigue?

The situation with persisting fatigue following COVID-19 infection is turning out to be far more complicated than what happens with most other viral illnesses. It can also be more serious - as fatigue and lack of energy are a very characteristic symptom of the acute COVID-19 infection.

The precise explanation for what causes post-viral fatigue remains uncertain. But one of the reasons why people have fatigue, increased sleep requirements, loss of energy, muscular aches and pains, and generally feel unwell when they have an acute infection, is the production of chemicals called cytokines by the body's immune system. These immune system chemicals form part of the front line inflammatory response against any viral infection.

LONG COVID AND ME/CFS

In people who develop serious respiratory complications with COVID-19, this appears to be partly due to an overactive immune response that kicks in during the second week involving what is termed a 'cytokine storm'.

When fatigue and flu-like symptoms persist for a longer period of time once the acute infection is over, as they do in ME/CFS, there is growing research evidence to indicate that what is a perfectly normal immune system response to the acute infection has not returned to normal and there is on-going immune system activation. In other words, the body's immune system has not switched itself off from fighting the initial infection.

Cytokines can pass through what is called the blood brain barrier and affect important control centres in the brain. In ME/CFS, this appears to involve a key part of the brain called the hypothalamus (an internal thermostat for controlling appetite, sleep and hormone production) as well as control centres in the brain for the autonomic nervous system (which regulates heart rate and blood pressure and where dysfunction can cause orthostatic intolerance and PoTS). The same situation could well be happening in Long covid.

As with ME/CFS there is emerging evidence in COVID-19 to indicate that cytokine-mediated neuroinflammation is playing a role in the causation of fatigue and other neurological symptoms.

<https://tinyurl.com/4dsphrrz>

It is also possible that, as happens with ME/CFS, there is a problem with the way in which energy production is taking place at a cellular level inside muscle in battery-like structures called mitochondria. There is now emerging research evidence to suggest that COVID-19 highjacks mitochondria of immune cells, replicates within mitochondrial structures, and impairs mitochondrial dynamics leading to cell death.

Mitochondria are the powerhouses of the cell and are largely involved in maintaining cell immunity, homeostasis, and cell survival/death. This evidence suggests that mitochondria from COVID-19 infected cells are highly vulnerable, and vulnerability increases with age.

<https://tinyurl.com/ym79td22>

Downregulation of the hypothalamic-pituitary-adrenal axis, resulting in a degree of hypocortisolaemia (ie lowered levels of blood cortisol), is something that occurs in ME/CFS and is another possibility in Long covid.

In relation to COVID-19 it is possible that small vessel (microvascular) immunothrombotic events in the lungs may still be playing a role with a recent research report indicating that D dimer levels (which indicate a blood clotting event) remain elevated in some people who remain symptomatic:

<https://tinyurl.com/ptn7emnt>

The presence of autoantibodies - harmful antibodies that are directed against the body's own tissues - has also been described in both ME/CFS and more recently in Long covid:

<https://tinyurl.com/p4kptjdu>

We are still on a very steep learning curve when it comes to understanding how this particular coronavirus behaves. However, there is no robust evidence to indicate that COVID-19 persists like hepatitis C infection or HIV, or remains in 'hidden pockets' in various organs. So the continuing fatigue does not appear to be due to a persisting viral infection. Consequently, people who have continuing fatigue, but no other coronavirus symptoms, appear to be no longer infective to others in our current state of knowledge.

While the vast majority of people with post-infection fatigue will improve and return to normal health, good management during the very early stage is an important factor in trying to help any natural recovery process take place. Patient evidence also indicates that good initial management of post-viral fatigue and post-viral fatigue syndromes reduces the likelihood of this turning into ME/CFS.

04.3

Post-Viral Fatigue Syndrome and ME/CFS: Symptoms

Where a period of post-viral fatigue persists and fails to improve after more than a few weeks, and is accompanied by other symptoms, a diagnosis of a post-viral fatigue syndrome is often more appropriate.

Symptoms that are typical of a general post-viral fatigue syndrome (PVFS), and ME/CFS where this follows on, are:

Activity-induced fatigue:

In practical terms this means no longer being able to carry out and sustain a normal range of physical activities in the home, at work or school, or anywhere else.

In terms of severity this can range from a relatively mild impairment to a really quite severe functional impairment.

A useful comparison here is trying to operate a mobile phone with a battery that no longer charges properly. The phone may work reasonably well for short periods of time but then starts to fail quite quickly. After a rest it will work again - but only for another short period.

In a similar manner, people with a PVFS find they can carry out short periods of physical and/or mental activity but then have to stop and rest and 'recharge their batteries'. They are no longer able to sustain their normal levels of physical activity and find anything that involves using a large amount of energy in a short period of time, such as going for a run, is no longer possible and leads to an exacerbation of symptoms or a relapse.

There is no loss of motivation to do things - as occurs in the 'tired all the time' fatigue that often forms part of a depressive illness.

Sleep disturbance:

Some form of sleep disturbance is very common.

During the actual infection, and shortly afterwards, this may involve sleeping for much longer than usual - as well as wanting to sleep for periods during the day. This type of excessive sleep requirement is known as hypersomnia and is a natural part of the way in which human body responds to and recovers from an infective illness.

As time goes on, hypersomnia usually decreases and is replaced by other types of sleep disturbance - including fragmented sleep and difficulty getting off to sleep. Sleep disturbance may be accompanied by abnormal leg muscle movements – restless legs syndrome.

Cognitive dysfunction:

Just as energy is required for physical activity, it is also required for mental/cognitive activity. So in a similar way to easily running out of energy when doing a physical task, people cannot cope with longer periods of mental/cognitive activity and start to lose concentration and their ability to process and retrieve information. Short-term (working) memory and word-finding abilities may also be affected.

Dysautonomia: Orthostatic intolerance syndromes, including PoTS :

This is caused by a problem with what is called the autonomic nervous system - a part of the brain that helps to regulate pulse and blood pressure when we move from lying or sitting to standing.

Orthostatic intolerance means being unable to stand up and do things for any length of time. This can be accompanied by a **postural orthostatic tachycardia syndrome/PoTS** (where the pulse rate rises by 30 or more beats per minute in adults, and 40 or more beats per minute in the 12 to 19 age group, within 10 minutes of assuming an upright posture) and makes people feel dizzy, faint, and nauseous or **postural hypotension** (where the blood pressure falls on standing). The medical term for these autonomic dysfunction symptoms is dysautonomia.

04.4 PVFS and possible progression to ME/CFS

Many cases of PVFS slowly resolve and people return to normal health. However, if PVFS symptoms persist for more than two to three months, and continue to cause a significant degree of functional impairment that prevents a return to education, employment or other key activities, a diagnosis of ME/CFS should be considered.

Other symptoms that can form part of a PVFS, and are also very suggestive of a diagnosis of ME/CFS include:

- Alcohol intolerance – a key diagnostic feature
- Balance problems
- Headaches – which may be migrainous in character
- Muscle or joint pain but without swelling or inflammation
- Sore throats, tender glands, flu-like feelings and generally feeling unwell
- Problems with temperature control - including increased sensitivity to hot and cold temperatures
- Post exertional malaise/symptom exacerbation

05

CLINICAL ASSESSMENT OF PEOPLE WITH POST-COVID SYNDROMES AND LONG COVID

Do let your GP know that you are having continuing health problems after having COVID-19, especially if symptoms are persisting for more than 4 weeks, are getting worse, or new symptoms develop. COVID-19 can also affect pre-existing medical conditions like diabetes - where normal blood sugar control may be upset and trigger the onset of conditions that may have been dormant before the infection occurred. .

Although a face-to-face consultation with your GP may be difficult to arrange, most GPs are happy to speak to their patients on the phone. Many GPs are now offering video consultations - which can be helpful if a more thorough assessment is required. A face-to-face consultation must be considered if the problem is more serious or urgent, or there are respiratory or heart symptoms that really do require a physical examination.

Assessing someone who may have a post-covid syndrome or Long covid in primary care should always involve:

Taking a detailed clinical history:

This should include questions about symptoms that are likely to be related to COVID-19 (eg breathlessness, chest pain, palpitations) and those which are consistent with PVFS or ME/CFS (eg cognitive function, dysautonomia, unrefreshing sleep).

In relation to breathlessness, this should aim to differentiate between respiratory (from persisting lung damage) and cardiovascular (from possible heart failure) causation. It is therefore important to physically examine people to check for signs such as peripheral oedema (ie fluid around the ankles).

In relation to palpitations, this should aim to differentiate between a cardiac causation (ie the possibility of COVID-19 myocarditis or pericarditis) and a sinus tachycardia caused by autonomic nervous system dysfunction – where the person can normally be reassured that there is no damage to the heart.

In relation to persisting gastrointestinal symptoms, consideration should be given to other possible explanations, especially the onset of an inflammatory bowel disease.

Baseline investigations:

- Full blood count and serum ferritin
- Inflammatory markers: ESR and CRP
- Liver, kidney and thyroid function tests
- Urea and electrolytes

- Calcium
- Blood sugar and HbA1c if new onset diabetes is being queried
- Body temperature - bring a temperature diary if you are having fluctuating fevers

Investigations in primary or secondary care – where clinically indicated:

- Brain natriuretic peptide test (BNP) where breathlessness could be caused by heart failure
- D dimer test. A positive D-dimer result indicates that there may be blood clot (thrombus) formation and breakdown in the body but it does not identify the location or cause. A normal level does not exclude a thromboembolic event such as pulmonary embolism.
- Calprotectin and coeliac disease screening if there are significant gastrointestinal symptoms
- B12 and folate - where there are sensory neurological symptoms
- Vitamin D
- Chest X-ray and spirometry – although a normal result does not exclude pulmonary pathology. Further assessment may require imaging investigations.
- Pulse oximetry to measure oxygen saturation levels. Refer on where there is evidence of low oxygen levels (hypoxaemia) or desaturation following activity.
- Sitting and standing pulse and blood pressure - where there are palpitations and there is a possibility of a co-existent postural orthostatic tachycardia syndrome (PoTS).

The NASA 10 -minute lean test can be helpful here:

<https://tinyurl.com/23ms5nby>

- 12 lead electrocardiogram, 24 hour ECG monitoring and echocardiography
- Cardiac MRI to further investigate chest pain where myocarditis or pericarditis is possible

Exercise testing

Great care needs to be taken if any form of exercise testing - eg the six minute walking test - is being considered to assess cardiopulmonary function or mobility status, especially in people who may develop exercise-induced hypoxia or have undiagnosed cardiac pathology (eg myocarditis) as a result of COVID-19 and therefore be at risk from exercise-induced cardiac arrhythmias.

The value of exercise testing in relation to assessing physical activity levels is very questionable in a condition that is often fluctuating on a day-to-day basis and where the effort of travelling to and attending an out-patient assessment will have already depleted energy levels.

It should also be noted that, as with ME/CFS, many people with Long covid will not be able to continually briskly walk for 6 minutes. The effort of doing so may lead to a significant exacerbation of symptoms.

If the six minute walking test is being used for clinical assessment of cardiorespiratory function the protocol should follow guidance issued by the American Thoracic Society:

<https://tinyurl.com/6x2vfjmd>

Making a diagnosis

The diagnosis of Long covid is going to be largely made on symptoms as there is no diagnostic blood test. However, a serious infection like this has the potential to unmask medical conditions that were previously not causing any obvious symptoms or physical signs. Examples include diabetes, low thyroid function/hypothyroidism, liver disease, inflammatory bowel disease (where abdominal pain or diarrhoea is present) and neuromuscular disease (eg polymyalgia rheumatica).

This is why it is important to check the same list of baseline blood tests, especially the ESR and CRP levels, which are indicators of active inflammation in the body, and which are normally used when the cause of chronic fatigue is being investigated.

Red flag symptoms

If any of the following symptoms are present, which are not part of normal post-viral syndromes, you must speak to your GP:

- Continuing fever or periodic spikes of fever
- Persisting cough, shortness of breath, or other respiratory symptoms
- Palpitations or chest pain
- Weight loss
- Feeling depressed or anxious
- Persisting diarrhoea or abdominal pain

A network of specialist multidisciplinary services – Long covid clinics - are being established where people can be referred by a GP for expert cardiological and respiratory assessment. Feedback to the MEA indicates that while these Long covid clinics are often very good at assessing and investigating symptoms, they may be less good at providing management advice, especially in relation to ME/CFS symptoms such as activity-induced fatigue, cognitive dysfunction, dysautonomia and unrefreshing sleep.

There are now over 70 Long covid clinics in England. At present there are no or very few clinics in Northern Ireland, Scotland and Wales. NHS directory of Long covid clinics:

<https://tinyurl.com/vcbpse23>

There have been proposals to have joint Long covid and ME/CFS clinics. The MEA position is that they should be kept separate at present - due to the need to have specialist input for the assessment and management of heart and lung problems - but to establish links to ME/CFS clinics and refer people over where appropriate. As with ME/CFS, we believe these hospital-based services for Long covid should be physician led.

NB: What has been term the systemic COVID-19 syndrome is usually accompanied by mild lymphopaenia (a reduction in white blood cells), neutrophilia (reduced levels of neutrophils, which act as a primary defence against infections), thrombocytopenia (a reduction in platelets that are involved in blood clotting), hyperferritinaemia (elevated levels of a protein that is involved in iron storage), and elevation of inflammatory and clotting factors.

■ The MEA has an information leaflet providing detailed guidance on the early and accurate diagnosis of ME/CFS and all the blood tests that should be checked before a diagnosis is confirmed.

<https://tinyurl.com/y62rbm6a>

06

MANAGEMENT OF POST-VIRAL/COVID FATIGUE AND
LONG COVID SYNDROMES

This information and guidance relates to post-covid fatigue, post-covid syndromes and Long covid syndromes where all or part of the symptomatology is consistent with the sort of post-viral fatigue syndromes that are either self-limiting, or have features that are very similar to ME/CFS.

The situation in relation to a Long covid syndromes where there are persisting and significant respiratory, heart or other symptoms that are not normally associated with ME/CFS is more complex. These aspects require assessment and management by health professionals with the necessary expertise and access to appropriate investigations.

06.1

Convalescence: Rest, relaxation and cautiously increasing activity levels

The most important initial aspect of management of any form of significant post-viral fatigue involves good old-fashioned convalescence. The aim is to make a gradual and flexible return to normal daily activities.

In practice, this means taking things easy, and having plenty of rest and relaxation during the immediate post-infection stage. This should be combined with very gentle physical activity that is always within your limitations, having a good night's sleep, eating a healthy diet, and avoiding stressful situations. Above all, do not return to work, school or domestic duties until you are well enough to do so.

Some people find that adding in approaches like meditation or yoga can help with relaxation. Others do not.

Overall, progress can be very variable with some people making a steady improvement back to normal health fairly quickly. Others follow a less predictable pattern with good days and bad days. Doing too much on a good day will often lead to an exacerbation of fatigue and any other symptoms the following day - this is called post-exertional malaise (PEM) or post -exertional symptom exacerbation.

06.2 Four important basics: Planning, Prioritising, Delegating and Explaining!

Planning: When you start each day with a very significant reduction in your energy reserve, and when this reserve is going to fluctuate from day-to-day, it's important to give careful thought to planning the day ahead, as well as the week ahead. So if you have important physical or mental/cognitive tasks that need to be done, try to spread them out throughout the day and in the week ahead.

If they are going to be time-consuming split them into small manageable chunks that can be completed one day at a time. This sort of planning needs to be very flexible and changed when you are clearly not having a good day or a good week.

Prioritising: When it comes to any of the energy-requiring activities - physical, mental/cognitive, social and family - that you would normally be doing, sort them into high priority items that still need to be done and lower priority items which can be deferred or omitted for the time being.

Delegating: Draw up a list of activities and actions that you might be able to delegate to other members of your family, or to friends.

Explaining: Having to cope with a major reduction in what you are able to do physically and mentally is bound to affect your close relationships, especially with partners and children. Explain to people close to you what has happened and, where appropriate, indicate how they might be able to offer some practical help. Hopefully, they will understand and accept that you are dealing with a serious medical problem that is going to impose significant restrictions on everything you normally do – work, family, social - for the foreseeable future.

06.3 Activity and Energy Management

To start with it's often helpful to think about having a daily energy reserve - rather like a tank of petrol. Most people learn to sense how full their energy reserve is at the start of each day. But this is very likely to fluctuate from day to day. So planning the day ahead, physically and mentally, in relation to what you hope to achieve is going to have to be within your likely energy limits for that day. There is no point in having a completely empty tank before the day is over! This isn't easy, especially at the start, and involves lots of trial and error to get it right. But it's a crucial component when it comes to providing the right basis for the body's natural ability to heal and improve.

As energy is required for any form of physical, cognitive and mental/emotional activity, it's important to make sure that you are not exceeding what you feel comfortable doing. Where possible, stop an activity before you are starting to feel more fatigued. Don't try to carry on with a task when you are starting to flag or not able to do so.

Finding the right balance on an individual basis between activity and rest is a process called **pacing**. Many people find it helpful to alternate small flexible amounts of physical and cognitive activities with a longer period of rest/relaxation in between.

Physical activities could include light household tasks and going for a short walk – when you feel ready to do so. Mental/cognitive activities could include social activities with people you can still be in contact with, reading, listening to the radio or music, watching TV, or doing a small amount of computer work. Whatever mix you choose, try to make sure that you are also doing things that you enjoy!

Limit screen time on computers, phones and TV, and avoid using electronic devices to catch up on your normal work!

Having established what is a fairly safe baseline of physical and mental/cognitive activity that is not exacerbating symptoms, the next step is to gradually try and increase the amount you are doing – whilst sticking to the rule of not exceeding limitations and living within your 'energy envelope'.

When it comes to physical activity, walking is a good option - starting off with very short walks and building up slowly. If you are progressing well and want to do something more active, swimming in a warm pool is worth considering, or going for a short slow jog if you enjoy running, or a gentle cycle ride. But do take medical advice if you still have any respiratory or heart symptoms. At this stage, the use of heart rate monitoring may also be helpful. This is explained in the video produced by the Physios4ME group.

Any kind of vigorous sport or exercise (e.g. running) should be given a complete miss until you have remained well for a reasonable period of time.

Graded exercise programmes are not appropriate for people with post COVID-19 fatigue – this has been confirmed by NICE. You cannot exercise your way out of post COVID-19 fatigue!

Finally, health professionals must appreciate that activity and energy management in post-viral fatigue syndromes requires a different and far more flexible approach than is used in cardiorespiratory rehabilitation.

Further information and guidance on activity and energy management:

■ MEA information leaflet on activity and energy management:

<https://tinyurl.com/u2n37vhs>

■ Section on activity management in the working draft of the new NICE guideline on ME/CFS:

<https://tinyurl.com/aatcs5t3>

■ NICE has made it clear that recommendations relating to graded exercise therapy are not appropriate for people with post-covid fatigue:

<https://tinyurl.com/4pz7pcv4>

■ **Letter to physicians on the dangers of inappropriate graded exercise therapy from the Workwell Foundation:**

<https://tinyurl.com/2nmexj7c>

■ **Physios for ME website – useful information on activity management in both ME/CFS and Long covid from physiotherapists for physiotherapists:**

<https://www.physiosforme.com/covid-19>

■ **Physios4ME Group: useful video on heart rate monitoring for activity management in ME/CFS:**

<https://tinyurl.com/cdk5eddz>

06.4 Sleep

As already noted, having an increased sleep requirement (hypersomnia) is an important part of the body's natural healing process during, and sometimes following, an acute infection.

So whilst going bed and staying there is not the solution, making sure that you have plenty of good quality sleep – preferably up to 7 hours solid uninterrupted sleep, possibly including a daytime nap if you need one in the early stages, is a key part of good management.

Simple self-help strategies that can improve sleep quality include:

- Relaxing before going to bed by having a warm bath (which lowers inner body/core temperature and helps to trigger the need to sleep) or listening to a relaxation CD.
- Avoiding caffeine-containing drinks – coffee, cola, tea – in the evening. Caffeine interferes with the natural process of going to sleep. Try a warm milky drink instead.
- Avoiding heavy meals and alcohol shortly before going to bed. Alcohol may help you to get off to sleep but it can disrupt sleep during the night.
- Trying to establish a regular routine for getting up and going to bed at roughly the same time each day but one that also accommodates any increased sleep requirements.
- Keeping the bedroom as a quiet, peaceful and relaxing place for going to sleep – not too hot or too cold and not a place for watching TV or doing computer work.

The MEA has an information leaflet covering all aspects of sleep management, and restless legs syndrome, in more detail:

<https://tinyurl.com/2mze5wad>

06.5 Neurological symptoms, cognitive dysfunction, orthostatic intolerance syndromes and pain

As already noted, people with PVFS, ME/CFS and Long covid are all likely to experience a range of neurological symptoms, especially cognitive dysfunction, dysautonomia (orthostatic intolerance and PoTS), pain (headaches – including migraine-type headaches, muscle and joint pain), problems with temperature control (thermoregulation), and sensory disturbances (pins and needles/paraesthesiae and patches of numbness).

In relation to PoTS there are a number of important self-help measures (eg increasing fluid and salt intake, leg muscle exercises) and drug treatments (eg beta blockers, fludrocortisone, midodrine) that may be appropriate in more severe cases.

The MEA Association has information leaflets covering all aspects of management of these symptoms. These leaflets can be obtained from the MEA website:

■ **Useful review paper that covers both orthostatic intolerance and PoTS in Long covid:**

<https://tinyurl.com/4j87bepx>

■ **Position statement from the American Autonomic Society on PoTS and Long Covid:**

<https://tinyurl.com/4fwc8mtu>

MEA information leaflets covering both self-help and drug treatment:

Cognitive dysfunction:

<https://tinyurl.com/4hwujtjd>

Orthostatic intolerance:

<https://tinyurl.com/rne9w83k>

Pain management:

<https://tinyurl.com/49644wu8>

Postural orthostatic tachycardia syndrome:

<https://tinyurl.com/2kvstrsb>

06.6 Drug treatments and symptom relief

At present, there are no drugs or supplements that have been shown to be effective at treating the underlying disease process in PVFS, ME/CFS or Long covid. There is no value in taking iron supplements (which are unnecessary and can even be harmful) and high doses of vitamin C, or any other high dose vitamins. However, if you are not having a healthy balanced diet, it would be worth taking a multivitamin supplement.

Although there are encouraging indications that some antiviral (i.e. remdesivir) and immunosuppressive drugs (i.e. dexamethasone) are beneficial in hospitalised patients during the acute infective stage of COVID-19, there is no evidence at present that they are useful in treating or preventing post-covid syndromes or Long covid.

There is some interesting patient evidence emerging to indicate that some people with Long covid are improving after receiving a COVID-19 vaccination. This could be linked to the immune stimulus of the vaccine somehow 'resetting' a dysfunctional immune system.

At present, the main use of drug treatment is for the relief of symptoms in the same way as they are used in ME/CFS. Examples include the use of low dose of a sedating tricyclic antidepressant drug such as amitriptyline - which may be helpful for both pain relief and sleep disturbance. Drugs used in the treatment of pain in ME/CFS, such as gabapentin and pregabalin, are options that could be considered for the management of more severe pain in Long covid.

Where there are symptoms suggestive of mast cell activation syndrome consideration could be given to the use of histamine receptor antagonist drugs and a low-histamine diet.

Where symptoms associated with PoTS are more severe, options include drugs such as beta blockers and midodrine. The drug treatment of PoTS should be initiated and monitored by a doctor with expertise in the treatment of dysautonomia.

The drug treatment of heart and lung symptoms resulting from COVID-19 is outside the scope of this guideline. Options here could include consideration of the use of colchicine for chest pain associated with myocarditis.

As some people who are more severely affected are no longer going outside in the sunshine, or only doing so for short periods, there is a risk of vitamin D deficiency. Vitamin D is made in the body in response to sunshine and is essential for bone and muscle health. So taking a daily 10 microgram vitamin D supplement is a sensible precaution.

06.7 Mental well being and relationships

Looking after mental and emotional health is another important part of management. In particular, this means avoiding stressful situations wherever possible.

Not surprisingly, all the restrictions that this illness imposes on what you are able to do can make people feel fed up, frustrated and sometimes even anxious or depressed.

If you are feeling anxious, or your mood is obviously low, and you are feeling depressed (with tearfulness, loss of interest in activities, loss of self-esteem), you must speak to your GP about how this should be managed.

06.8 Nutrition and fluid intake

Some people lose a significant amount of weight during a serious acute infection. This type of weight loss will need to be built up again if you are not overweight before being ill.

Try to stick to a healthy balanced diet with plenty of fresh fruit and vegetables, possibly with small frequent meals if you find this easier.

Make sure your fluid intake is adequate. It is probably better to avoid alcohol, or cut right down and abstain, especially if alcohol is making you feel worse. Alcohol intolerance is an important diagnostic feature of post-viral fatigue syndromes and ME/CFS.

If your appetite is still poor, or you need to put on some weight again, ask for help from a dietitian on foods that are worth trying. Your GP can refer you to an NHS dietitian. Self referral may also be possible.

06.9 Education and Employment

The simple message here is to switch off from anything to do with work, school or college and do not go back to work until you are fit to do so.

This is especially important if your job involves a significant amount of sustained hard physical activity, intense cognitive activity or high levels of mental stress.

But do keep in touch with your employer or school/college/university - as there may be a number of options to explore once you start to improve and reach a point where a limited or gradual return to work or school/college/university looks possible. This could involve doing some work from home, or having a part-time or flexible return to normal activities at school/college/university or duties in the workplace.

MEA information leaflet covering COVID-19 and Employment:<https://tinyurl.com/ub9pznag>

As with ME/CFS, problems caused by activity-induced fatigue, cognitive dysfunction and orthostatic intolerance are all going to be very relevant to a person's ability to return to employment, even where suitable modifications to hours and duties are made.

The MEA has a detailed guide to all aspects of occupational health and the practicalities of returning to work - much of which will also be applicable to people with Long covid:

<https://tinyurl.com/27sp7cuz>

06.10 Finances

If you are employed, and entitled to state or other sickness benefits, you will need to discuss sick pay, including what is called statutory sick pay, with your employer and obtain a fit note from your GP, or other health professional, who can confirm that you are unable to return to work. A fit note will inform your employer that the health professional has confirmed that you are either 'not fit for work' or 'may be fit for work' and outline what sort of work you may be able to do.

Information from the Citizens Advice Bureau on Statutory Sick Pay:<https://tinyurl.com/r63p2x34>

There are other state benefits from the DWP, including Employment and Support Allowance, Personal Independence Payment (to help with care and mobility needs), and Universal Credit, that you may be entitled to.

The MEA has information on all the sickness and disability benefits that may be needed in the longer term if your health does not improve. The MEA website shop has a section providing information on all the DWP benefits that people with both Long covid and ME/CFS can apply for:

<https://tinyurl.com/2hwecwyj>

The MEA website shop has information leaflets covering all aspects of management of symptoms that are common to post-viral fatigue syndromes and to ME/CFS:

<https://meassociation.org.uk/shop/>

07

PROGNOSIS

The outlook for people with Long covid is very uncertain in our current state of knowledge.

Patient evidence indicates that some people are steadily improving and returning to normal health, especially where there is no evidence of on-going damage or dysfunction affecting organs such as the heart or lungs.

Others are remaining unwell with what may be turning into a more long-term illness that often fluctuates in symptom severity with periods of relative remission and relapse – just like ME/CFS – especially where no significant improvement has occurred over the course of a year.

A small group have more severe symptoms that are imposing major restrictions on all aspects of daily life. However, progressive deterioration appears to be unusual.

We will have a much clearer picture about what is happening to people with Long covid over the course of time once research into long-term outcomes has been carried out and published.

08

MANAGEMENT OF POST-COVID ME/CFS

As already noted, a wide range of viral infections can trigger ME/CFS, including other coronavirus infections like SARS. So we are expecting to see a growing number of people who currently have a diagnosis of a Post or Long covid syndrome being diagnosed as having Long covid ME/CFS.

To confirm a diagnosis of ME/CFS there should be activity-induced muscle fatigue, post-exertional malaise/symptom exacerbation and all or most of three core symptoms of ME/CFS: cognitive dysfunction/brain fog, unrefreshing sleep and orthostatic intolerance. The symptoms should have persisted for three months or more, and be causing a substantial (50% or more) reduction in capacity to carry out aspects of normal daily living. Other medical explanations for chronic fatigue should have been considered and excluded.

Self-management of ME/CFS is broadly along the lines of that for a post-viral fatigue syndrome. There are no drugs that can treat or cure the underlying condition. So medication - prescribed and over the counter - is only used for symptomatic relief of symptoms such as pain.

Management of post-covid ME/CFS will also have to take account of other symptoms that relate to the direct effect of COVID-19 at the time of the initial infection. These symptoms may include involvement of the lungs (breathlessness, chest pain), heart (palpitations), blood-clotting mechanisms, etc. As already noted, management of these problems should be undertaken by health professionals with expertise in these areas and are outside the scope of this guidance.

More information on the diagnosis of ME/CFS can be found on the MEA website:

<https://tinyurl.com/y62rbm6a>

09

RESEARCH INTO WHAT CAUSES POST-VIRAL/COVID-19
FATIGUE AND LONG COVID

Several possible explanations have been put forward to explain the long-term effects after infection caused by COVID-19.

Firstly, those with long-term symptoms might still harbour infectious virus in some reservoir organ – this now seems unlikely.

Secondly, persisting fragments of viral genes, though not infectious, may still be remaining inside cells and triggering an immune system reaction to their presence.

Thirdly, although the virus is cleared, the immune system continues in an overactive state with the on-going production of immune system chemicals called cytokines. As with ME/CFS there is also some research evidence involving the presence of low levels of autoantibodies – which are harmful antibodies that are directed against the body's own tissues. But there is not enough evidence at present to justify the term autoimmune disease in relation to Long covid.

As with ME/CFS there is emerging evidence in COVID-19 to indicate that cytokine-mediated neuroinflammation could be playing a role in the causation of fatigue and other neurological symptoms.

<https://tinyurl.com/4dsphrrz>

Fourthly, there may be the same sort of problem with energy production at a cellular level in parts of skeletal muscle called mitochondria that occurs in ME/CFS. There is now emerging research evidence to indicate that COVID-19 can affect mitochondrial function.

<https://tinyurl.com/ym79td22>

Finally, it should be noted that COVID-19-related damage that is affecting the function of heart, lungs, liver or kidneys is also likely to cause fatigue.

09.1

Research into PVF and PVFS

Several epidemiological studies have looked at the development of fatigue syndromes following an acute viral infection.

An Australian research group followed up 253 people with glandular fever (Epstein Barr virus infection), Q fever (*Coxiella burnetii*) and Ross River Fever (epidemic polyarthritis) in a rural part of Australia at regular intervals over a period of 12 months.

Approximately 12% developed a post-infection fatigue syndrome involving fatigue, cognitive dysfunction, musculoskeletal pain and mood disturbance. The predictability of developing a post-infectious fatigue syndrome was largely determined by the severity of the triggering infection and not by any demographic or psychological factors, or the type of infection that triggered the symptoms.

Reference: <https://tinyurl.com/36pck74m>

During an outbreak of SARS (Severe Acute Respiratory Syndrome - another coronavirus infection) in Toronto during 2002 and 2003, 273 people were diagnosed with the infection, of whom 44 died. After the outbreak ended, Dr Harvey Moldofsky and colleagues at the University of Toronto, studied 22 people, mostly health workers, who had on-going health problems that prevented them from returning to work.

They concluded that there was a chronic post-SARS infection syndrome characterised by persistent fatigue, non-restorative sleep, daytime fatigue, pain and weakness in muscles all over their body, and depression.

Reference: <https://tinyurl.com/an4cscmb>

A second study from Toronto, which reported on one-year outcomes on patients who were hospitalised, reported that survivors of the acute respiratory distress syndrome had persistent and significant functional disability one year after discharge. Most of these patients had extra-pulmonary conditions, with muscle wasting and weakness being most prominent.

Reference: <https://tinyurl.com/44nnp659>

40% of 233 survivors of SARS in Hong Kong were reported to have chronic fatigue after 3 to 4 years. 27% met the CDC criteria for ME/CFS.

Reference: <https://tinyurl.com/faqj96dn>

A large number of research studies both here and abroad are now collecting data from people who are not recovering from COVID-19.

09.2

Assessment of organ damage in people with Long Covid

Lung damage

In some people with Long covid, the lungs may become scarred. The scarring causes stiffness in the lungs, which can make it difficult to breathe and get oxygen to the bloodstream, resulting in long-term breathlessness and difficulty managing daily tasks. This inflammation and scarring of the lungs is called 'interstitial lung disease'.

A new national research study that is centred on Imperial College in London will be investigating the long-term effects of lung inflammation and scarring from COVID-19.

<https://tinyurl.com/yswcbzb7>

Coverscan study of multiple organ impairment

The prospective Coverscan study examined the impact of Long covid (ie persistent symptoms three months post infection) across multiple organs in low risk people who are relatively young and had no major underlying health problems. Assessment was done using results from magnetic resonance imaging scans, blood tests, and online questionnaires.

Initial data from 201 patients suggests that almost 70% had impairments in one or more organs four months after their initial symptoms of SARS-CoV-2 infection.

The study enrolled participants at two UK sites in Oxford and London between April and August 2020. Two hundred and one individuals (mean age 44) completed assessments after SARS-CoV-2 infection a median of 140 days after initial symptoms.

The most commonly reported ongoing symptoms - regardless of hospitalisation status - were fatigue (98%), muscle ache (88%), shortness of breath (87%), and headache (83%). There was evidence of mild organ impairment in the heart (32% of patients), lungs (33%), kidneys (12%), liver (10%), pancreas (17%), and spleen (6%).

Two-thirds (66%) of participants had impairment in one or more organ systems and there was evidence of multi-organ impairment in a quarter (25%) of individuals, with varying degrees of overlap across multiple organs.

According to the researchers the results signal the need for monitoring and follow-up in at least the medium and longer-term, especially for extrapulmonary sequelae and demonstrate that Long covid requires management across clinical specialties.

The authors observed that neither symptoms nor blood investigations were predictive of organ impairment.

<https://tinyurl.com/y9j6422f>

Microvascular thrombosis

In relation to COVID-19 it is possible that microvascular immuno-thrombotic events in the lungs may still be playing a role with a recent research report indicating that D dimer levels remain elevated in some people who remain symptomatic:

<https://tinyurl.com/ptn7emnt>

Immune and endocrine system research

When it comes to laboratory-based research into post COVID-19 we need to look at how the immune system is responding, especially the levels of various cytokines and T cell status (as T cells play a crucial role in anti-viral protection), as well as the hypothalamic-pituitary-adrenal axis in relation to cortisol output.

Key findings (not yet peer reviewed) into immune system dysfunction in COVID-19 and Long covid research at the University of Cambridge has found:

- Individuals who have asymptomatic or mild disease show a robust immune response early on during infection.
- Patients requiring admission to hospital have impaired immune responses and systemic inflammation (that is, chronic inflammation that may affect several organs) from the time of symptom onset.

- Persistent abnormalities in immune cells and a change in the body's inflammatory response may contribute to 'long COVID'.

<https://tinyurl.com/jat43tbb>

09.3

Other Research

The most recent and comprehensive review of all the research studies taking place on an international basis into the pathoaetiology of Long covid, including some of the overlaps with ME/CFS, was published in Nature on 28th April 2021:

<https://tinyurl.com/d4zx3fmw>

Among other interesting research findings to emerge are three case reports in the Annals of Internal Medicine of COVID-19 triggering the autoimmune muscle disease myasthenia gravis:

Reference: <https://tinyurl.com/3yvb7pry>

The MEA Ramsay Research Fund would be very happy to consider research proposals to investigate immune system status in coronavirus infection.

Research into COVID-19 and ME/CFS must now become a two-way process. What we already know about causation and management of ME/CFS is clearly going to be of considerable help to many people with Long covid. At the same time, research into COVID-19 may lead to a much clearer understanding of why some people develop post-viral syndromes and ME/CFS and what role is being played by the body's immune system.

<https://tinyurl.com/2f5wkdwd>

10 FURTHER INFORMATION

10.1 Information and guidance from NHS sources

Royal College of Occupational Therapists: guidance on the management of post-covid syndrome:

<https://tinyurl.com/nmwthyww>

NHS England: guidance on the management of post-covid symptoms, including fatigue. **NB:** The MEA does not agree with some key parts of this guidance on fatigue management. We have written to Professor Stephen Powis at NHS England about our concerns.

<https://tinyurl.com/ysvjsn9d>

NICE: rapid guideline covering Long COVID:

<https://tinyurl.com/t3jetj4>

The MEA believes that this guideline needs significant improvement, especially in relation to the lack of information and guidance on activity and energy management and symptomatic management. We have responded as follows:

<https://tinyurl.com/22anuchh>

NICE guideline on ME/CFS (working draft) This publication contains far more helpful information and guidance on activity and energy management than the rapid NICE guideline on Long covid:

<https://tinyurl.com/aatcs5t3>

10.2 Health professional responses

Among the helpful information from clinicians and researchers is that from Professor Frances Williams at Kings College Hospital, who is carrying out research into post-covid fatigue as part of the Yeo symptom-monitoring App study:

<https://tinyurl.com/ynx2esvh>

BMJ review: Management of post-acute covid-19 in primary care by Professor Trisha Greehalgh:

BMJ 2020; 370 doi: <https://tinyurl.com/yp9fs7v3>

In America, Dr Anthony Fauci, one of the main government advisers from the National Institutes of Health, has stated that some people with post COVID fatigue will go on to develop post COVID ME/CFS:

<https://tinyurl.com/wrmn2cxr>

Second report on Long covid from the NIHR – this is mainly a literature review of important publications relating to Long covid:

<https://tinyurl.com/447tndce>

10.3 Media Responses

Since April 2020, there has been growing interest in the media about the problems faced by people who are not recovering from COVID-19.

The more useful articles are being made available in the news section of the MEA website as we receive them.

This article in The Observer relates to the how previously fit young adults are developing post COVID syndromes:

<https://tinyurl.com/7k7ee2ww>

The media are also now starting to express an interest in the overlap between Long COVID and ME/CFS:

Cosmopolitan magazine:

<https://tinyurl.com/yumdmw88>

Time magazine:

<https://tinyurl.com/2tyj3c2j>

The Doctor – BMA publication:

<https://tinyurl.com/ypj98j6v>

Pharma Technology Focus:

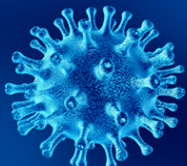
<https://tinyurl.com/ypj98j6v>

10.4

ME Association portfolio of information on COVID-19

The ME Association has a full range of free downloadable leaflets covering all aspects of COVID-19 and ME/CFS:

<https://meassociation.org.uk/covid-19-and-me-cfs/>



The ME Association
7 Apollo Office Court, Radclive Road
Gawcott, Buckinghamshire MK18 4DF
www.meassociation.org.uk

