COVID education for SA GPs

Post-acute COVID-19 syndrome and oral therapies

Presented by:

Dr Emily Kirkpatrick
Executive Lead Quarantine - Community COVID Response Branch
Deputy Chief Medical Officer / Deputy Chief Public Health Officer, SA Health

Dr Renjy Nelson
Infectious Diseases Physician
The Queen Elizabeth Hospital, Royal Adelaide Hospital

Nathan Ward
Principal Physiotherapist, Royal Adelaide Hospital

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SA GP COVID update

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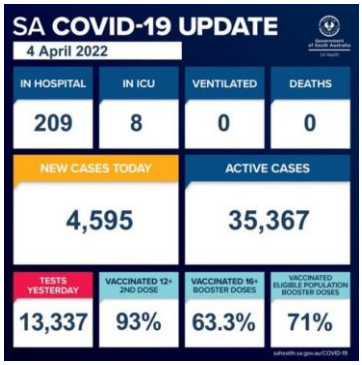
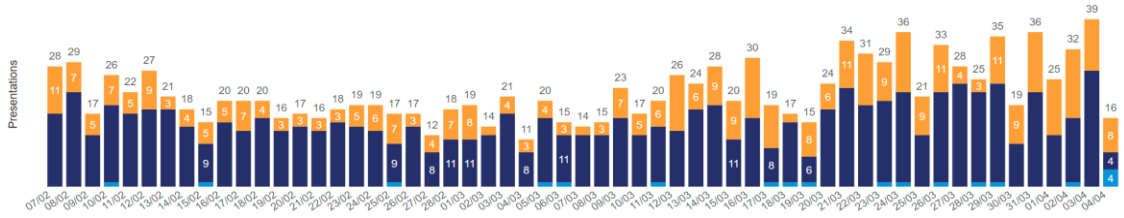
Case Update

- Overall occupancy still moving at ~1% increase on seven-day average
- Increase in ICU (erratic variable)
- CALHN at 40% state-wide admissions
- Very busy weekend for RAH ED, and eight in at 1400 today (04/04/22)
- New cases running to modelling, hence expected occupancy peak still later this week





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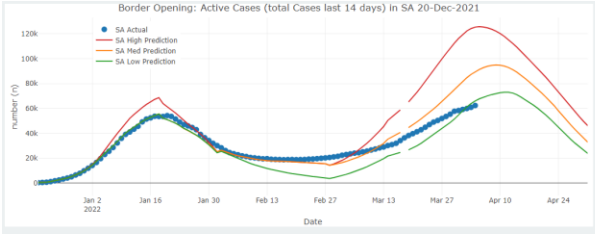

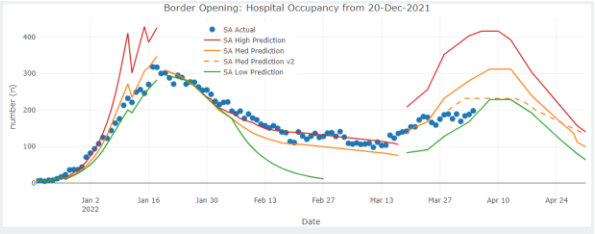

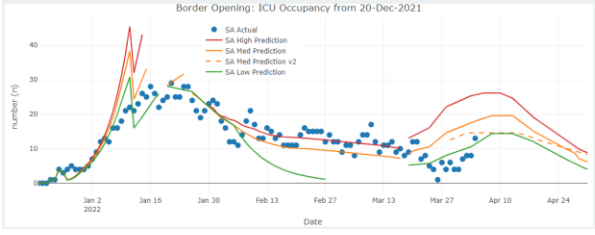

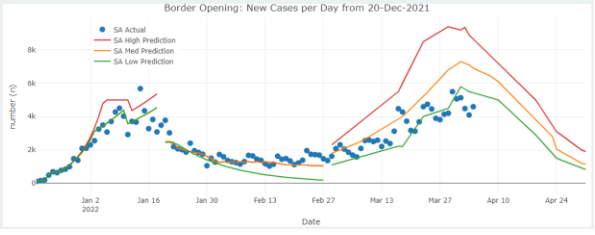

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Exposure risks for GP and private practices

- Ongoing work on close contacts to return to work, noting feedback.
- The matrix detailing exposure risk in primary care was removed from the SA Health website some time ago now. This was to ensure consistency with broader community close contact requirements.
- The close contact definition applies for GP practices. To be considered a close contact, a person must have an exposure for a cumulative period of 4 hours or more in close physical proximity and where masks are not worn.
- Please note that PPE must be worn in accordance with clinical requirements, i.e., N95 and goggles should be worn if conducting aerosol generating procedures.
- For more information on close contact requirements, visit www.sahealth.sa.gov.au/COVIDContacts.

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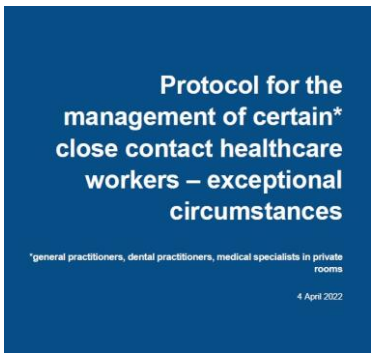
Close contact GPs returning to work

- New policy signed today to all GPs to return to work as CC
- Current pressures on GPs who cannot attend work, especially in regional areas
- Return to work provisions with daily RATs and PPE – days 1 – 7
- Practice manager will need to send details to SA Health
- For more information on close contact requirements, visit www.sahealth.sa.gov.au/COVIDContacts.



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Winter COVID + flu vaccine dose

- Ongoing SA Health clinics
- ATAGI recommends an additional booster dose of COVID-19 vaccine before winter (from April) for selected population groups who are at greatest risk of severe illness from COVID-19 and who have received their primary vaccination and first booster dose.
- These groups are:
  - Adults aged 65 years and older
  - Residents of aged care or disability care facilities
  - People aged 16 years and older with severe immunocompromise (as defined in the ATAGI statement on the use of a 3rd primary dose of COVID-19 vaccine in individuals who are severely immunocompromised)
  - Aboriginal and Torres Strait Islander people aged 50 years and older.

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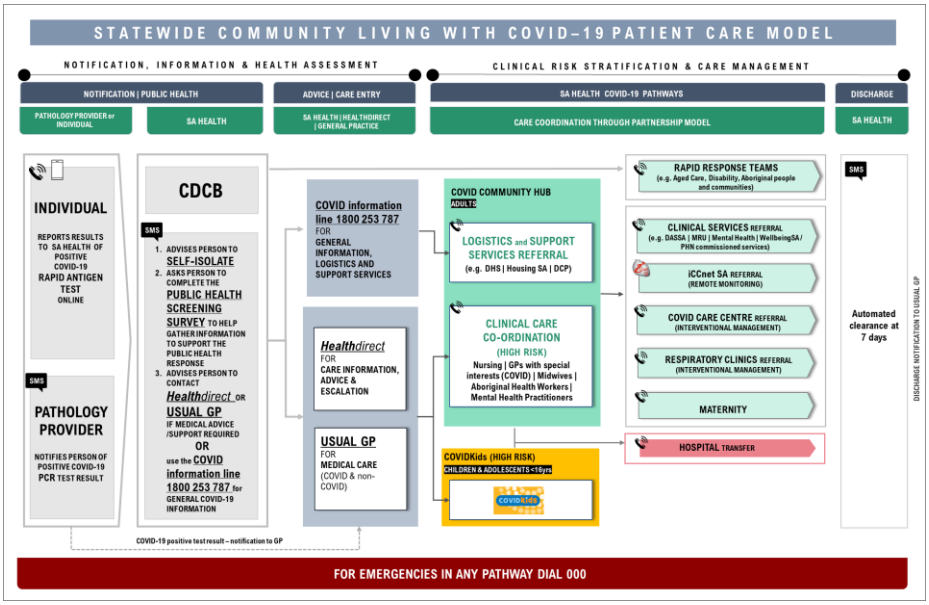
Community living with COVID patient care model

(from 28 March 2022)

KEY FEATURES

- COVID patients access to:
  - ***Health**direct*
  - Usual GP
  - Use the COVID Information line for general COVID queries.
- CDCB to refer vulnerable groups (ie. aged care, disability, Aboriginal people and communities) to Rapid Response Teams
- High Risk COVID patient escalation pathway:
  - **ADULTS:** COVID Community Hub
  - **CHILDREN & ADOLESCENTS:** COVIDKids
- **COVID Community Hub** for adults (high risk) with access to:
  - Logistics support services
  - Clinical care coordination
  - Referral pathways
- **Escalation pathways** to:
  - **Hospitals** (for adults, children and adolescents and pregnant women)
- **Automated clearance** at 7 days (via SMS).



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COVID Virtual Home Monitoring - iCCnet

A tool to help manage COVID positive patients at home

What can iCCnet offer you:

- Daily home monitoring of your patient
- Daily phone calls from iCCnet nurses
- For use when you are concerned about patients at higher risk for deterioration
- Advice to you, or GPAT, if the patient requires further assessment and care
- Through a direct referral from you to iCCnet
- Available in metropolitan and regional South Australia
- Builds off successful models for chronic disease implemented in previously in country South Australia.

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GP Referrals - iCCnet

Target Patient Groups

On treatments that increase risk of severe illness:

- immune suppressive therapy, chemotherapy, radiotherapy, immunotherapy, bone marrow transplant.

Patients with co-morbidities:

- cancer
- primary or acquired immunodeficiency
- chronic renal failure
- chronic lung disease
- heart disease
- Diabetes (particularly insulin dependent)
- chronic liver disease
- neurological conditions
- severe mental health conditions
- severe obesity (BMI ≥ 40 kg/m2)
- poorly controlled blood pressure.

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Monitoring kits

Equipment:

- NoninConnect Elite 3240 pulse oximeter
- A&D Medical UA-651BLE Blood Pressure Monitor
- A&D Medical NT22B Infrared thermometer
- Samsung Galaxy Tab A7 SM-T505
- Samsung fast charger.

Instructions:

- Rural COVID-19 interview instructions
- Kit identification card
- iCCnet contact details card.

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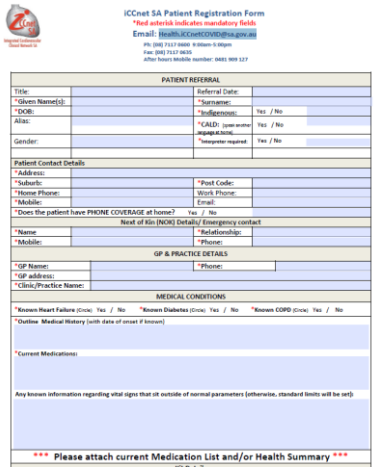
GP referral process

- You can email iCCnet (using the Referral Form) to request a monitoring kit for your patient
- When the kit arrives at the patient's isolation address, iCCnet Covid support scientists will undertake an installation interview and provide any support required.
- Patient monitoring will be undertaken for 7-10 days depending on clinical condition.

iCCnet Contacts:

- **You can call the iCCnet On Call Nurse Consultant on 0421 878 779 for urgent referrals and enquiries.**
- **For non-urgent enquiries can SMS the above number for a return call during office hours, or email Health.iCCnetCOVIDNURSES@sa.gov.au.**



iCCnet SA Patient Registration Form

*Red asterisk indicates mandatory fields

Email: Health.iCCnetCOVID@sa.gov.au

PATIENT REFERRAL

Title:		Referral Date:	
*Given Name(s):		*Surname:	
*DOB:		*Indigenous:	Yes / No
Alias:		*CALD: (speak another language at home)	Yes / No
Gender:		*Interpreter required:	Yes / No

Patient Contact Details

*Address:			
*Suburb:		*Post Code:	
*Home Phone:		Work Phone:	
*Mobile:		Email:	

*Does the patient have PHONE COVERAGE at home? Yes / No

Next of Kin (NOK) Details/ Emergency contact

*Name		*Relationship:	
*Mobile:		*Phone:	

GP & PRACTICE DETAILS

*GP Name:		*Phone:	
*GP address:			
*Clinic/Practice Name:			

MEDICAL CONDITIONS

*Known Heart Failure (Circle) Yes / No *Known Diabetes (Circle) Yes / No *Known COPD (Circle) Yes / No

*Outline Medical History (with date of onset if known)

*Current Medications:

Any known information regarding vital signs that sit outside of normal parameters (otherwise, standard limits will be set):

*** Please attach current Medication List and/or Health Summary ***

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Long COVID program

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Epidemiology

- Natural history, clinical course and consequences of this new disease - still not completely understood
- Most patients with COVID-19 return to baseline after acute infection with SARS-CoV-2
- Published literature -10 – 35% of COVID-19 patients - lingering symptoms for weeks to months following acute SARS-CoV-2 infection (Office of National Statistics in the United Kingdom - 13.7%)
- More than 18M people worldwide - living with Long COVID

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Burden

- 10-35% patients can experience prolonged symptoms
- Questionnaire at 60 days
- Median age 62 years
- Only 18 (12.6%) were completely free of any COVID-19–related symptom
- 32% had 1 or 2 symptoms and 55% had 3 or more.
- 44.1% - worse QoL, fatigue (53.1%), dyspnea (43.4%), joint pain (27.3%) and chest pain (21.7%).

COVID Symptom Study. How long does COVID-19 last? Kings College London, 2020. https://covid19.joinzoe.com/post/covid-long-term?fbclid=IwAR1RxIcmmdL-EFjh_aI-.
Sheehy LM. Considerations for postacute rehabilitation for survivors of COVID-19. JMIR Public Health Surveill 2020;6
Tenforde MW, Kim SS, Lindsell CJ, etalIVY Network InvestigatorsCDC COVID-19 Response TeamIVY Network Investigators. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network — United States, March-June 2020. MMWR Morb Mortal Wkly Rep 2020;69:993-8
Carfì A, Bernabei R, Landi F, Group ftGAC-P-ACS. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020.
Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395:1054-62

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- Patients with severe disease –

	Post COVID	Pre-COVID	
Dyspnoea	113 /152 (74%)* (IQR 0-5)	47/152 (31%) (IQR 0-1)	P < 0.001
Physical Health	43.8 (SD 9.3) #	54.3 (SD 9.3)	P < 0.001
Mental Health	43.7 (SD 9.3) #	54.3 (SD 7.8)	P < 0,001

PROMIS Global Health-10 and PROMIS Dyspnoea Characteristics
*Median score 3/10
Normal US score >50

- 52/148 (35.1%) patients without pre-COVID oxygen requirements - home O2 after hospital discharge; 20/148 (13.5%) reported still using oxygen at 6 weeks.

Weerahandi, H. *et al.* Preprint at medRxiv https://doi.org/10.1101/2020.08.11.20172742 (2020).

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- *Heightman et al.* - service evaluation of the first 12-month experience of the first UK dedicated post-COVID clinic in the United Kingdom. Analysis limited to healthcare utilization (e.g., diagnostic tests) of
- 1325 assessed individuals
  - similar rates of onward specialist referrals between non-hospitalized and hospitalized patients and
  - incapacity of 50% of the cohort to return to work full-time at their first assessment.

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Post COVID-19 condition occurs in individuals with **a history of probable or confirmed SARS-CoV-2** infection, **usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.** Common symptoms include **fatigue, shortness of breath, cognitive dysfunction** but also others* and generally have an **impact on everyday functioning.** Symptoms may be **new onset** following initial recovery from an acute COVID-19 episode or **persist** from the initial illness. Symptoms may also **fluctuate** or **relapse** over time.

A separate definition may be applicable for children.

Notes:
There is no minimal number of symptoms required for the diagnosis; though symptoms involving different organs systems and clusters have been described.
*A full list of described symptoms included in the surveys can be found in Annexes 2 .

Definitions:
Fluctuate – a change from time to time in quantity or quality.
Relapse – return of disease manifestations after period of improvement.
Cluster – two or more symptoms that are related to each other and that occur together. They are composed of stable groups of symptoms, are relatively independent of other clusters, and may reveal specific underlying dimensions of symptoms *(32)*.

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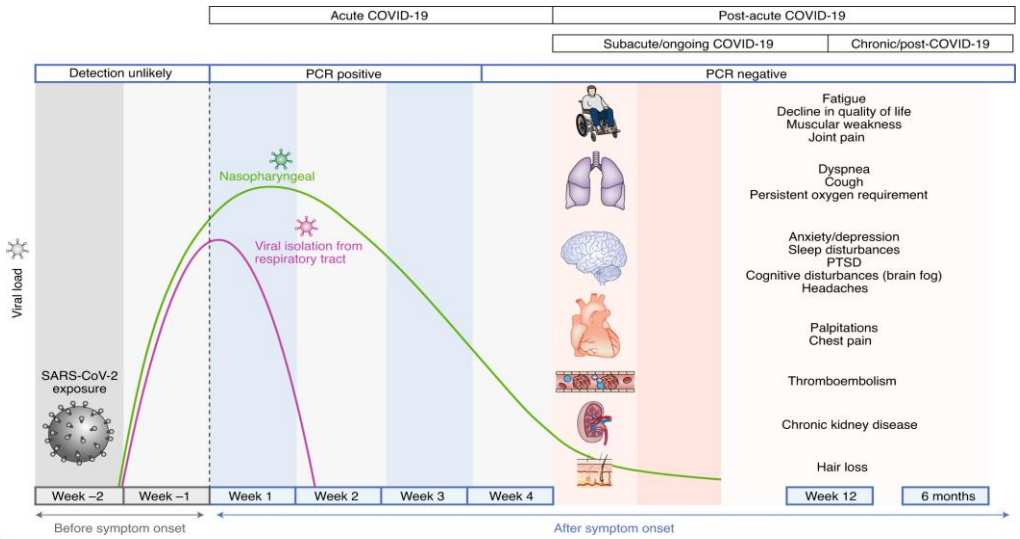
Complications post-acute COVID-19



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***Panel:* Conditions experienced by members of the UK doctors #longcovid group**

- Myocarditis or pericarditis
- Microvascular angina
- Cardiac arrhythmias, including atrial flutter and atrial fibrillation
- Dysautonomia, including postural orthostatic tachycardia syndrome
- Mast cell activation syndrome
- Interstitial lung disease
- Thromboembolic disease (pulmonary emboli or cerebral venous thrombosis)
- Myelopathy, neuropathy, and neurocognitive disorders
- Renal impairment
- New-onset diabetes and thyroiditis
- Hepatitis and abnormal liver enzymes
- New-onset allergies and anaphylaxis
- Dysphonia

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Pathogenesis

- Sustained inflammation detectable for at least eight months following initial infection, particularly in unvaccinated patients (30% of patients from ADAPT study
- No data as to whether different variants like Omicron cause the same changes, or what role vaccination may play in reducing the risk of developing long COVID.

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- Persistently elevated levels of Type I and Type III interferons that stimulate T cells present for longer than 6 months
- More than 400 genes differentially expressed in those convalescent individuals referred to a long COVID clinic compared to those convalescents who were not.
- Strong downregulation of platelet and megakaryocyte gene sets among individuals referred to a long COVID clinic with fatigue. Consistent with other data, reports of thrombocytopenia
- Lower gas exchange (Tlco) despite normal CT scans using Hyperpolarized Xenon Magnetic Resonance Imaging (Hp-XeMRI) and PFT.
- Present many months after the initial infection

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Conditions associated with Long COVID syndrome

- **Pulmonary symptoms**
  - Shortness of breath
  - Cough
- **Cardiac symptoms**
  - Chest pain
- **Neurological symptoms**
  - Fatigue
  - Headache
  - Cognitive dysfunction
  - Sleep disturbance
  - Loss of smell
  - Paraesthesia
- **Renal disease Thromboembolism**

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- **Psychological symptoms**
  - Anxiety
  - Depression
  - Mood swings
  - Note that fatigue and sleep disturbance may also indicate the emergence of a mental health condition
- **Musculoskeletal symptoms**
  - Non-specific pain
  - Myalgia
- **Fever**
  - Low grade fevers
- **Reduced activity and functional level**
- **Reduced nutritional status and weight loss**

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		Number of Subjects	Percent of subjects
General	Referred to long COVID clinic	21	30.4
	Any reported symptoms?	33	57.9
Non-specific	Fatigue	23	40.4
	Dyspnoea	20	35.1
	Decreased muscle strength	19	33.3
	Worsened sleep quality	16	28.1
	Palpitations	4	7.0
	Dizziness	4	7.0
	Hair loss	6	10.5
Neuropsychiatric	Anxiety/depression	14	24.6
	Worsened memory/concentration	20	35.1
Pain	Headache	10	17.5
	Chest pain	7	12.3
	Joint pain	6	10.5
	Myalgia	6	10.5
Oral/pharyngeal	Worsened sense of smell/taste	11	19.3
	Difficulty swallowing /sore throat	5	8.8
Gastrointestinal	Diarrhoea	4	7.0
	Nausea	3	5.3
	Vomiting	1	1.8

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Healthcare professionals and medical specialties included in care models

- Pulmonary/respiratory specialists (100%)
- Cardiovascular specialists (92%)
- Psychiatry and psychology (83%),
- Physiotherapy (83%),
- Occupational therapy (75%),
- Social work (75%),
- Neurology specialists (75%),
- Primary care physicians (58%)
- Nutrition (58%)
- Speech and language therapists (50%)

Health care professionals / Authors	Santosh	Parkin	Gutenbrunner	Siso-Almirall	Brigham	Ladds	Singh	Pinto	Sivan	Nalbandian	NHS	Heightman	Total N (%)
Pulmonary/Respiratory	■	■	■	■	■	■	■		■	■	■		12 (100)
Cardiovascular	■	■	■	■	■	■	■		■	■	■		11 (92)
Psychiatry/Psychology	■	■		■	■	■	■	■	■		■		10 (83)
Physiotherapy	■	■	■	■	■		■	■	■		■		10 (83)
Occupational therapy	■	■	■	■	■	■	■		■		■		9 (75)
Social work	■		■	■	■	■	■		■	■	■		9 (75)
Neurology	■	■		■	■	■	■	■		■	■		9 (75)
Primary care	■	■			■	■			■	■	■		7 (58)
Nutrition		■	■		■	■	■		■	■	■		7 (58)
Speech and Language therapy team		■	■		■		■		■		■		6 (50)
Nursing		■	■		■				■		■		5 (42)
Hepatology	■				■	■				■			4 (33)
Otolaryngology	■				■	■					■	■	4 (33)
Dermatology	■				■	■					■		4 (33)
Neuropsychiatry			■						■	■			3 (25)
Hematology	■				■					■			3 (25)
Nephrology	■				■					■			3 (25)
Pharmacy	■				■						■		3 (25)
Endocrinology / Metabolism						■				■	■		3 (25)
Infectious disease	■				■						■		3 (25)
Rehabilitation Medicine		■	■	■									3 (25)
Gastroenterology										■	■		2 (17)
Rheumatology						■					■		2 (17)
Immunology						■				■			2 (17)
Pediatrics										■	■		2 (17)
Geriatrics	■												1 (8)
Integrative medicine	■												1 (8)
Emergency medicine	■												1 (8)
Pathway coordinators		■											1 (8)
Radiology					■								1 (8)
Community health													1 (8)
Telemedicine					■								1 (8)
Intensive care									■				1 (8)

Screenshot

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The team (TQEH and RAH)

- Rheumatologist
- Immunologist
- Respiratory Physician
- Cardiologist
- Psychiatrist
- Neurologist
- Neuropsychologist
- Psychologist
- General Physician (MACS Clinic)
- Renal Physician
- Ear Nose Throat Surgeon
- Rehabilitation Physician
- Occupational therapist and physiotherapist Exercise physiologist
- Specialist Nurse – Clinical liaison
- *Social Worker*
- Infectious Diseases
- *Dermatologist*

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The Team (TQEH and RAH)

- *Dr Andrew Beckwith Psychiatry*
- *Dr Cathy Short Neurology*
- *Neurology Nurse Practitioner – Judy Deimel*
- *Neuropsychology – Suzanna Hackett, Rochelle Whelan*
- *Psychology - Anne Burke*
- *Dr Aneas Yeo Respiratory Medicine*
- *Dr Anil Roy Respiratory Medicine*
- *Dr Pravin Hissaria Immunology*
- *Dr Sam Whittle Rheumatology*
- *Dr Genevive Gabb General Medicine*
- *Dr Rami Tadros General Medicine*
- *Dr Sepehr Shakib General Medicine*
- *Dr Angela Molga General Medicine*
- *Dr Nicholas Farinola General Medicine*
- *Dr Tam Le Cong General Medicine*
- *Dr John Beltrame Cardiology*
- *Dr Alicia Chan Cardiology*
- *Dr Michael Stokes Cardiology*
- *Dr Renjy Nelson Infectious Diseases*
- *Physiotherapy and Exercise Physiology– Linda Nimmo, Briana Bates, Nathan Ward*
- *Occupational therapy*
- *Speech therapist, Dietician*
- *Dr Anupam Dutta-Gupta Rehab physician*
- *Pain Specialists – Dr Tim Semple, Dr Irina Hollington*
- *Haematologists – Dr Yvonne Brennam and Dr Chee Wee Tan*
- *Nurse – Robyn Pumpa*

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Holistic care

- Clinical assessment
- Investigations
- Managing comorbidities
- Medical management
- Self-management
- Social, financial and cultural support - where possible
- Mental health

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- Refer to RAH as “Long COVID”
- Referral form will be emailed soon

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Inclusion criteria	Yes	No
≥ 18 years of age and symptoms ≥ 12 weeks from acute infection and lasting ≥ 8 weeks		
New onset or persisting dyspnoea		
New onset or persisting cough		
New onset or persisting musculoskeletal pain		
New onset or persisting fatigue		
New onset or persisting neurological symptoms		
New onset or persisting psychological symptoms or mental health issues		
Anosmia or olfactory disorder		
Any new symptom/condition with no other explanation and thought to be linked to acute COVID infection		

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Urgent – discuss with Triage Nurse (may need direct referral to specialist)	Yes	No
Oxygen desaturation or signs of severe lung disease		
Syncope		
Palpitations or arrhythmias		
Cardiac chest pain		
Suspected VTE		
Risk of suicide		

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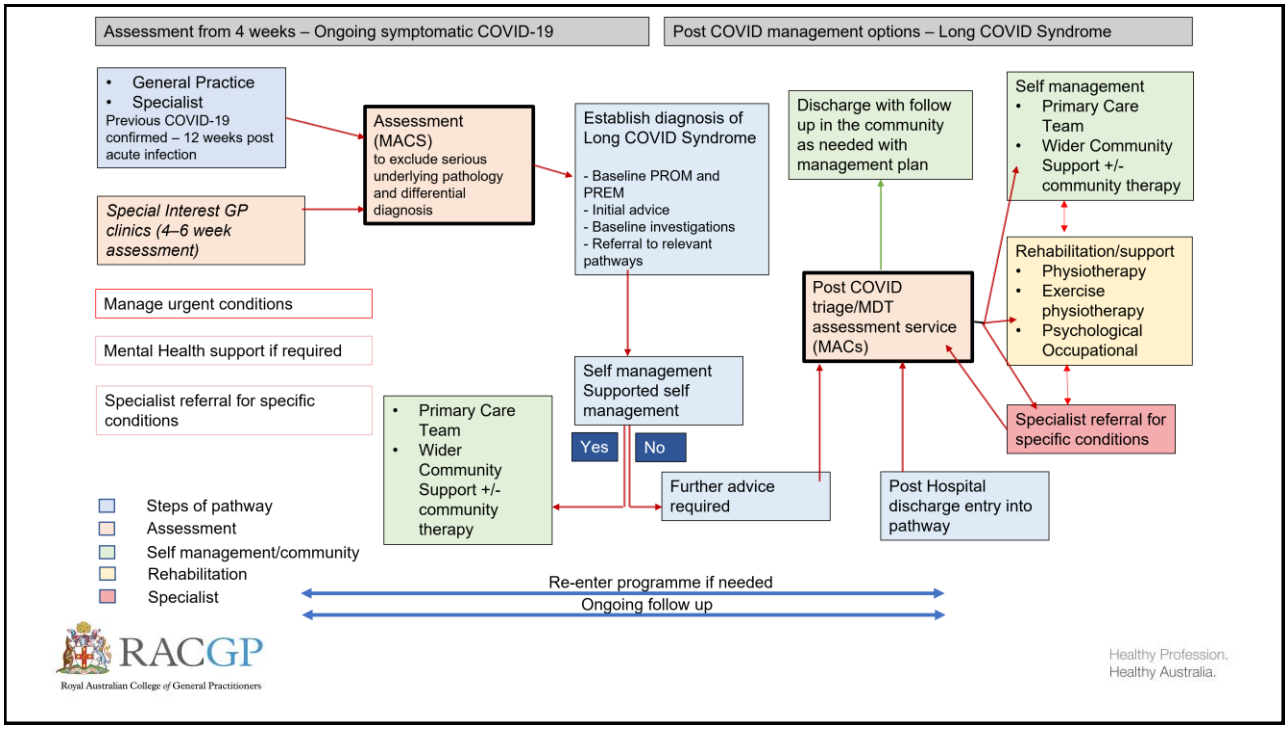
Assessment from 4 weeks – Ongoing symptomatic COVID-19
Post COVID management options – Long COVID Syndrome
• General Practice
• Specialist
Previous COVID-19 confirmed – 12 weeks post acute infection
Special Interest GP clinics (4–6 week assessment)
Assessment (MACS) to exclude serious underlying pathology and differential diagnosis
Establish diagnosis of Long COVID Syndrome
- Baseline PROM and PREM
- Initial advice
- Baseline investigations
- Referral to relevant pathways
Discharge with follow up in the community as needed with management plan
Self management
• Primary Care Team
• Wider Community Support +/- community therapy
Rehabilitation/support
• Physiotherapy
• Exercise physiotherapy
• Psychological Occupational
Post COVID triage/MDT assessment service (MACs)
Specialist referral for specific conditions
Manage urgent conditions
Mental Health support if required
Specialist referral for specific conditions
Self management Supported self management
Yes
No
• Primary Care Team
• Wider Community Support +/- community therapy
Further advice required
Post Hospital discharge entry into pathway
Steps of pathway
Assessment
Self management/community
Rehabilitation
Specialist
Re-enter programme if needed
Ongoing follow up
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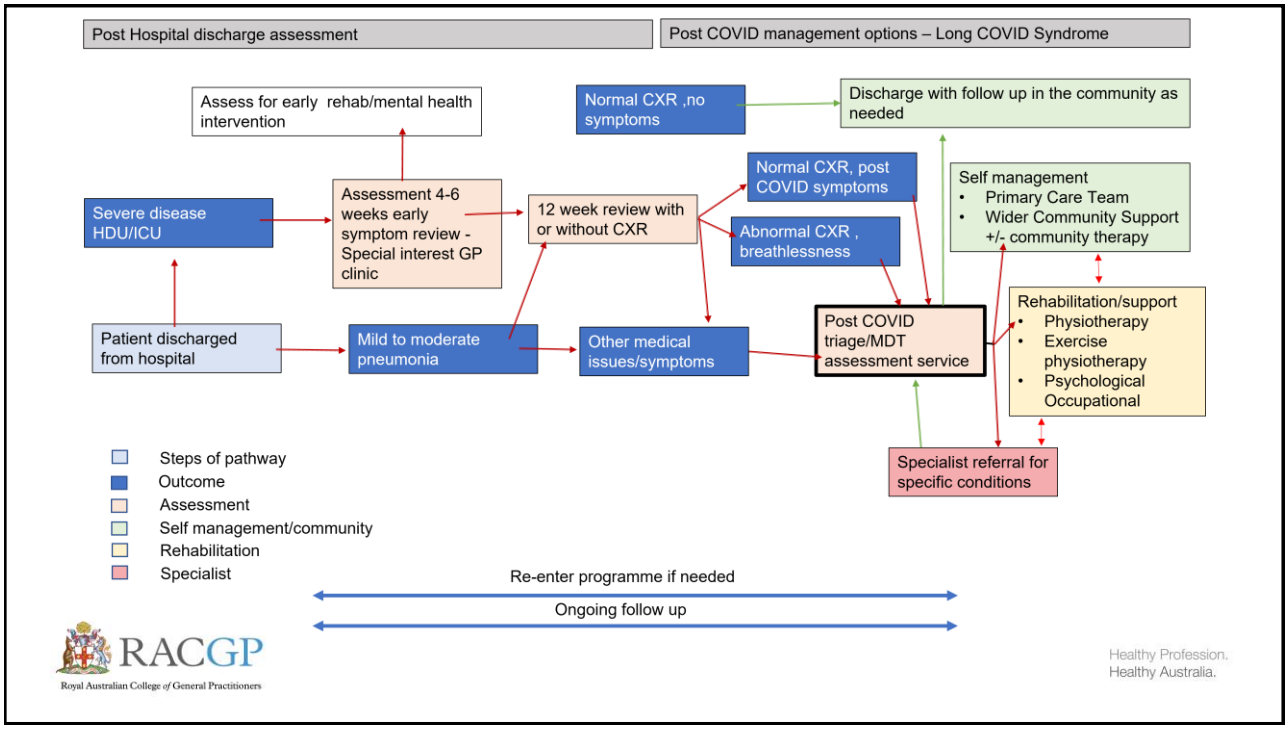
Post Hospital discharge assessment
Post COVID management options – Long COVID Syndrome
Assess for early rehab/mental health intervention
Normal CXR ,no symptoms
Discharge with follow up in the community as needed
Severe disease HDU/ICU
Assessment 4-6 weeks early symptom review - Special interest GP clinic
12 week review with or without CXR
Normal CXR, post COVID symptoms
Abnormal CXR , breathlessness
Self management
• Primary Care Team
• Wider Community Support +/- community therapy
Patient discharged from hospital
Mild to moderate pneumonia
Other medical issues/symptoms
Post COVID triage/MDT assessment service
Rehabilitation/support
• Physiotherapy
• Exercise physiotherapy
• Psychological Occupational
Specialist referral for specific conditions
Steps of pathway
Outcome
Assessment
Self management/community
Rehabilitation
Specialist
Re-enter programme if needed
Ongoing follow up
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Baseline assessment

- History of acute COVID-19 (suspected or confirmed)
- Nature and severity of previous and current symptoms
- Timing and duration of symptoms since the start of acute COVID-19
- History of other health conditions
- Exacerbation of pre-existing conditions.

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Criteria

- COVID-19 confirmation
  - Symptoms and PCR/RAT positive/laboratory notification of result
  - ~~*COVID serology test if no previous confirmed swab and unvaccinated (will need discussion with Long COVID clinic)*~~

- Check the current symptoms and ask the person about their concerns, functioning and wishes in terms of their needs.
- Assess whether the current symptoms are likely to be related to acute COVID-19.
- Assess whether the symptoms may be related to, or are exacerbated by, comorbid conditions

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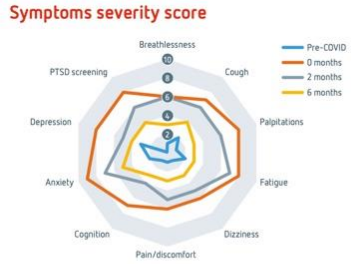
Fig 1. Digital display of C19-YRS scores on the application



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	Before COVID	Now	Total Score
Symptom severity			
1. Breathlessness	0	6	39/100
2. Cough / Voice Change / Noisy Breathing	0	0	
3. Swallowing / Nutrition	0	0	
4. Fatigue	0	9	
5. Continence	0	0	
6. Pain / Discomfort	2	5	
7. Cognition	0	6	
8. Anxiety	2	4	
9. Depression	1	7	
10. PTSD Screen	0	2	
Functional disability			
11. Communication	0	4	25/50
12. Mobility	0	3	
13. Personal-Care	0	4	
14. Other activities of daily living	0	6	
15. Social Role	0	8	
Overall health			
16. Overall Health	8	3	3/10
Other Symptoms			
Rate the severity of any Dizziness you've encountered	-	6	
Rate the severity of any Palpitations you've encountered	-	7	
Rate the severity of any Weakness you've encountered	-	2	
Rate the severity of any Sleep Problems you've encountered	-	7	
Rate the severity of any Fevers you've encountered	-	0	
Rate the severity of any Skin Rash you've encountered	-	0	

Overview

	Before COVID	Now	
Symptom severity (out of 100)	5	39	
Functional disability (out of 50)			
Overall health (out of 10)			

Screenshot

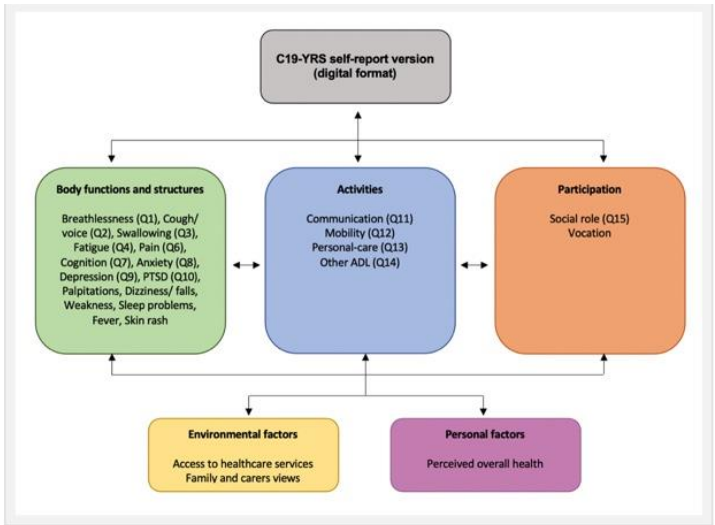

Fig 3. Mapping of the C19-YRS tool onto ICF framework

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Objectives

- A coordination unit to centrally receive referrals from both hospitalized and community-based patients
- Access to medical specialty clinics for advanced testing and diagnoses.
- Integrated local organization of multidisciplinary rehabilitation teams
- Training/liaising with primary care teams (Critical and central to integrated care model) to screen and support medical needs

These four elements can work as a network putting the needs of each person living with Long COVID at the center.

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Summary

- When investigating new symptoms or decline in organ function in patients, consider the possibility of Post COVID syndrome as a cause eg; cognitive decline
- Rule out organic eg; PE, MI, stroke, etc. Consider the possibility of association with recent COVID infection
- Fluctuating symptoms
- Don't attempt to predict likelihood of Long COVID using risk factors, cluster of symptoms or severity of symptoms or hospitalisation
- Avoid dismissing symptoms – anxiety, 'in your head', not coping

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- Assessment cannot be ‘one size fits all’ – tailored investigations
- Need for 4-6 week assessment for all patients
- Consider supported self-monitoring at home, through shared decision making as part of the person’s assessment. Eg; heart rate, blood pressure, pulse oximetry or symptom diaries
- Encourage patients to keep a record of, or use a tracking app to monitor, their goals, recovery and any changes in their symptoms
- Look for ‘Red flags’
- Refer to **“Long COVID clinic”** at CALHN (referral to be sent to RAH)

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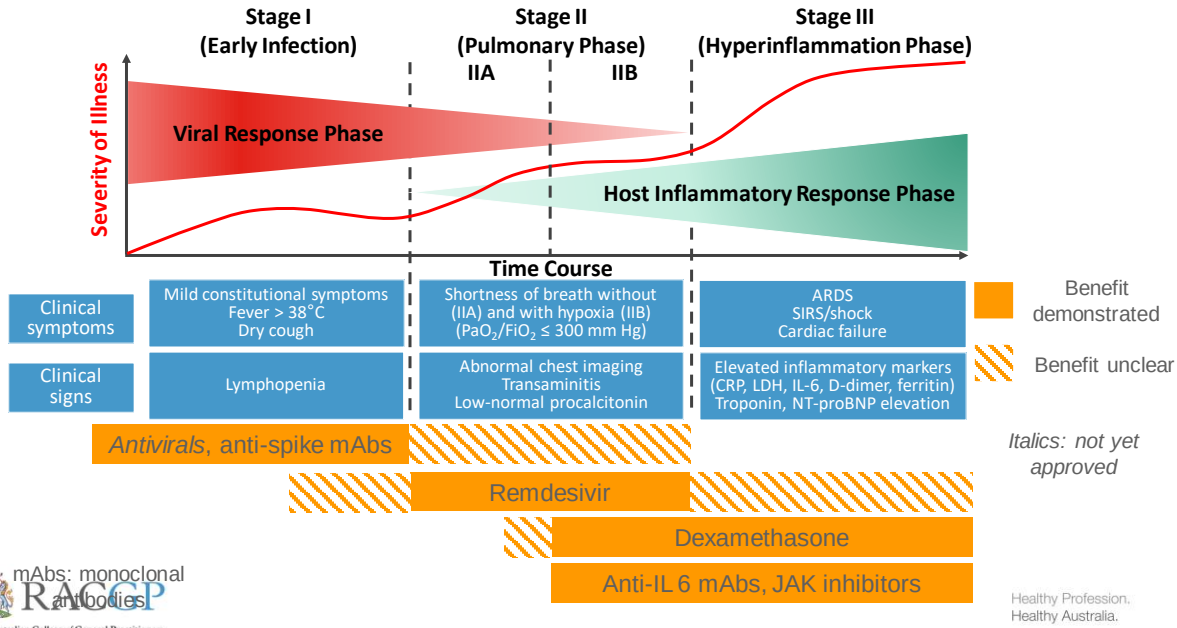

mAbs: monoclonal antibodies

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Adapted from Siddiqi. J Heart Lung Transplant. 2020;39:405.

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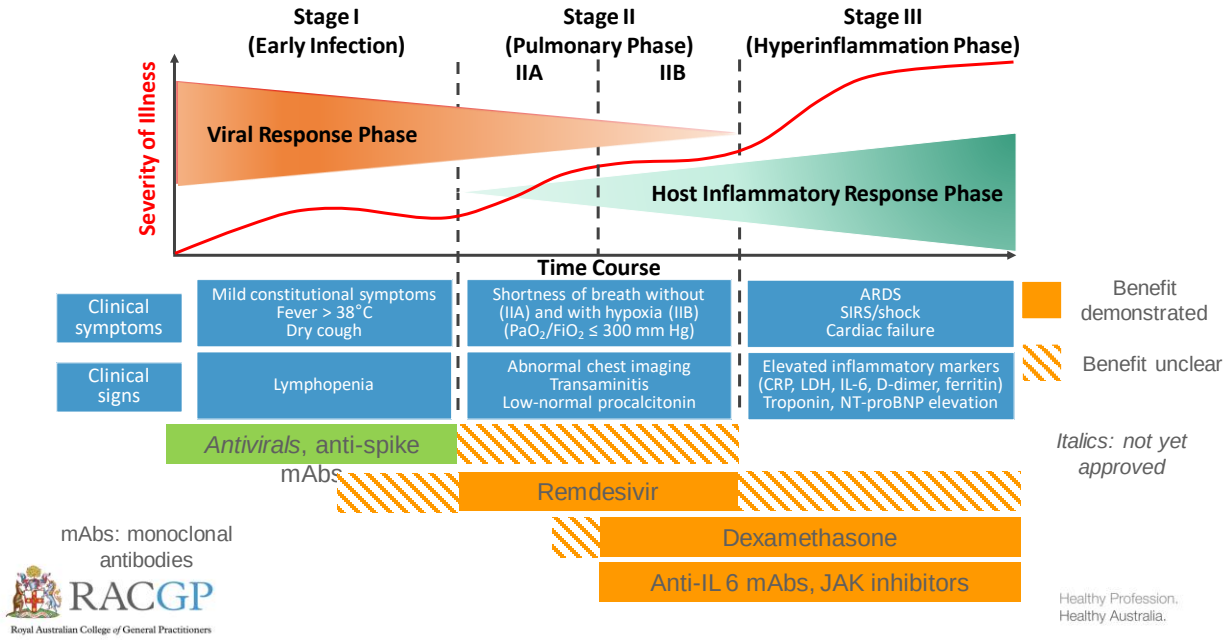

Adapted from Siddiqi. J Heart Lung Transplant. 2020;39:405.

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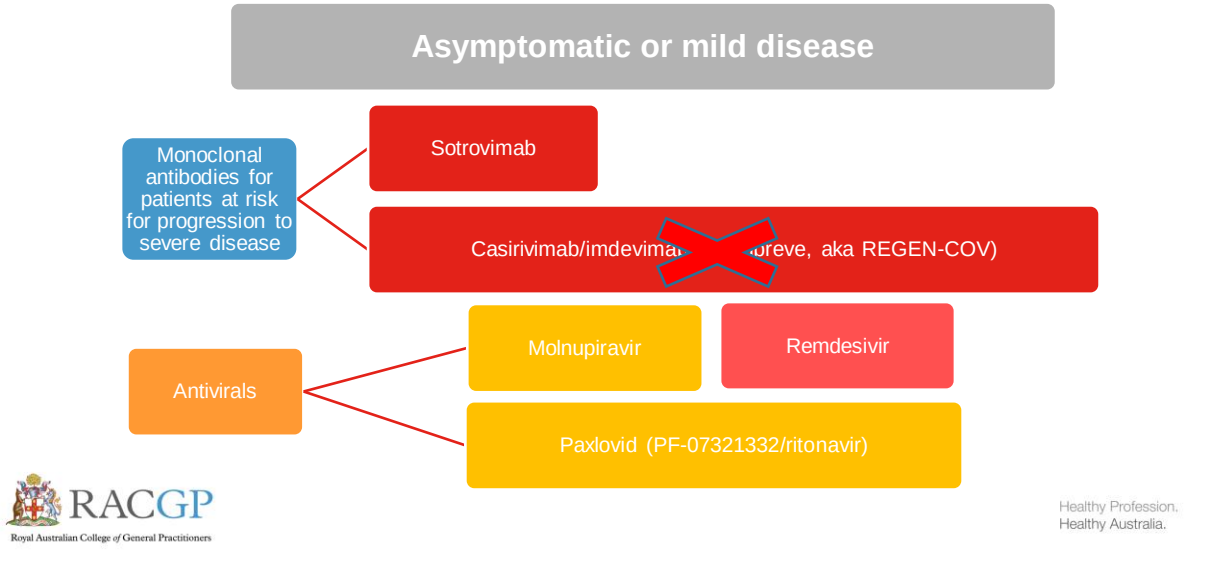
Early infection (Viral phase)



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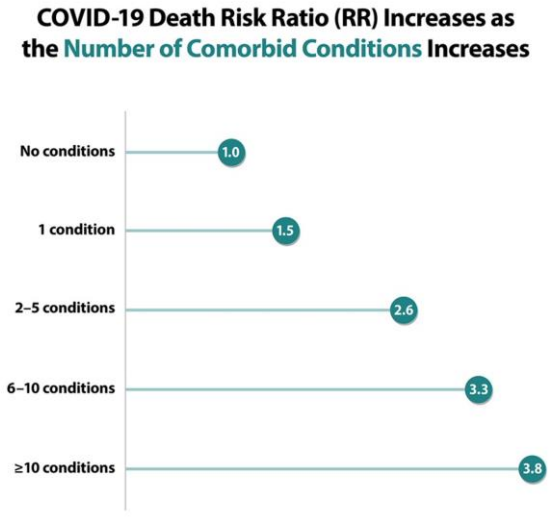
Treatment



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Factors to determine who may be at highest risk for progression

- Age- older → younger
- Vaccination status –
  - unvaccinated or unable to mount a response vaccinated → Vaccinated
- Immune status –
  - severely immunocompromised → immunocompetent
- Clinical factors –
  - obesity, diabetes mellitus, heart failure, etc → no risk factors

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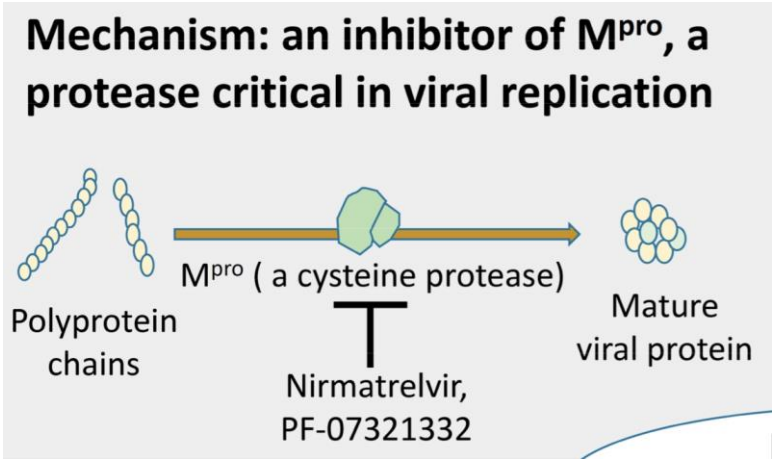
Paxlovid (Nirmatrelvir/ritonavir)



Main protease (Mpro, also referred to as 3CLpro) required to cleave viral polyprotein into functional proteins

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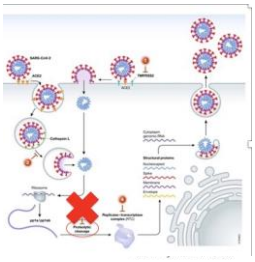
Paxlovid (nirmatrelvir + ritonavir)



Oral antiviral, protease inhibitor (PF-07321332) with ritonavir

- Broad activity against all (!) coronaviruses including SARS-CoV-1, MERS, 'common cold' coronaviruses

EPIC-HR phase 2/3

- International randomised, double-blinded, placebo controlled; n = 1219
- Non-hospitalised adults with mild-moderate COVID-19, randomised within 5 days of symptom onset
- Hospitalisation or death reduced by 89% if given within **3 days** (0.8% vs 7%, p<0.0001)
  - If given with 5 days results were similar (1% vs 6.7%)
- No deaths in treatment group (10 in placebo group)
- Dose (2 tab of 150mg nirmatrelvir, 1 tab ritonavir 100mg), BD for 5 days

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- Hepatic Impairment
  - No dosage adjustment needed for mild or moderate hepatic impairment.
  - **Not recommended for severe hepatic impairment (Child-Pugh Class C), PaxlovidTM** due to lack of pharmacokinetic and safety data for nirmatrelvir or ritonavir in that population.
- Pregnancy and Lactation
  - No available clinical data on PaxlovidTM in pregnancy or with breast feeding.
  - In animal studies, reduced fetal body weights were seen at ~10X the nirmatrelvir exposure seen in humans with the authorized dose; no other adverse developmental effects were seen.
- Pediatrics
  - No available clinical data for PaxlovidTM in children.
  - The authorized adult dose is expected to result in comparable serum exposures in patients 12 years of age and older and weighing at least 40 kg.

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eGFR*	PAXLOVID™ Dose
Greater than 60 mL/min (normal renal function or mild renal impairment)	300 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
≥30 to ≤60 mL/min (moderate renal impairment)	150 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
<30mL/min (severe renal impairment)	PAXLOVID™ is not recommended (the appropriate dose has not been determined)

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As a healthcare provider, you should:

- Inform patients that PaxlovidTM may interact with some drugs and is contraindicated for use with some drugs
- Obtain a complete medication list from your patient (including nonprescription drugs and herbals)
- Check for clinically significant drug interactions:
  - https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug- interactions/
  - Based on the drug interactions, decide if:
  - PaxlovidTM use is appropriate versus an alternative authorized treatment

If appropriate, whether your patient should hold, change, or dose-reduce other medications while taking PaxlovidTM, or if additional monitoring may be needed

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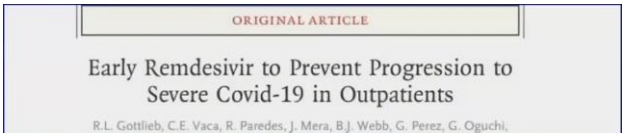
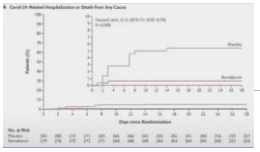
Remdesivir

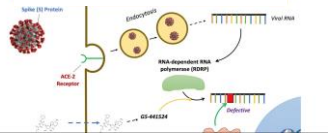

ORIGINAL ARTICLE

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi,

- Phase 3 study of remdesivir for non-hospitalised high-risk individuals with COVID-19
  - Randomised, double-blinded placebo controlled
  - n = 584 (stopped early due to slow enrollment)
  - 3 days of IV remdesivir within 7 days of symptom onset
  - At 28 days, hospitalisation or death reduced by 87% (0.7% vs 5.3%); HR 0.13 (95% CI 0.03 – 0.59)
  - Any COVID-19 related medical visit or death reduced by 81% (1.6% vs 8.3%); HR 0.19 (95% CI 0.07- 0.56)
  - No deaths in either group





Acts as a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses including SARS-CoV-2.

Incorporated by the RdRp into the growing RNA product and allows for addition of three more nucleotides before RNA synthesis stalls

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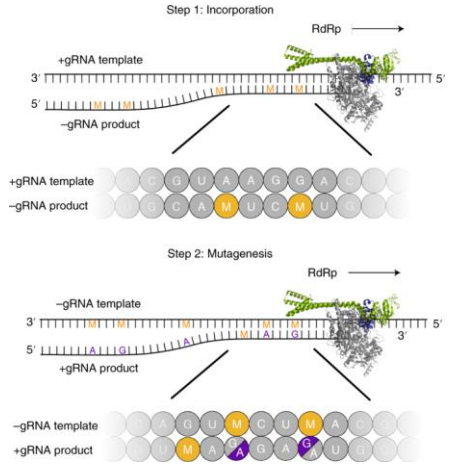
Molnupiravir



Inhibits SARS-CoV-2 by incorporating into RNA-dependent RNA polymerase (RDRP) → pairs ambiguously with nucleobases causing mutation and 'error catastrophe'

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Molnupiravir

Oral antiviral, nucleoside analogue

- Broad activity against many coronaviruses (including SARS-CoV-1, MERS)

MOVe-OUT trial: phase 3 study

- International randomised, double-blinded placebo-controlled trial; n = 750
- Non-hospitalised adults (no pregnant women) with at least one risk factor for progression to severe disease
- Onset of mild-moderate COVID-19 within 5 days of randomisation
- Hospitalisation or death reduced by 30%
- No deaths in treatment group
- 800mg (4 pills) BD for 5 days

Mutagenesis in mammalian DNA?

- Some evidence with prolonged exposure (e.g. 30 days), significance unclear

https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/

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- **MOV is not authorized for use in patients < 18 years of age** – May affect bone and cartilage growth
- MOV may be used regardless of COVID-19 vaccination status
- No drug interactions have been identified based on the limited available data
- No dosage adjustment is recommended in patients with any degree of renal or hepatic impairment

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- **MOV is not recommended for use during pregnancy**
  – Based on animal data, MOV may cause fetal harm when administered to pregnant individuals
- Males have to use barrier contraception for four months after treatment
- Breastfeeding is not recommended during treatment with MOV and for 4 days after the final dose

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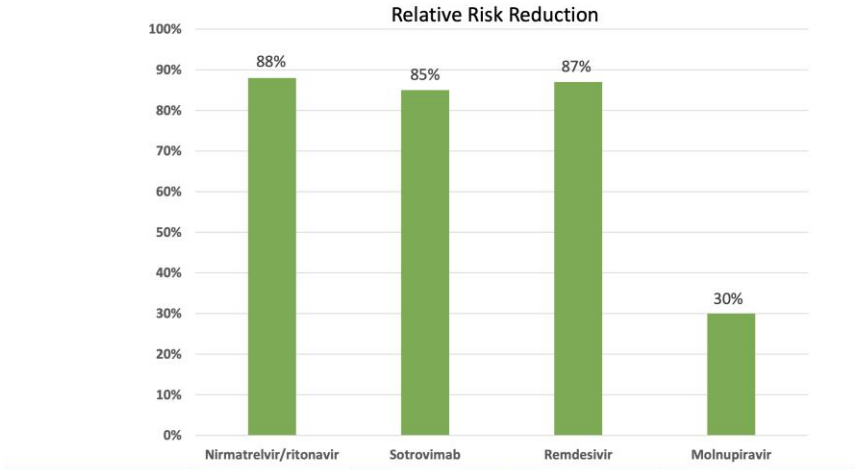
Clinical Efficacy Comparison



Events* (%) Drug vs. placebo	0.8% vs. 6.3%	1% vs. 7%	0.7% vs. 5.3%	6.8% vs. 9.7%

Screenshot

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Comparisons of Recommended Outpatient Therapies

	Paxlovid™ (1)	Sotrovimab (2)	Remdesivir (3)	Molnupiravir (4)
Age allowed for use	≥ 12 yr	≥ 12 yr	≥ 12 yr	≥18 yr
Initiate within # days of symptom onset	< 5 days	< 10 days	< 7 days	< 5 days
Route of Administration	PO	IV	IV	PO
Duration of Therapy	5 days	1 time	3 days	5 days
Pros	-High efficacy -Oral	-High efficacy -Single IV infusion	-High efficacy -Greater experience	-Oral -No drug-drug interaction concerns
Cons	Ritonavir-related drug-drug interactions	Requires IV infusion	-Requires 3 days of IV infusion -Not FDA approved for outpatient	-Low efficacy -Not authorized for age 12-17 years -Not approved for pregnancy -Concerns for mutagenciity
Supply Availability	Limited supply	Limited supply	Commercially available	More supply than Paxlovid™ & Sotrovimab

Screenshot

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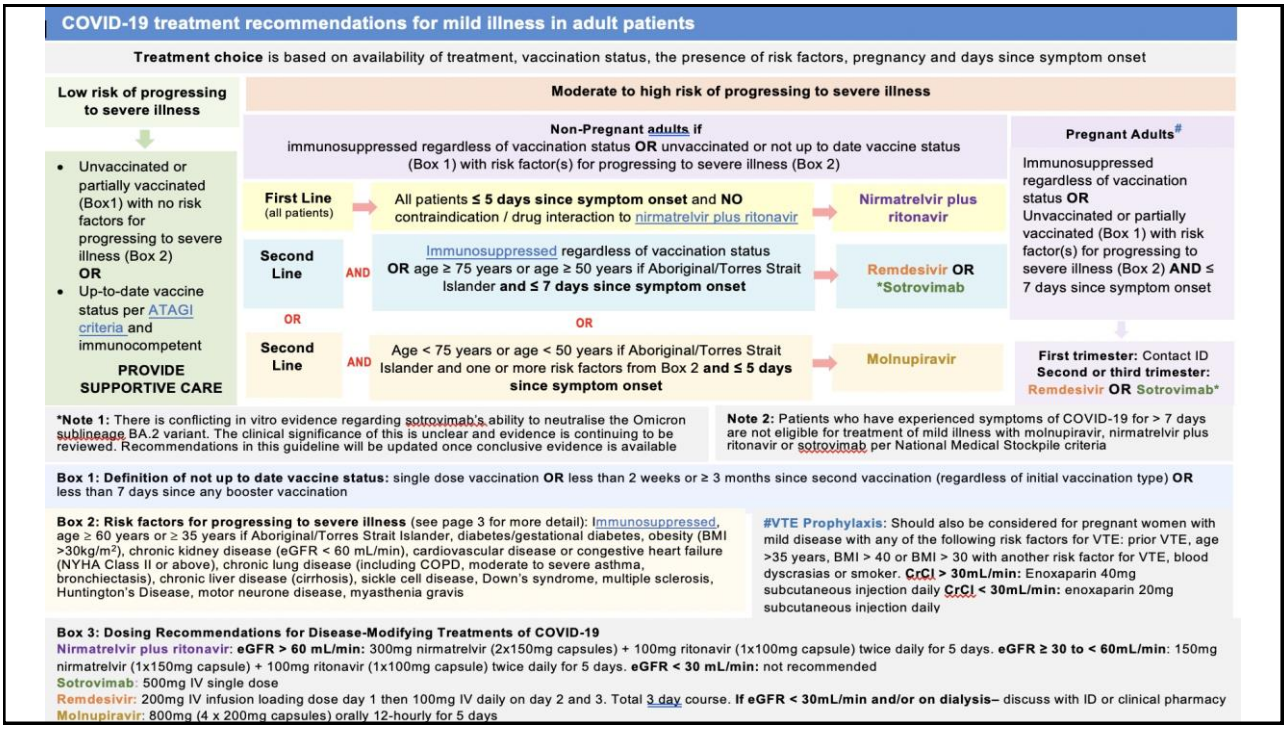

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Summary

- 5-day window – EARLY REFERRAL/ PBS SCRIPT
- Lower invitro efficacy of sotrovimab against Omicron BA.2, clinical relevance unclear
- Paxlovid remains 1st line drug for all patients but limited due to drug interactions
- Remdesivir and sotrovimab restricted to pregnant women and immunocompromised patients (7 day window)
  - Limited options
  - Short supply
  - Administration challenges
- Molnupiravir as per PBS criteria, if Paxlovid not possible for all other patients

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- Discuss with patient
  - check and counsel regarding pregnancy and contraception
  - renal function
  - drug interactions including drugs such as marijuana, and chelators such as zinc
- Include cost of drug when counseling patient

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Rehabilitation for Post COVID-19 Syndrome

Nathan Ward

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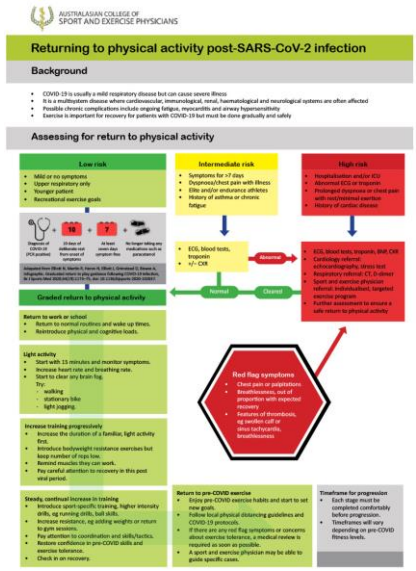
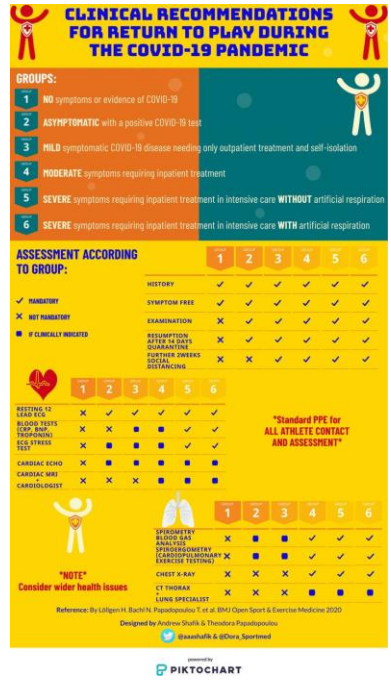
Return to exercise





https://www1.racgp.org.au/ajgp/coronavirus/life-after-covid-19

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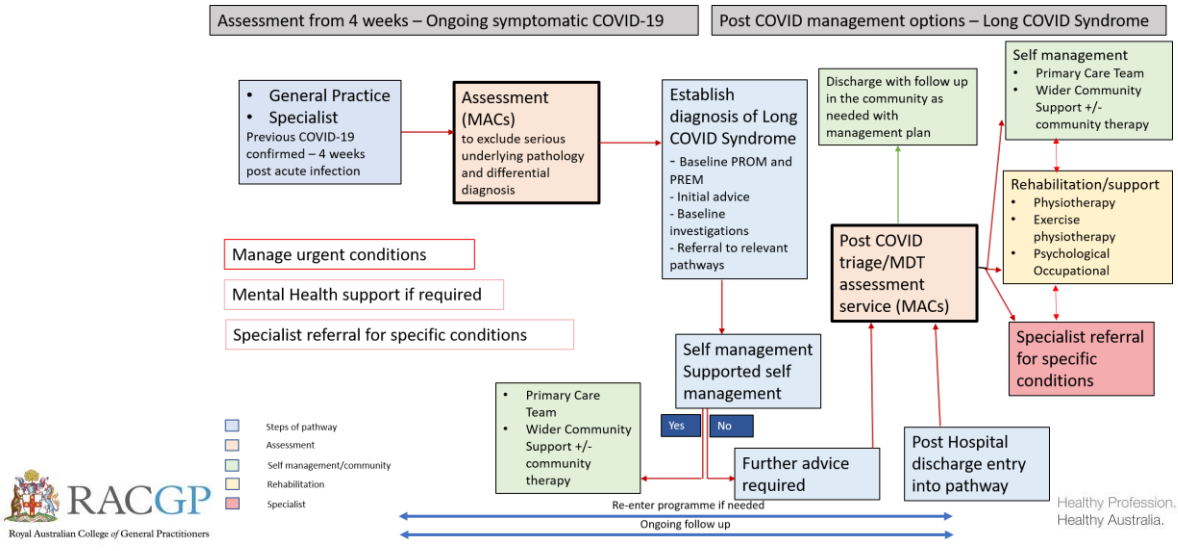
Post-COVID assessment



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Self management advice

World Health Organization
Europe

Support for Rehabilitation Self-Management after COVID-19-Related Illness

Name:

Discharge date:

Hospital where treated:

Healthcare professional providing leaflet:

Name and contact of local healthcare professional:

https://www.who.int/publications/m/item/support-for-rehabilitation-self-management-after-covid-19-related-illness

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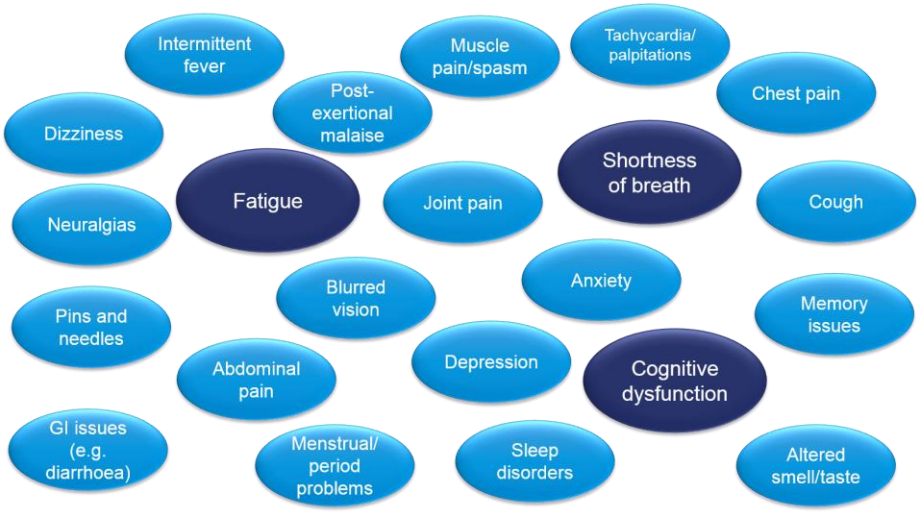
Post COVID symptoms



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World Health Organization 2021. A clinical case definition of post COVID-19 condition by a Delphi consensus. https://apps.who.int/iris/bitstream/handle/10665/345824/WHO-2019-nCoV-Post-COVID-19-condition-Clinical-case-definition-2021.1-eng.pdf Accessed 31

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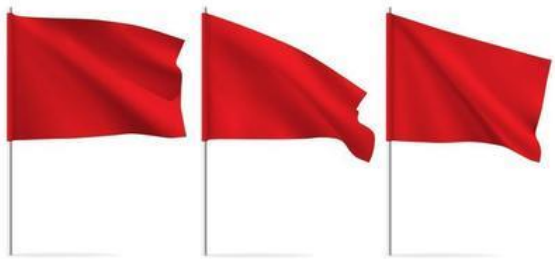
Red flags

- New, increasing or severe shortness of breath
- Palpitations or arrhythmias
- Unexplained chest pain
- Syncope
- Confusion
- New focal neurological signs or symptoms



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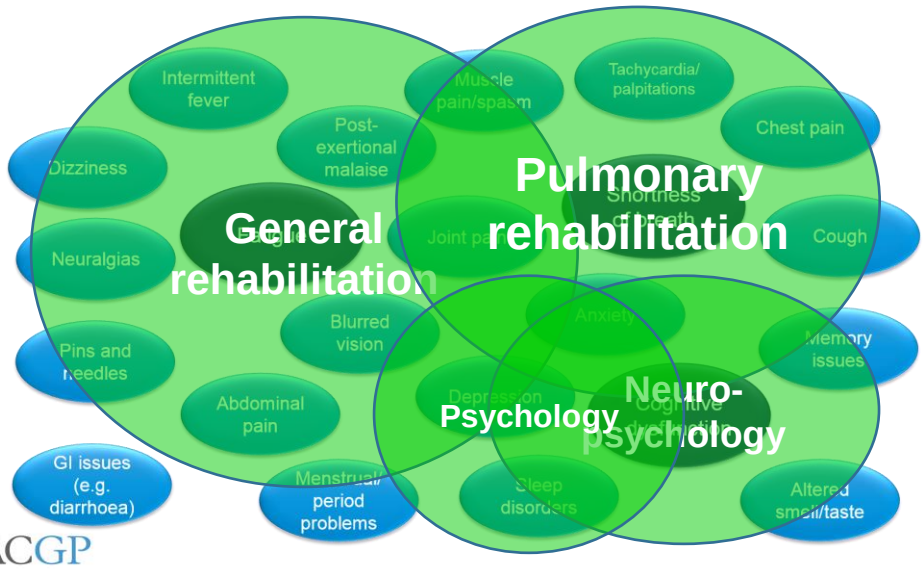
Return to exercise



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Exercise training considerations

Post-exertional symptom exacerbation
- Day of and day post increased physical activity
- 'Stop. Rest. Pace' instead of graded program
- 'Energy maximisation' versus 'energy conservation'

Cardiac impairment
- Myocarditis and pericarditis
- ECG/holter

Exertional desaturation
- Desaturation ≥ 3% or < 92% requires investigation
- 40-step walk or 1-minute sit to stand test

Autonomic dysfunction and orthostatic intolerances
- Orthostatic hypotension
- Postural orthostatic tachycardia syndrome

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Summary

- All people post COVID should undertake a progressive return to physical activity and exercise
- Assessment at 6-8 weeks post acute infection or hospital discharge
- Mild symptoms = self management advice
- Moderate-severe breathlessness = pulmonary rehabilitation
  - Programs across metro and country LHNs
- Multiple moderate-severe symptoms = specialist Long COVID clinic
  - Individualised rehabilitation program
  - Exercise, cognitive, mental health, nutrition, return to work
- Progressive or new symptoms = immediate assessment

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