

Risk Factors for progressing to severe or critical COVID-19 illness

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Risk Factors for progressing to severe or critical COVID-19 illness

1. Background

Studies have demonstrated that the risk of severe COVID-19 increases with age and number of comorbidities. Supplies of medications from the National Medical Stockpile (NMS) can vary according to outbreaks and demand and in the setting of limited supply certain risk factors or patients with greater than 1 risk factor may be prioritised for treatment of mild disease.

2. Risk factors for progressing to severe or critical COVID-19 illness

NOTE: Access to medications may need to be considered in the context of an outbreak and in these circumstances certain risk factors may be prioritised.

- Immunosuppressed patients (see section 3)
- Chronic kidney disease (eGFR < 60mL/min or equivalent renal impairment for pregnant women)
- Congenital heart disease
- Age ≥ 65 years or age ≥ 50 years if Aboriginal/Torres Strait Islander
- Diabetes (requiring medications) or gestational diabetes (requiring medication) in pregnant women
- Obesity (BMI > 30 kg/m² or > 40 kg/m² for pregnant patients)
- Chronic liver disease (cirrhosis)
- Cardiovascular disease
- Congenital heart disease
- Congestive Heart Failure (New York Heart Association Class II or above)
- Chronic lung disease including history of chronic bronchitis, cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease, or emphysema with dyspnoea on physical exertion
- Moderate-to-severe asthma requiring an inhaled steroid to control symptoms or prescribed a course of oral steroids in the previous 12 months
- Sickle cell disease
- Down's syndrome
- Rare neurological conditions: multiple sclerosis, motor neurone disease, myasthenia gravis, Huntington's disease
- Pregnancy

3. Classification of Immunosuppressed Patients

Immunosuppressed patients are not expected to mount an adequate immune response to COVID-19 vaccination or the COVID-19 infection due to their underlying conditions, regardless of their vaccine status.

NOTE asplenic or hyposplenic patients are not classified as immunosuppressed

Medical conditions associated with reduced immune response	
Haematological disease and stem cell transplant recipients	<ul style="list-style-type: none"> • Allogenic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months • Active graft vs host disease regardless of time from transplant (including HSCT for non-malignant diseases) • Autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases) • Individuals with haematological malignancies who have: <ul style="list-style-type: none"> ○ Received chimaeric antigen receptor (CAR)-T therapy within the last 2 years OR ○ Radiotherapy in the last 6 months • Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months except: <ul style="list-style-type: none"> ○ patients with chronic phase chronic myeloid leukaemia (CML) in molecular response OR ○ first or second line tyrosine kinase inhibitors (TKI) – see medications section below for more information • All patients with myeloma (excluding MGUS) or chronic B-cell lymphoproliferative disorders (e.g. chronic lymphocytic leukaemia, follicular lymphoma) or myelodysplastic syndrome (MDS) who do not fit the criteria above • Individuals with non-malignant haematological disorder (e.g. aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (see medication section below) within the last 12 months
Patients with non-haematological malignancies	<p>Active metastatic cancer and active solid cancers where patients have received:</p> <ul style="list-style-type: none"> • Lung cancer on active chemotherapy +/- immunotherapy within 3-6 months • Moderate intensity chemotherapy within the past 2 weeks • Radiotherapy within the last 6 months
Solid organ transplant	<p>All solid organ transplant patients receiving immunosuppressive therapy</p>
Primary immune deficiencies	<ul style="list-style-type: none"> • Primary immunodeficiency associated with impaired type I interferon signalling • Good's syndrome (thymoma plus B-cell deficiency) • X-linked agammaglobulinaemia (and other primary agammaglobulinaemias) • Any patient with a secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy • Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Severe Combined Immunodeficiency (SCID) syndromes • Autoimmune polyglandular syndromes /autoimmunepolyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • Aplastic anaemia on active therapy
HIV/AIDS	<ul style="list-style-type: none"> • Advanced or untreated HIV with CD4 counts < 250/μL or those with a higher CD4 count unable to be established on effective antiretroviral therapy.

Medications associated with a reduced immune response to COVID-19 vaccination

Clinicians may use their judgement for medications which are not listed

Corticosteroids	High dose corticosteroid treatment equivalent to $\geq 20\text{mg/day}$ of prednisone for ≥ 14 days in a month, or pulse corticosteroid therapy.
Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)	<ul style="list-style-type: none"> • mycophenolate • methotrexate (≥ 10 mg/week) • leflunomide • azathioprine ($\geq 1\text{mg/kg day}$) • 6-mercaptopurine ($\geq 0.5\text{mg/kg/day}$), • alkylating agents (e.g. cyclophosphamide, chlorambucil) • systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus).
Moderate intensity chemotherapy agents	Agents with a high risk of severe neutropenia (neutrophils $<0.5 \times 10^9/\text{L}$) for 3-5 days duration post-chemotherapy)
Biologic and targeted therapies including	<p>Anti-CD20 antibodies</p> <ul style="list-style-type: none"> • rituximab, obintuzumab, ocrelizumab, ofatumumab within 12 months <p>BTK inhibitors</p> <ul style="list-style-type: none"> • ibrutinib, acalabrutinib, zanubrutinib within 6 months <p>JAK inhibitors</p> <ul style="list-style-type: none"> • tofacitinib, baricitinib, ruxolitinib, upadacitinib <p>Sphingosine 1-phosphate receptor modulators</p> <ul style="list-style-type: none"> • fingolimod, siponimod <p>Anti-CD52 antibodies</p> <ul style="list-style-type: none"> • Alemtuzumab within 6 months <p>Anti-complement antibodies</p> <ul style="list-style-type: none"> • eculizumab <p>Anti-thymocyte globulin (ATG)</p> <ul style="list-style-type: none"> • anti-thymocyte globulin (e.g. ATGAM[®], Thymoglobuline[®], ATG-Grafalon[®]) <p>Pyrimidine and purine synthesis inhibitors</p> <ul style="list-style-type: none"> • teriflunamide, cladribine <p>Other agents</p> <ul style="list-style-type: none"> • abatacept, belimumab, blinatumomab, dimethyl fumarate, venetoclax, daratumumab
Multiple immunosuppressants or combination immunosuppression	Combination therapy where the cumulative effect is severely immunosuppressive (for examples see below)

Medications not associated with a reduced response to COVID-19 vaccination

The following therapies, when **not** given in combination with other immunosuppressive therapies, are likely to have a minimal effect on COVID-19 vaccine response. Patients prescribed these therapies are **not** eligible for monoclonal antibody therapy for treatment of COVID-19 illness:

- Anti-TNF- α antibodies (e.g. infliximab, adalimumab, etanercept, golimumab, certolizumab)
- Anti-IL1 antibodies (e.g. anakinra)
- Anti-IL6 antibodies (e.g. siltuximab, tocilizumab and sarilumab)
- Anti-IL17 antibodies (e.g. apremilast, secukinumab, ixekizumab)
- Anti-IL4 antibodies (e.g. dupilumab)
- Anti-IL23 antibodies (e.g. guselkumab, risankizumab, tildrakizumab, ustekinumab)
- Immune checkpoint inhibitors (e.g. atezolizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab)
- Integrin receptor inhibitors (e.g. natazilumab, vedolizumab)
- Interferons
- Glatiramer
- VEGF, EGFR and HER2 blockers (e.g. cetuximab, panitumumab, pertuzumab, trastuzumab, bevacizumab)

5 Resources

- [National COVID-19 Clinical Evidence Taskforce \(The Australian Living Guidelines\)](#)
- [COVID-19 Resources: NSW Therapeutic Advisory Group](#)
- [COVID–19 \(SARS–COV–2\) – Management Guide \(CALHN–PRC05409\)](#)
- [Anaphylaxis: Management Guidelines \(CALHN-OWI04038\)](#)
- [COVID-19: Disease-modifying therapy recommendations for hospitalised adults \(CALHN-GDE05778\)](#)
- [CALHN COVID–19 internet page](#)
- [World Health Organisation. Therapeutics and COVID-19: Living Guideline](#)
- [Australian Technical Advisory Group on Immunisation \(ATAGI\)](#)
- [Clinical Excellence Commission: Medication Safety Updates](#)
- [COVID-19 Treatment: Nirmatrelvir-Ritonavir \(Paxlovid®\) \(IH-CIS05842\)](#)

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7 Document Ownership

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8 Document History

Version	Date approved	Approved by	Amendment notes
3	14/04/22	CALHN Drug and Therapeutics Committee COVID-19 Medicines Advisory Group	Amended risk factors for disease progression to align with updated pathway for the medication management of mild COVID-19 illness in the outpatient setting.
2	18/02/22	CALHN Drug and Therapeutics Committee COVID-19 Medicines Advisory Group	Add molnupiravir and nirmatrelvir plus ritonavir. Added link on sotrovimab monograph for breastfeeding advice.
1	19/01/22	South Australian Medicines Advisory Committee	New guideline to provide a pathway for the medication management of mild COVID-19 illness in the outpatient setting.