

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

Immunosuppression and COVID-19

Rapid review question

What is the evidence for the risk and management of people with immunosuppression and COVID-19?

In brief

- Currently evidence is low quality and based on a small number of cases. Evidence is continuing to emerge on these patients.

Patients with immunosuppression and COVID-19

- A systematic review showed that people with immunosuppression showed favourable disease course when compared to the general population. Cancer patients experienced more severe COVID-19 infections but did not necessarily have a poor prognosis. The review is subject to bias due to the limited number of included papers and small sample size.
- Additional small case series suggest that patients with immunosuppression generally have similar risk profiles to the general population in terms of COVID-19 outcomes and severity, however patients with cancer have been shown in some studies to have more severe disease. Results for transplant patients regarding disease severity varies and is based on small numbers.
- People with cancer provide the majority of the evidence on immunosuppression during COVID-19. Expert opinion varies on whether cancer patients with a diagnosis of COVID-19 should continue cancer treatment. However there is agreement that decisions should be based on balancing risks and benefits of treatment in the context of the pandemic and infection control principles.
- A systematic review showed that there is no definitive evidence that specific cytotoxic drugs, low-dose methotrexate for autoimmune disease, NSAIDs, Janus kinase (JAK) kinase inhibitors or anti-TNF α agents are contraindicated in people with COVID-19.
- The National Institute for Health and Care Excellence (NICE) recommends continuing systemic anticancer treatment only if it is needed for urgent control of the cancer, and if possible, defer treatment until the patient has at least one negative test for COVID-19.
- NICE have also released guidance on children and young people who are immunocompromised with COVID-19.

Patients with immunosuppression in the context of COVID-19

- A Centre for Evidence Based Medicine review, which focused on people with chronic respiratory health conditions, concluded that evidence regarding how to manage people on long term oral immunosuppression during COVID-19 is very limited, and that there is no evidence to suggest long-term immunosuppression should be stopped.
- Strategies for cancer services during COVID-19 may include pre-screening patients, visitors and staff and/or limiting visitors, telemedicine, limiting exposure to caregivers, altering/delaying some treatments and rescheduling appointments for some patients.

Limitations

- Currently evidence is low quality and based on a small number of cases. Evidence is continuing to emerge on these patients.
- The summary of the guidance provided in this review is not detailed and only describes some of the general principles.
- The search terms focused on immunosuppression and not individual conditions that may be affected by this. Additionally, some publications do not make clear from the title and abstract that empirical data is included in the publication, therefore some of the evidence may be omitted.
- Evidence on COVID-19 is emerging rapidly, and this review contains some publications that are in preprint or pre-peer review.

Background

Immunocompromised or immunosuppressed individuals have increased susceptibility to viral infections such as influenza. People with cancer make up the largest proportion of the literature on people with immunosuppression. Cancer care delivery during this time will be challenging, given the competing risks of death from cancer versus death or serious complications from COVID-19.(1, 2) Additionally, the workforce and delivery of care is impacted, with high rates of illness among healthcare workers due to COVID-19 reducing the number of staff, changes to delivery of care such as considering the risk-benefit of surgery, and different ways to deliver chemotherapy and radiotherapy such as through less intensive treatment regimens or hypofractionation.(3)

Methods (Appendix 1)

PubMed and Google searches were undertaken on 30 April 2020. Cancer makes up the largest proportion of the literature on people with immunosuppression, so a supplementary search on this population was run. Studies reporting empirical data and reporting on three or more cases were included in the results tables.

Results (Table 1 and 2)

A recently published systematic review of 110 people in 16 studies on children and adults with immunosuppression showed that people with immunosuppression seem to have a favourable disease course, as compared to the general population, however the review was limited in its small sample sizes.(4) The Centers for Disease Control and Prevention (CDC) in the United States list people who are immunocompromised are at higher risk for severe COVID-19 illness.(5)

Many case reports of transplant patients with COVID-19 have been published since the publication of the systematic review. Most cases report COVID-19 in people with renal transplants having positive outcomes have been reported.(6-12) There are also reports of bone marrow transplant and renal transplant patients who have died.(13, 14)

Cancer

There is a large amount of guidance for organisation of cancer services during the COVID-19 pandemic. General principles of this guidance includes:

- There is debate among oncologists about whether people with cancer who have a COVID-19 infection should continue cancer treatment while they are recovering from the infection. NICE guidance states that staff should follow infection control guidelines and be aware that patients with COVID-19 are at risk for more severe disease following systemic anticancer treatment.
- Organisational aspects of cancer care that have been considered in the literature, including resource conservation and allocation, personal protective equipment (PPE) conservation, effect of workflow changes on cancer centre activity, delayed non-urgent visits, telemedicine, mitigation strategies, wellness resources, triage and early identification, pre-screening patient and infection control.(15-26)

In addition to the general guidance, there is considerable cancer-specific guidance including publications on gynaecological cancers,(27) breast cancers,(28-31) colposcopy,(32) head and neck cancers,(33-37) oral cancer,(38) haematological cancers,(39, 40) digestive and oncology surgery,(41) lung cancer,(42-44) prostate cancer,(45) gastrointestinal cancers,(46, 47) colorectal cancer,(48, 49) gliomas,(50) and lymphoid malignancies.(51)

Specific cancers produce immune suppression to different extents - haematological cancers often directly compromise the immune system and these patients are most likely at risk, compared to colon, breast and lung cancer, which typically do not cause immune suppression.(52) According to expert opinion published in the Medical Journal of Australia, for people with haematological cancers, temporary discontinuation of cancer therapies will be warranted for some patients who develop COVID-19 symptoms in order to reduce the risk of drug interactions and minimise treatment-related immunosuppression. Immunocompromised patients with suspected or confirmed COVID-19 should be discussed with an infectious disease or clinical microbiology specialist.(40)

With the scarcity of knowledge about COVID-19, estimating the risk versus benefit of administering potentially immunosuppressive treatment to patients with cancer while balancing individual versus societal benefits in regards to stretched resources, poses acute ethical dilemmas to oncologists.(53)

American Society of Clinical Oncology (ASCO) have released guidance on recommendations for cancer regarding ethics and resource scarcity. They recommend:

- the allocation of scarce resources be based on maximising health benefits
- the development of fair and consistent prioritisation and allocation policy
- the use of existing ethical models as frameworks to guide decisions about scarce resource allocation, separate from bedside decision making
- joint efforts between oncologists and their institutions to decide how to best use resources
- communication of allocation plans with patients
- engagement in advance care planning discussions.(54)

Other conditions

Specific guidance also exists for management of people with immunosuppression for conditions including but not limited to:

- Transplant: general guidance includes maintaining an individualised approach, teleconsultations, regular monitoring.(55-61) The transplantation society also have guidelines for transplant clinicians on COVID-19.(62)
- Inflammatory bowel disease: guidance generally advises to continue with some treatments, reduce the dose of corticosteroids where possible, postpone all elective endoscopic procedures, online appointments, categorising patients in risk categories, continuation of immunomodulators and biologics.(63-67) The international organisation for the study of inflammatory bowel disease has detailed guidance about individual drug use.(68)
- Rheumatic diseases: do not discontinue immunosuppressive treatment, infection control, reduce the risk of transmission.(69, 70)
- Autoimmune bullous diseases: some treatments to be stopped when symptoms occur while others can continue.(71)
- Chronic dysimmune neuropathies: teleconsultations, infection, risk and benefit of treatment decisions.(72)
- Dermatitis: patients continue all immune-modulating treatments, including immuno-suppressive therapy.(73)
- Neuromuscular disorders: close monitoring of high risk patients, telehealth, discussion around additional corticosteroids, other immunosuppression is held or continued based on clinical status.(74)
- Cutaneous immune-mediated diseases: available data suggests not at increased risk compared with general population, patients can continue treatment unless they have an active COVID-19 diagnosis.(75)
- Autoimmune liver disease: stratify patients based on risk.(76)

The National Institute for Health and Care Excellence have a COVID-19 rapid guideline on children and young people who are immunocompromised, covering communication, managing the underlying conditions in patients known, suspected or not known to have COVID-19, modifications to usual care and healthcare workers.(77)

A Centre for Evidence Based Medicine review regarding people with chronic respiratory health problems and on long term oral immunosuppressants, concluded that patients should continue use during the COVID-19 pandemic, unless they show signs of infection, at which point they should be stopped (with the exception of long term steroids).(78)

A survey of patients with rheumatic diseases in COVID-19 identified four key themes: emotions in response to COVID-19, perceptions of risks from immunosuppressive medications, protective measures to reduce risk, and disruptions in accessing rheumatic disease medications.(79)

Table 1: Cancer during COVID-19

Author, year and title	Findings
Peer reviewed journals	
Associations between immune-suppressive and stimulating drugs and novel COVID-19 – a systematic review of current evidence Russell et al., 2020(80)	<ul style="list-style-type: none"> • 89 studies were included • Cytotoxic chemotherapy was shown to be a specific inhibitor for severe acute respiratory syndrome coronavirus in in-vitro studies. No specific studies exist for COVID-19 • No conclusive evidence was found for or against the use of NSAIDs in the treatment of COVID-19 patients • Some evidence showed that corticosteroids were beneficial in the treatment of SARS-CoV, but no studies were found specific to COVID-19 • No evidence was found indicating that TNFα blockade is harmful to patients in the context of COVID-19 • COVID-19 has been observed to induce a pro-inflammatory cytokine generation and secretion of cytokines, such as IL-6, but there is no evidence of the beneficial impact of IL-6 inhibitors on the modulation of COVID-19
Clinical Characteristics of COVID-19-infected Cancer Patients: A Retrospective Case Study in Three Hospitals Within Wuhan, China Zhang et al., 2020(81)	<ul style="list-style-type: none"> • 28 COVID-19-infected cancer patients were included • A total of 15 (53.6%) patients had severe events and the mortality rate was 28.6%. If the last antitumour treatment was within 14 days, it significantly increased the risk of developing severe events • Cancer patients show deteriorating conditions and poor outcomes from the COVID-19 infection. It is recommended that cancer patients receiving antitumour treatments should have vigorous screening for COVID-19 infection and should avoid treatments causing immunosuppression or have their dosages decreased in case of COVID-19 coinfection
Flash Survey on Severe Acute Respiratory Syndrome coronavirus-2 Infections in Paediatric Patients on Anticancer Treatment Hrusak et al., 2020(82)	<ul style="list-style-type: none"> • Flash survey on COVID-19 incidence and severity among children on anticancer treatment • 25 countries, approximately 10,000 patients at risk were followed up. More than 200 were tested, 9 of which were positive for COVID-19 • Eight of the nine cases had asymptomatic to mild disease and one was just diagnosed with COVID-19

Author, year and title	Findings
Peer reviewed journals	
<p>Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China</p> <p>Liang et al., 2020 (2)</p>	<ul style="list-style-type: none"> • 18 of 1590 COVID-19 cases had a history of cancer • Lung cancer was most frequent type (5 patients) • Patients with cancer were observed to have a higher risk of severe events compared with patients without cancer • Moreover, patients who underwent chemotherapy or surgery in the past month had a numerically higher risk of clinically severe events than those not receiving chemotherapy or surgery
<p>SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China</p> <p>Yu et al., 2020 (83)</p>	<ul style="list-style-type: none"> • The estimated infection rate of SARS-CoV-2 in patients with cancer from this single institution was 0.79% (12 of 1524 patients; 95% CI, 0.3%-1.2%). • This was higher than the cumulative incidence of all diagnosed COVID-19 cases over the same time period • Seven of 12 patients had non–small cell lung carcinoma. Five were being treated with either chemotherapy with or without immunotherapy (n = 3) or radiotherapy (n = 2). • Three patients developed SARS and one patient required intensive-level care. As of 10 March 2020, six patients had been discharged and three deaths were recorded
<p>COVID-19 and Cancer: Lessons From a Pooled Meta-Analysis (correspondence)</p> <p>Desai et al., 2020</p>	<ul style="list-style-type: none"> • Pooled prevalence analysis of cancer among patients with COVID-19 • Authors searched PubMed, Medline, and Web of Science databases until 14 March 2020 • A total of 11 articles were selected • They found that the overall pooled prevalence of cancer in patients with COVID-19 in these studies was 2.0% • Subgroup analysis based on sample size, they found studies with a sample size <100, prevalence was slightly higher at 3.0%, but in larger studies with a sample size >100, there was a lower overall prevalence of 2.0%
<p>COVID-19 in persons with haematological cancers</p> <p>He et al., 2020 (39)</p>	<ul style="list-style-type: none"> • Cohort study at two centres in Wuhan, China, of 128 hospitalised people with haematological cancers, 13 developed COVID-19. • They studied 226 healthcare providers, 16 developed COVID-19 and 11 were hospitalised • Case rates for COVID-19 in hospitalised people with haematological cancers was 10% compared with 7% in healthcare providers. • The 13 people with haematological cancers had more severe COVID-19 and more deaths compared with hospitalised healthcare providers with COVID-19 • Case fatality rates were 62% (32, 85%) and 0 (0, 32%; P = 0.002).

Table 2: People with immunosuppression in other conditions during COVID-19

Author, year and title	Findings
<p>Peer reviewed journals</p> <p>An Italian programme for COVID-19 infection in multiple sclerosis (letter)</p> <p>Sormani, 2020 (84)</p>	<ul style="list-style-type: none"> • Case series of 232 patients in 38 centres with multiple sclerosis and confirmed or suspected COVID-19 • 96% had mild disease; 2% were severe and 3% (6 patients) were critical (5 died) • This suggests immunosuppressive therapies do not confer additional risks but there is insufficient evidence to suggest that they are protective
<p>Covid-19 in Immune-Mediated Inflammatory Diseases — Case Series from New York (letter)</p> <p>Haberman et al, 2020 (85)</p>	<ul style="list-style-type: none"> • Single-centre case series of 86 patients with known immune-mediated inflammatory disease and COVID-19 (confirmed or highly suspected) • 14 patients (16%) were hospitalised, of whom 11 had been discharged at the time of data collection, 2 were still in hospital and 1 had died • The incidence of hospitalisation was similar to patients with COVID-19 generally in New York City, suggesting baseline use of biologics therapies is not associated with worse COVID-19 outcomes • Those with COVID taking methotrexate, oral glucocorticoids or hydroxychloroquine were more likely to require hospital admission than those who were not taking these drugs
<p>Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic (letter)</p> <p>D’Antiga, 2020 (86)</p>	<ul style="list-style-type: none"> • Preliminary experience in Bergamo, approximately 700 children received a liver transplant, 3 of which occurred in the last 2 months • Among approximately 200 transplant recipients at the centre, including 10 inpatients, 100 with autoimmune liver disease and 3 under chemotherapy for hepatoblastoma, none have clinical pulmonary disease, despite 3 testing positive for COVID-19.
<p>Management of Patients on Dialysis and With Kidney Transplantation During the SARS-CoV-2 (COVID-19) Pandemic in Brescia, Italy</p> <p>Alberici et al., 2020 (57)</p>	<ul style="list-style-type: none"> • Preliminary data of a nephrology unit • 20 patients who underwent transplantation were admitted, 5 patients died, 4 were admitted to the intensive care unit and 3 were discharged after an average of 13 days • 21 patients with COVID-19 infection receiving haemodialysis, including 5 patients who died and 4 who were discharged between 7 and 17 days after admission (mean length of hospitalisation 12 days) • A total of 5 patients with CKD were admitted, of whom 2 have died and the other 2 have been discharged after 6 and 17 days from admission
<p>Identification of Kidney Transplant Recipients With Coronavirus Disease 2019</p>	<ul style="list-style-type: none"> • Four patients received a reduced dose of maintenance immunosuppressive therapy during hospitalisation.

Author, year and title	Findings
Peer reviewed journals	
Zhang et al., 2020 (87)	<ul style="list-style-type: none"> As of 4 March 2020 nucleic acid testing was negative for COVID-19 in three patients, twice in succession, and their computed tomography scans showed improved images
<p>Uneventful course in IBD patients during SARS-CoV-2 outbreak in northern Italy</p> <p>Norsa et al, 2020 (88)</p>	<ul style="list-style-type: none"> 522 patients with IBD in Bergamo Over the analysis period, patients were recommended not to modify their treatment regimen No cases of COVID-19 in this cohort were detected 59% of patients were exclusively on salicylates treatment, 22% of patients were on immunosuppressive treatments such as thiopurines or methotrexate, steroids or other immunosuppressants, 16% of patients were on biologic treatment (Infliximab, Adalimumab, Vedolizumab and Ustekinumab, Golimumab) and continued their current dosage
<p>Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies (letter)</p> <p>Monti et al, 2020 (89)</p>	<ul style="list-style-type: none"> 320 patients, of which there were 4 confirmed cases of COVID-19, 4 with symptoms highly suggestive of COVID-19 and 5 patients who reported certain contacts remained asymptomatic at the end of the 2 week observation period There were no significant relapses of the rheumatic disease. None of the patients with a confirmed diagnosis of COVID-19 or with a highly suggestive clinical picture developed severe respiratory complications or died Only one patient, aged 65, required admission to hospital and was placed on low-flow oxygen supplementation for a few days
<p>Early Description of Coronavirus 2019 Disease in Kidney Transplant Recipients in New York</p> <p>Columbia University Kidney Transplant Program (90)</p>	<ul style="list-style-type: none"> 15 kidney transplant recipients with confirmed COVID-19 Patients were managed with immunosuppression reduction and the addition of hydroxychloroquine and azithromycin. 27% of patients needed mechanical ventilation but over half were discharged home by the end of follow-up Kidney transplant recipients with COVID-19 have presentations that are similar to that of the general population
<p>COVID-19 Infection in Patients with Sickle Cell Disease (letter)</p> <p>Hussain et al, 2020 (91)</p>	<ul style="list-style-type: none"> A series of four cases of COVID-19 infection in patients with sickle cell disease Patient 1 was extubated after 4 days and discharged home after 13 days of hospitalisation Patient 2 was discharged home after 8 days Patient 3 defervesced on the second day of hospitalisation, her pain gradually improved, and she was discharged after two days Patient 4 was afebrile throughout hospitalisation and did not develop any respiratory symptoms. His pain continued to improve and he was discharged after 4 days

Author, year and title	Findings
Peer reviewed journals	
<p>COVID-19 in Solid Organ Transplant Recipients: Initial Report From the US Epicenter</p> <p>Pereiera et al, 2020 (92)</p>	<ul style="list-style-type: none"> • 90 patients with solid organ transplant and COVID-19 • Among the 68 hospitalised patients, 12% required non-rebreather and 35% required intubation • 16 patients died (18% overall, 24% of hospitalised, 52% of ICU) • 37 patients (54%) were discharged • In this initial cohort, transplant recipients with COVID-19 appear to have more severe outcomes, although testing limitations likely led to undercounting of mild and asymptomatic cases
<p>Coronavirus Disease 2019 Pneumonia in Immunosuppressed Renal Transplant Recipients: A Summary of 10 Confirmed Cases in Wuhan, China</p> <p>Zhu et al., 2020 (93)</p>	<ul style="list-style-type: none"> • Total of 10 renal transplant recipients with laboratory-confirmed COVID-19 pneumonia • The severity of COVID-19 pneumonia was greater in the transplant recipients than in the control group • Five patients developed transient renal allograft damage • After a longer time of virus shedding and a longer course of illness, nine of the 10 transplant patients recovered successfully after treatment • One patient developed acute renal graft failure and died of progressive respiratory failure
<p>Characteristics and prognosis of patients with inflammatory bowel disease during the SARS-CoV-2 pandemic in the Basque Country (Spain)</p> <p>Rodrigues-Lago et al., 2020 (94)</p>	<ul style="list-style-type: none"> • Patients with IBD and COVID-19 • After the detection of SARS-CoV-2, most patients stopped immunomodulator (82%) or biologic (43%) maintenance therapy • No patient was admitted to the ICU • Treatment-related adverse events were reported in two patients • Good overall prognosis
<p>COVID-19 in Long-Term Liver Transplant Patients: Preliminary Experience From an Italian Transplant Centre in Lombardy</p> <p>Bhoori et al., 2020 (95)</p>	<ul style="list-style-type: none"> • Transplant centre in Italy • 3 of 111 long-term liver transplant survivors (transplanted more than 10 years ago) have died following severe COVID-19 • All were male, older than 65 years, receiving antihypertensive drugs, overweight (BMI >28kg/m²), with hyperlipidaemia and diabetes • The post-transplant course had been uneventful for all three patients and their immunosuppressive regimen had been gradually tapered off, with very low trough concentrations of calcineurin inhibitors (two patients receiving ciclosporin [28 and 35ng/ml, respectively] and one receiving tacrolimus [2.1ng/mL]). • The patients died between 3 and 12 days after the onset of pneumonia

Author, year and title	Findings
Peer reviewed journals	
	<ul style="list-style-type: none">• By contrast, three of the 40 recently transplanted (within the past 2 years) patients tested SARS-CoV-2 positive, and although quarantined, are all experiencing an uneventful course of disease

Appendix

Search strategy and strings

PubMed

- (2019-nCoV[title/abstract] or nCoV*[title/abstract] or covid-19[title/abstract] or covid19[title/abstract] OR "covid 19"[title/abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[title/abstract] OR sars-cov-2[title/abstract] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) AND ("immunocompromised"[title/abstract] OR "immunosuppressed" [title/abstract])
- ((2019-nCoV[title/abstract] or nCoV*[title/abstract] or covid-19[title/abstract] or covid19[title/abstract] OR "covid 19"[title/abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[title/abstract] OR sars-cov-2[title/abstract] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) AND (immunosuppress*[title/abstract] OR immunocomp*[title/abstract] OR immune-suppress*[title/abstract] OR "Immunocompromised Host"[Mesh])) (Limit year 2020)
- (2019-nCoV[title/abstract] or nCoV*[title/abstract] or covid-19[title/abstract] or covid19[title/abstract] OR "covid 19"[title/abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[title/abstract] OR sars-cov-2[title/abstract] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) AND (cancer)

Google Search One: (immunosuppression* OR immunocompromised*) AND ("covid-19" OR "coronavirus")

Google Search Two:

("Immunocompromised") AND ("guidelines") AND ("covid-19" OR "coronavirus")

Studies not in English were not included. One study where it was very unclear whether all the transplant patients had COVID-19 was excluded.(96)

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Original publication	Updates
30 April 2020	
19 May 2020	<ul style="list-style-type: none"> <li data-bbox="499 1744 1453 1809">• Updated in-brief to reflect limitation and clarified the findings from one study in the table