# Australian and New Zealand Consensus Statement on the Management of Lymphoma, Chronic Lymphocytic Leukaemia and Myeloma During the COVID-19 Pandemic

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## Endorsements

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# Introduction

Since the emergence of the COVID-19 pandemic, multiple epidemiologic studies have described the clinical presentation and biological features in the general population.[1, 2] The estimated overall case fatality rate has varied, however is likely at least 1%,[3] and the intensive care unit admission rate for infected patients may be as high as 12%.[4] Although we acknowledge that the potential impact of COVID-19 infection in immunocompromised haematology patients is largely unknown, it is potentially severe. Viral pneumonias are known to cause disproportionately severe disease in cancer patients, such as the H1N1 pandemic which saw high rates of hospitalisation (50%), pneumonia (23%), and death (9.5%).[5, 6] Bacterial co-infection occurs in up to 25% of cancer patients with viral pneumonia, and is an independent predictor of mortality.[7, 8]

The COVID-19 pandemic is likely to significantly impact healthcare resources including clinical staff and acute care services and as a consequence the routine delivery of care to patients with haematological malignancies. There will be geographic and temporal variation in community transmission and individual institutions will need to consider the local resource limitations and patient risk as the pandemic evolves. This consensus statement was developed amongst experts in the field and may not reflect practice within their individual institutions. This statement is intended to support clinical decision making in this evolving COVID-19 pandemic with supportive evidence including National Health and Medical Research Council levels wherever possible.

# General Principles

Building upon recently published Australian and New Zealand guidelines,[9] we aim to provide consensus-based potential strategies to consider when attempting to mitigate risk in patients with lymphoma, chronic lymphocytic leukaemia (CLL) and myeloma in a continuously developing situation with potential limitations on clinical resources. In general we suggest:

- Patients should be informed of their vulnerability to COVID-19 infection due to their impaired immune system.
- The importance of adherence to current state and federal government recommendations to reduce COVID-19 transmission should be stressed to patients. This includes recommendations relating to good hygiene (frequent hand washing, coughing and sneezing into tissues or elbow, cleaning frequently used surfaces and objects), social distancing, limits for public gatherings, avoiding unnecessary travel and self-isolation.
- Not deferring or omitting treatment options with a clear established benefit in terms of survival outcomes. In the setting of low-grade lymphomas, CLL, low-risk myeloma and palliative treatment, the strategies to mitigate risk and rationalise clinical resources may include treatment omission or deferral, curtailment of treatment, alternate regimen choice and/or delivering standard therapies in different environments.
- Mitigating risk of COVID-19 exposure by reducing patient time spent in clinical settings such as outpatient departments/consulting rooms, hospital stay and infusion suites. Measures include the use of telemedicine, use of non-hospital pathology services, changing intravenous preparations to subcutanous and direct-to-home delivery of oral medications. Outpatient management of neutropenic fever as per established guidelines may be considered.[10]
- Taking all available measures to optimise the patient's immune status, and minimise the risk of infection and hospitalisation. This should include advice about smoking cessation.
- Variation in practice based on an altered patient risk-benefit analysis should be clearly documented in a virtual multidisciplinary team environment or by other means.

- The informed consent process for chemotherapy should include documenting a discussion about the risks of COVID-19 and strategies to avoid infection, as well as the potential risks of reduced hospital capacity to deliver on-time chemotherapy and routine supportive care.
- In the event of infection with COVID-19 during chemotherapy, the decision to continue or re-initiate chemotherapy needs to made on a case-by-case basis, weighing up the urgency of treatment which can often be deferred until the convalescent period.
- Patients should be referred to the most up to date government patient information regarding the evolving COVID19 pandemic.
- Enrolment in clinical trials should remain a consideration for all appropriate patients. It is acknowledged, however, that the availability of clinical trials may also be curtailed during the pandemic.

# Testing for COVID-19

## *Screening and diagnostic testing*

Current indications for testing are rapidly evolving in response to the COVID-19 pandemic and should proceed as per institutional and jurisdictional guidelines. With increasing community transmission, the threshold for testing in an immunosuppressed patient may change. We suggest developing contemporaneous local protocols, based on public health advice and in consultation with infectious disease specialists, specific to the malignant haematology patient.

## *Additional testing in patients with COVID-19 at time of diagnosis*

We recommend full blood count with differential white cell count, C-reactive protein, ferritin, immunoglobulin levels, lymphocyte subsets, routine coagulation profile, fibrinogen, D-dimer, troponin, routine respiratory virus upper respiratory tract swab for co-infection, baseline ECG and chest imaging (X ray or CT).[11]

## *Progress testing*

Recent data indicates the median duration of viral shedding in surviving patients is 20 days, with shedding observed as late as 37 days post diagnosis.[12] In consultation with infectious diseases, COVID-19 testing periodically (every two to three weeks) to ensure clearance may be considered depending on availability of testing kits. Immune profile surveillance testing, including ferritin, every three to four

days until clinical stabilisation may be clinically useful as the cytokine profile of COVID-19 infection is reminiscent of that seen in macrophage activation syndrome/haemophagocytic syndrome.[11]

# Non-Hodgkin Lymphoma

## *Diffuse large B cell lymphoma and high-grade B non-Hodgkin lymphoma*

*Newly diagnosed diffuse large B cell lymphoma and high grade B cell non-Hodgkin lymphoma*

We do not recommend delay of therapy in circumstances where the delay itself is likely to be deleterious to patient outcome as dose intensity and timeliness is important.

*R-CHOP 14 vs R-CHOP 21*

R-CHOP21 and R-CHOP14 have similar efficacy. We suggest growth factor support with both regimens.[13]

*Stage I/II diffuse large B cell lymphoma, non-bulky disease*

We suggest considering four cycles of R-CHOP if the end of treatment PET is negative, as a number of studies have demonstrated this is likely comparable to six cycles of R-CHOP (II). This is most applicable in patients with an age adjusted IPI=0 and age <60, although the S1001 study suggests this approach may be applicable more broadly (III).[14-16]

*High-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements ("double-hit" or "triple-hit")*

We suggest weighing up the resources needed and the immunosuppression risks associated with intensified regimes such dose-adjusted R-EPOCH, particularly in those with low IPI and older patients who may experience increased toxicity. It may be reasonable to treat such patients with R-CHOP (II,III).[17-19]

*Consolidation radiotherapy to bulky disease:*

It is reasonable to consider hypofractionation or omitting consolidation radiotherapy in those who are in complete metabolic response after induction therapy, as reflected in the upcoming International Lymphoma Radiation Oncology Group (ILROG) Emergency Guidelines.[20]

## *Relapsed high grade B cell non-Hodgkin lymphoma*

*Salvage regimen choice*

We suggest the use of R-GDP as opposed to R-DHAP or R-ICE, given lower rates of infection and haematological toxicity, with similar efficacy, as well as deliverability in the outpatient setting (II).[21, 22]

*Autologous stem cell transplantation delays*

Prolonged delays of more than two months post last dose of salvage chemotherapy should be avoided where possible (II).[23] Given the poorer outcomes with autologous stem cell transplant (ASCT) in patients who fail primary therapy with a rituximab-based regimen, we suggest proceeding to ASCT where chemosensitivity is demonstrated, at a minimum with partial response by CT scan (II).[21, 22] If there is residual PET positivity post-salvage, the decision to proceed with ASCT should be individualised given poorer outcome, particularly in primary refractory disease (III).[24]

*Relapse after autologous stem cell transplantation*

Relapse following ASCT will prove challenging to treat in the COVID-19 environment. CAR-T cell therapy and allogeneic stem cell transplantation are resource intensive and highly immunosuppressive and are likely to be less accessible. We suggest consideration of other treatment options, such as polatuzumab vedotin (if available) (II),[25] or enrolment in clinical trials if possible. Referral to palliative care and appropriate end-of-life planning should be discussed.

## *Primary mediastinal B-cell lymphoma*

Six cycles of R-CHOP with consolidation radiotherapy is comparable to dose adjusted R-EPOCH, however R-CHOP is associated with less haematological toxicity (III).[26] Consider hypofractionation of radiotherapy in line with upcoming ILROG Emergency Guidelines, or omission in older patients if the end of treatment PET is negative.[20, 27] Ultimately the choice between these two regimens will be based on clinical and resource factors.

## *Burkitt lymphoma*

R-CODOX-M/R-IVAC remains a reasonable choice provided resources are available considering it is usually given in the inpatient setting. GMALL is a reasonable alternative in terms of efficacy and is deliverable in an outpatient setting (II).[28] Dose-adjusted R-EPOCH with intrathecal CNS prophylaxis can be considered on an individualised basis in low risk patients with no CNS involvement (IV).[29] Given the relative rarity of Burkitt lymphoma, institutional resources and familiarity with regimen choice is a relevant consideration.

## *Peripheral T Cell Lymphoma*

*Regimen choice*

For most patients, and those over 60 years of age in particular, consider six cycles of CHOP rather than CHOEP, as the latter is associated with higher treatment-related toxicity without a proven overall survival benefit (III).[30, 31]

*Autologous stem cell transplantation*

Consider deferral or omission of consolidation ASCT in first complete remission depending on resource availability as the role of ASCT is not well established in this setting (III).[32]

## *Low-grade non-Hodgkin lymphoma*

For low-grade lymphomas, consideration should be given to the delay of planned initiation of therapy where possible. Ultimately, initiation of treatment will be based on a risk-benefit discussion between patient and physician, taking into account disease characteristics, in particular the tempo of disease progression, individualised infectious risk and patient preference. We suggest:

- Where there is clinical equipoise between the use of a higher and lower intensity regimen, or if the use of a higher intensity regimen is based on relatively low quality evidence, lower intensity regimens are preferred.
- The traditional GELF/BNLI thresholds for the initiation of therapy can be relaxed in patients who tolerate them.[33, 34]
- Consider a higher treatment threshold when based on constitutional symptoms.
- For patients with symptomatic sites of disease, low dose radiotherapy (4Gy in one to two fractions) can provide effective palliation and may be an effective temporising measure.[35]
- In patients who are already receiving treatment and have a had a good response, consideration should be given to abbreviating the number of treatment cycles.

## *Follicular lymphoma*

*First line therapy*

This should be highly individualised based on local resources, pandemic evolution and patient characteristics. R-CVP (or obinutuzumab-CVP) or R-CHOP (or obinutuzumab-CHOP) may be considered over bendamustine-based regimens considering the concerns around risks of delyed infection with the latter. Consideration should be made to continue with chemotherapy on a cycle-by-cycle basis and it may be reasonable to reduce bendamustine cycles from six to four cycles in patients with a good response (III). [36-40]

*Maintenance immunotherapy*

If there is significant community transmission of COVID-19, maintenance immunotherapy should be avoided if possible due to increased rates of neutropenia and infection, without proven overall survival benefit (II).[41]

## *Mantle cell lymphoma*

Younger, fit patients should continue with current institutional practices, such as regimes containing high-dose cytarabine, but consolidation ASCT may need to be deferred in the setting of limited acute care services. For older or unfit patients, consider R-CHOP or R-CVP therapy with growth factor support, based on patient characteristics, and the concerns around risks of infection with bendamustine-based regimens (III).[42]

## *Lymphoplasmacytic lymphoma*

*Immunochemotherapy regimen choice*

If chemotherapy is being considered, while R-bendamustine is associated with superior progression-free survival, rituximab with cyclophosphamide and dexamethasone (DRC) is less immunosuppressive. Regimen choice needs to consider individual patient characteristics and pandemic evolution.

*Patients on Bruton kinase (Btk) inhibitors*

If these patients develop COVID-19, careful deliberation should be made before stopping due to the risk of exacerbating any potential cytokine release syndrome and rapid symptomatic disease progression on cessation. Conversely, the possibility of blunted immune response and cardiac toxicity are also considerations.

# Hodgkin lymphoma

## *Classical Hodgkin lymphoma*

In general, local treatment practices for classical Hodgkin lymphoma (HL) should continue to apply, however we advise consideration of resource-limitations and the following treatment strategies which involve reduced toxicity with comparable outcomes.

Of note, symptoms of pulmonary toxicity of bleomycin, check point inhibitors and radiotherapy toxicities may mimic those of COVID-19 disease.

*Early stage favourable HL*

Where radiotherapy services can be provided, two cycles of ABVD followed by 20Gy involved site radiotherapy (ISRT) will likely remain standard of care in many centres. Where radiotherapy services are limited or an alternate strategy is more desirable, an approach based on the RAPID trial is to treat with three cycles of ABVD without radiotherapy, provided an interim PET after two cycles is negative (II).[43]

*Early stage unfavourable HL*

Consider four cycles of ABVD followed by ISRT, in an effort to reduce toxicity and resource allocation, as the approach of two cycles of ABVD after two initial cycles of escalated BEACOPP in the HD14 trial was not associated with an overall survival benefit (II).[44] Patients commencing on ABVD who have a positive interim PET after two cycles could be considered for intensification to escalated BEACOPP provided patient fitness permits (II).[45]

*Advanced stage HL*

- Expert opinion regarding first line therapy is mixed.[46-48] However, when using escalated BEACOPP we suggest abbreviating to four cycles rather than delivering six in patients with a negative PET after two cycles (II).[49]
- For patients experiencing significant toxicity or infection during the first two cycles of escalated BEACOPP, we suggest considering descalation to ABVD if an interim PET after cycle 2 is negative as described in the AHL2011 trial (II). [50]
- For patients treated with six cycles of ABVD, we recommend the omission of bleomycin after cycle two in patients with advanced-stage disease treated with ABVD with a negative interim PET, in line with the RATHL study (II).[51]
- Radiotherapy to initial bulky disease may be omitted where interim PET after cycle two is negative.

*Relapsed HL*

- Salvage chemotherapy and ASCT should not be delayed as this is potentially curative therapy.
- Alternatively in patients at higher risk of treatment-related toxicity, brentuximab vedotin as a single agent may be considered as salvage (depending upon accessibility) prior to ASCT (IV).[52]
- ASCT in patients with residual PET-positive disease should not be prioritised in the setting of limited acute care services, due to poor outcomes (III).[53] Consider using second line salvage with a novel agent instead, to improve response.
- Options for second salvage, or transplant-ineligible patients, include both brentuximab vedotin and pembrolizumab.The risk of respiratory complications with PD-L1 inhibitors in the context of the COVID-19 pandemic is unknown (III).[36, 54, 55]

# Chronic Lymphocytic Leukaemia

CLL patients are likely to be at increased risk of severe disease and mortality with COVID-19. Many patients with CLL are immunocompromised, even with early stage disease, and have additional risk factors such as age and comorbidities. Consideration should be given to the delay of planned initiation of therapy where possible.

*Frontline immunochemotherapy*

In the event that front-line therapy is essential, consider the use of oral therapies if accessible. If immunochemotherapy with FCR is considered appropriate, in IgHV-mutated CLL intravenous administration for six cycles remains standard of care, however in IgHV-unmutated CLL dose reduction and oral administration of both fludarabine and cyclophosphamide based on the CLL5 protocol could be considered (II).[56, 57] Early cessation of therapy could be considered if clinically significant treatment-related cytopenias occur, or once disease control is achieved. Growth factor support should be given to avoid neutropenia. For older patients with comorbidities, chlorambucil plus obinutuzumab or rituximab may also be appropriate, with early cessation of therapy once disease control is achieved.

*Relapsed or refractory CLL*

If therapy is required, the Btk inhibitor ibrutinib or bcl-2 inhibitor venetoclax should be standard of care (II). Ibrutinib is generally well tolerated and allows outpatient administration with minimal hospital visits. When considering venetoclax in combination with rituximab, consider deferring rituximab and administering venetoclax as monotherapy, both to limit the need for day unit attendance, and potentially to reduce the degree of immune compromise. The need for tumour lysis syndrome prophylaxis during venetoclax ramp-up and the desire to avoid associated hospital visits should also be considered.

*Mitigating Potential Risks of Novel Agents*

The risk of severe COVID-19 disease among patients receiving Btk inhibitors and venetoclax is unknown, but could plausibly be increased. Pulmonary infections are among the severe adverse events observed during clinical trials of Btk inhibitors and venetoclax.

Cardiac toxicity associated with ibrutinib may become a factor for those who acquire COVID-19, as hypertension and cardiac disease are risk factors for severe COVID-19, and are also recognised adverse events of ibrutinib. Cardiac injury itself is common in severe COVID-19 and associated with malignant arrhythmias and higher mortality.[11] To limit the potential for cardiac toxicity and treatment-related

immunosuppression and drug interactions, temporary cessation of ibrutinib or venetoclax should be considered for CLL patients who develop COVID-19, for the period of time that they are unwell.

# Myeloma

The treatment of patients with multiple myeloma (MM) during the COVID-19 pandemic may ultimately be dictated by the available health care resources. Nonetheless, the overarching principle that should guide management within clinical resource constraints rests on the balance between the need for optimal disease control in high-risk patients and avoiding unnecessary treatment-related immune suppression in low-risk patients. Therapeutic decisions must be individualised, taking into consideration: disease factors including newly diagnosed versus relapsed disease; stage and cytogenetics/FISH; disease burden and rate of progression; patient factors including age, frailty, comorbidities and social circumstances, and; the capacity of the health care system.

For otherwise fit patients, particularly those with high-risk or rapidly progressive MM, prompt treatment is warranted to avoid further end-organ damage, deterioration in performance status and ultimately a loss of a window for treatment. Treatment delay in this group may result in complications which may necessitate hospitalisations that place further stress on the existing inpatient capacity. In contrast, for patients with disease stability, particularly in the elderly and frail patients, considerations must be given to mitigate further immune suppression by ceasing immunosuppressive agents that may not be essential for immediate disease control, such as ongoing dexamethasone.

The more difficult decision is whether to delay treatment for otherwise well patients with slow biochemical progression of MM but without end organ damage, as the duration of this pandemic and its consequent impact on health care capacity remain unknown. Such a decision may ultimately be dictated by the stage of the pandemic faced at the time. In general for MM we suggest:

- Preferential utilisation of oral agents lenalidomide, pomalidomide and thalidomide as immunomodulatory drugs (IMIDs) and if available, ixazomib as an oral proteasome inhibitor (PI). If feasible, home or self administration of subcutaneous bortezomib could be considered.
- The use of dexamethasone should be minimised, if not ceased, once maximal disease response is achieved and tumoricidal effects become less important.
- Cyclophosphamide, if needed, should be given orally rather than intravenously.
- For bortezomib and carfilzomib, weekly schedules are preferred over twice weekly schedules (III, II).[58, 59]
- For patients on daratumumab, a shorter infusion time of 90 minutes can be considered from the third infusion onwards (IV).[60]

- Amino-bisphosphonates (zoledronic acid or pamidronate) remain an important aspect of MM treatment in preventing skeletal related events and have been shown to improve OS based on the MRC Myeloma IX study (II).[61] If the peak of the pandemic necessitates minimisation of hospital visits, consider reducing bisphosphonate infusions to every 3 monthly (IV).[62]

## *Asymptomatic patients (monoclonal gammopathy of uncertain significance and smouldering multiple myeloma)*

Establish telemedicine follow-up or GP management for all patients at the frequency dictated as standard of care by the Myeloma Australia Medical and Scientific Advisory Group (MSAG) Guidelines.[63]

## *Newly diagnosed multiple myeloma*

In patients with MM as defined by the presence of positive biomarkers as opposed to overt end organ damage or "CRAB" features,[64] the need for immediate treatment must take into consideration the available health care capacity to avoid placing patients at risk of hospitalisation at the height of the pandemic. Treatment delay in these patients is not unreasonable but as risk of developing overt end organ damage in these patients is in the order of 70% within two years, closer monitoring is warranted. We suggest monthly monitoring of paraproteins and serum free light chain in addition to routine standard of care investigations. If overt end organ damage occurs, immediate treatment is recommended.

## *Transplant Eligible Patients*

*Standard-risk patients who achieve a partial response (PR) to induction*

Consideration should be given to deferring ASCT if healthcare capacity is limited.

*Patents who do not achieve a PR after four cycles or who progress during induction therapy.*

In this setting the risk of MM outweighs the risk of COVID-19 and we advise proceding with salvage therapy as per the MSAG Guidelines.[63]

*High risk MM (as per R-ISS or other factors e.g. extramedullary disease)*

We recommend proceeding to ASCT without delay if possible.

*Stem cell collection*

Stem cell collection should depend on local resources and, if feasible, outpatient mobilisation should be considered. A GCSF-only (+/- plerixafor) mobilisation technique should be considered (III).[65]

## *Transplant Deferral*

If ASCT is delayed, consideration should be given to continuing CyBorD beyond an initial four cycles of induction as per the transplant ineligible approach. Additional cycles beyond four cycles have recently been approved by the Pharmaceutical Benefits Advisory Committee in Australia.

Based on the StaMINA study, delay in ASCT during the COVID-19 pandemic for up to 12 months after induction therapy could be acceptable (although the majority of these patients received bortezomib, lenalidomide and dexamethasone (VRd) induction) (II).[66] Beyond 12 months the value of proceeding to ASCT is controversial.

## *Transplant Ineligible Patients*

Oral combinations such as lenalidomide and dexamethasone are preferred to minimise hospital/outpatient service visits. For responding patients who are beyond the ninth cycle of lenalidomide and dexamethasone, it is safe to cease dexamethasone and continue with lenalidomide monotherapy (II).[67]

Bortezomib-based treatments remain preferable in patients with impaired renal function or high risk cytogenetics.[63] Consideration for doublet rather than triplet therapy ought to be given to elderly or frail patients in whom the risk for neutropenia is higher. Reduced dexamethasone of 20mg weekly rather than 40mg should be used.

## *Relapsed Disease*

The timing and type of salvage therapy for patients with relapsed MM should take into consideration available clinical resources and the safety of treatment delay.

Many, but not all, patients will require immediate treatment at first detection of myeloma relapse. For patients with worsening or new end organ damage, immediate treatment is indicated as the risk of myeloma outweighs the risk of COVID19. In the absence of worsening or new "CRAB" symptoms, immediate treatment may also be warranted in patients with rapidly progressive pararaprotein or serum free light chain levels to prevent the onset of irreversible end organ damage as per MSAG Guidelines.[63] Otherwise, in patients with slow biochemical relapse, close monitoring monthly until significant progression occurs is acceptable.

The optimal salvage therapy for myeloma should be based on the patient's prior treatment exposure and associated response or toxicity.[63] If all else is equal with respect to the efficacy and toxicity profile between two or more salvage therapies, then the option with less immune suppression and hospital visits is preferred. We recommend considering using oral treatment combinations. If patients are

receiving carfilzomib at a stage when minimisation of hospital visits is necessary, consider weekly dosing (70mg/$m^2$) rather than twice weekly dosing as per the ARROW study,[58] recognising that this schedule has only been compared favourably to carfilzomib 20/27mg per $m^2$ rather than the PBS reimbursed schedule of 20/56mg per $m^2$ as per the ENDEAVOUR study (II).[68] In addition, this schedule may not be possible for patients with BSA>1.7$m^2$ given that the maximum carfilzomib dose reimbursed on the Australian PBS is capped at 120mg. If weekly dosing of carfilzomib is used, it is not unreasonable to consider adding cyclophosphamide (KCd) as this weekly schedule has been shown to be effective and safe in the upfront treatment setting (IV).[69]

## Systemic AL Amyloidosis

Treating patients with AL amyloidosis during the COVID-19 pandemic should be considered on a case-by-case basis. Rapid initiation of therapy is likely to remain the standard of care in line with MSAG Guidelines, in particular in patients with cardiac or extensive renal involvement.[70]

Patients with early stage disease could potentially have treatment postponed several months.[71] In patients who have achieved at least a very good partial response, or PR with an organ response, a reduced number of treatment cycles or intensity could be considered.

# Supportive Care

The general principles of social distancing apply to the delivery of care of haematology patients during the COVID-19 pandemic. As outlined by others,[72] face-to-face contact with patients, patient presentation to infusion suites, radiotherapy and for pathology, and radiology testing should be minimised as much as possible for the safety of patients and health care workers. Where appropriate, oral therapy should be chosen over parenteral. Chemotherapy treatment in the patient's home can also be considered if available. Rearrangement of chemotherapy suites to increase spatial distancing is recommended.

*Subcutaneous rituximab*

In patients with low grade lymphoma, subcutaneous rituximab should be delivered in lieu of intravenous rituximab where possible to reduce time spent in infusion suites.[73, 74]

*Growth factor support*

In the context of the COVID-19 pandemic, we generally recommend adding growth factor support to all chemotherapy regimens with an anticipated neutropenic nadir of less than $1.0x10^9$/L, in an effort to decrease infection risk and consequent hospital presentation.

Primary prophylactic GCSF is in most cases not required for ABVD, however it could be considered in older patients or in patients not receiving bleomycin.

In the context of neutropenic fever, we suggest considering growth factor support use as it has been shown to reduce the duration of neutropenia and duration of hospitalisation, both desirable.[75]

*Antibacterial prophylaxis*

Bacterial coinfection occurs in up to 25% of cancer patients with viral pneumonia, and is an independent predictor of mortality. This has been shown in data generalizable to COVID-19 infection in patients being treated for haematological malignancy.[7, 8]

We suggest considering the use of antimicrobial prophylaxis in high-risk patients, defined as a patient expected to be neutropenic ($<0.5x10^9$/L) for at least seven days or prior neutropenic fever episodes.[76-78] Primary prophylaxis should take into account local infectious diseases advice and local resistance profiles.

*HSV/VZV prophylaxis*

We suggest the use of antiviral primary prophylaxis with aciclovir or valaciclovir as per institutional practice.

*Pneumocystis Jerovicii (PJP) Prophylaxis*

We recommend the use of prophylaxis as per institutional practice. Specific consideration should be given to patients with lymphoma treated with higher-intensity regimes, patients with a CD4+ count of <200/µL, or those on sustained use of prednisone at a dose >20mg daily (or dose-equivalent corticosteroids) inline with a meta-analysis and published guidelines.[77, 79-81]

*Antifungal Prophylaxis*

For primary prophylaxis in patients with lymphoma and myeloma, we recommend the use of antifungal prophylaxis as per local protocols.

Acute, severe COVID-19 infection is associated with the development of immune dysregulation and lymphopenia, and is likely a risk for secondary fungal infection.[36] Fungal prophylaxis may be considered in this context.[2]

*Immunoglobulin Supplementation*

There is currently no strong evidence to support the practice of routine supplementation with immunoglobulin therapy for primary prophylaxis, however it is reasonable in patients with recurrent infection (I,II).[82-84] Subcutaneous immunoglobulin should be considered in appropriate patients if this results in reduced time spent in the hospital setting.

Supplemental immunoglobulin is unlikely to provide meaningful protection against COVID-19 itself due to the presumed absence wide-spread immunity amongst donors in the early months of the pandemic. In patients with COVID-19 infection, supplementation for hypogammaglobulinaemic patients is reasonable in an effort to minimise the risk of coinfection.

*Vaccinations*

Immune compromised patients are at a higher risk of influenza infection and invasive pneumococcal disease. We recommend all lymphoma and MM patients receive routine influenza and pneumococcal vaccination[85-87]

# Conclusion

The COVID-19 pandemic is providing an unprecedented risk to patients with haematological malignancies. It is critical that health professionals work quickly to reduce the risk of transmission through creative and technological means to limit hospital contact whilst still providing the relatively intensive care required to mitigate the well-known side effects of treatment and disease complications. It may also be important to reduce the degree of immunosuppression in order to reduce mortality for those infected, provided this does not compromise efficacy and safety from the perspective of the underlying malignancy. Careful consideration, informed consent and a multidisciplinary approach are now more important than ever to tailor therapy to at-risk individuals, and thus, hopefully, reducing the impact of COVID-19 in our vulnerable patients.

Table 1.

| Level of evidence | Study design |
|---|---|
| I | Systematic reviews of relevant randomised controlled trials |
| II | At least one randomised controlled trial |
| III | Comparative studies, including non-randomised studies, cohort studies, case-control studies, two or more single-arm studies |
| IV | Case series, single single-arm studies |

Table 1. NHMRC Levels of evidence. Adapted from Merlin T, Weston A, Tooher R. *BMC Med Res Methodol*. 2009; **9**: 34.

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