Long-term management of elderly patients taking immunosuppressive medications

CPD

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Background
General practitioners are increasingly likely to encounter elderly patients who are receiving immunosuppressants for the management of autoimmune diseases or solid organ transplants.

Objective
The aim of this article is to provide an overview of the long-term management of the elderly patient treated with immunosuppressants. Recommendations for monitoring, preventing and managing adverse effects of immunosuppressants are summarised.

Discussion
Elderly patients prescribed immunosuppressants may present a number of unique challenges. Immunosenescence, altered pharmacokinetics and the presence of multiple comorbidities can all affect response to immunosuppressants. Through close collaboration with tertiary care providers and regular screening, the general physician is well placed to recognise medication-related complications.

ELDERLY PATIENTS, generally defined as those aged >65 years, face a number of unique medication-related challenges. The elderly are more likely to have multiple comorbidities and are at increased risk of adverse medication reactions.[1] As the population ages, the use of immunosuppressants for the prevention of organ rejection following transplant or for the treatment of autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease is expected to increase. The average age of patients receiving solid organ transplants (SOTs) has increased over the past 20–25 years, and the majority of patients receiving SOTs are now aged >50 years.[2] Age is not considered an absolute contraindication to transplant if the elderly recipient has minimal comorbidities. However, frailty is associated with poorer outcomes before and after transplantation.[3,4]

The management of elderly patients taking immunosuppressants is heavily dependent on close collaboration with tertiary care providers. Regular review at the tertiary institution for short- and long-term complications allows timely adjustment of treatments and early interventions. General practitioners (GPs) are often the primary source of contact for patients, and they may need to manage various aspects of the patients' care, such as hypertension or diabetes. The GP is therefore ideally placed to recognise medication-related complications (eg adherence difficulties, medication interactions from multiple sources and medication toxicity). Coordinating care with other specialty services will ensure regular screening to recognise complications associated with immunosuppressive therapies.

Immunosenescence

Immunosenescence is a physiological part of ageing typified by an impairment of adaptive and innate immunities.[5] Ageing in general has broad consequences for immune responses, organ function, repair mechanisms and metabolic function. Immunosenescence is linked to higher rates of diabetes, bacterial infections and malignancies.[5] Immunosenescence may predispose elderly patients to the risks of over-immunosuppression. Theoretically, elderly transplant recipients may benefit from less immunosuppression than younger patients, but further studies are needed.[6]

Immunosuppressant regimens

The selection of immunosuppressive medication regimens in the elderly

is complex as there are no specific guidelines. Specific recommendations for the elderly are difficult to ascertain as the elderly are generally excluded from studies or clinical trials.[5] A summary of the available immunosuppressants, medication monitoring and main adverse effects is reported in Table 1 (available online only). The introduction of biological agents has transformed the treatment of many autoimmune diseases. It is likely that further compounds will be introduced in the future, creating challenges for maintaining up-to-date clinical knowledge required in the monitoring of these highly effective agents.

Immunosuppression regimens and protocols are in a constant state of evolution and at present there is no universally agreed consensus to guide therapy. Immunosuppressant doses and serum target levels are individualised according to indication, disease response, side-effect profile, age and frailty of the individual patient. The frequency of monitoring may decrease over time but will reflect the individual patient's comorbidities and complications.

Therapeutic drug monitoring (TDM) is available for the narrow therapeutic index (NTI) immunosuppressants such as tacrolimus, cyclosporin, everolimus, sirolimus and mycophenolate. However, TDM may not accurately reflect the effects of immunosenescence or the total degree of immunosuppression.[7] As a result of immunosenescence, many clinicians may intuitively use lower immunosuppressant doses for elderly patients to minimise the risk of infection and side effects. However, there is no widespread consensus guiding specific TDM of immunosuppressants for the elderly.

Pharmacokinetics of immunosuppressants

In the elderly population, age-related physiological changes can result in clinically significant alterations in the pharmacokinetic parameters of immunosuppressants. The pharmacokinetics of medications, particularly calcineurin inhibitors (CNIs), may be altered in older patients. Initial CNI doses that are similar to those recommended for younger patients may result in higher serum concentrations. A recent study investigating the optimal dosing of CNIs in elderly kidney transplant recipients (aged ≥65 years) found that serum CNI trough levels were 50% higher in the elderly when normalised for dose and weight.[8] The reason that elderly patients may require lower doses of CNIs to obtain the same therapeutic levels is because of a reduction in metabolism from CYP3A4 isozymes and reduced P-glycoprotein activity, resulting in improved bioavailability.[8]

Elderly patients require higher doses of mycophenolic acid (MPA) when compared with younger patients. The reason may be that MPA is strongly bound to serum albumin, and lower albumin levels in elderly patients result in increased clearance of unbound MPA. A pharmacokinetic study comparing MPA exposure in elderly (63 ± 1 years) versus younger (41 ± 5 years) transplant patients showed lower overall exposure and trough concentrations in the elderly.[9] Data from liver and renal transplant recipients showed that mycophenolate doses were significantly higher in patients with lower serum albumin when compared with patients who had normal serum albumin.[10,11]

The metabolism and excretion of methotrexate is affected by age. Elderly patients in particular require close monitoring, as high rates of discontinuation as a result of toxicity have been observed in this cohort of patients.[12] Accumulation of methotrexate is likely to lead to side effects such as nausea and vomiting, myelosuppression and liver enzyme elevations.[13] Many pharmacokinetic studies of mammalian target of rapamycin (mTOR) inhibitors in the elderly showed no difference with excretion and ageing.[14] The effects of ageing on the pharmacokinetics of prednisolone are unknown.[15]

Generics

Generic substitution of NTI immunosuppressants remains a contentious issue within the transplant community. Bioequivalence studies are performed in healthy young volunteers and do not take into account chronic disease, repeated dosing or medication interactions.[16,17] In a prospective single-centre study evaluating a generic formulation of tacrolimus in elderly patients following kidney transplant, the generic product did not meet the bioequivalent standards when compared with the innovator version. The generic formulation had higher trough concentrations and higher exposure.[18]

Elderly patients receiving CNIs or mycophenolate should consistently receive the same brand of immunosuppressant once they are stabilised. Interchanging brands is likely to result in variability of immunosuppressant levels, potentially exposing the patient to an increased risk of adverse effects.

The introduction of biologics has transformed the treatment of many autoimmune diseases. However, the prohibitive high cost has limited the use of and access to these agents. The lower cost biosimilars are required to be highly similar to the reference product with regard to their clinical efficacy, safety and pharmacokinetics.[19] Concerns about immunogenicity when switching from the reference product have limited their widespread uptake. However, clinical trials to date have not shown significant changes in immunogenicity.[20]

Comorbidities in patients receiving immunosuppressants

Immunosuppressants can cause or exacerbate comorbidities such as hypertension, renal dysfunction, diabetes and hyperlipidaemia.[21] Table 2 (available online only) has a suggested frequency of monitoring for comorbidities or side effects exacerbated by long-term immunosuppression. Even in the absence of immunosuppression, older patients have an increased risk of cardiovascular-related disease or death. Mortality related to cardiovascular disease ranges from 40% after cardiac and renal transplantation, to 20% after liver transplantation, to 5% after lung transplantation.[21]

The most clinically significant change in the elderly is the decline in renal function, with age-related decline in renal function at approximately 10% per decade of increasing age.[22] Close monitoring of renal function in the elderly is essential during methotrexate therapy, as many methotrexate-related adverse effects can be related to impaired renal function.[12,23] Elderly recipients of lung transplants have higher rates of severe renal dysfunction over long-term follow up than younger receipients of lung transplants.[24] CNI minimisation strategies with mTOR inhibitors to preserve renal function may provide benefits in the elderly transplant population.[25,26]

The risk of developing new-onset diabetes mellitus after transplantation (NODAT) increases 1.5-fold for every decade increase in age following kidney transplant.[27] The incidence of NODAT varies across SOT: 4–25% in renal transplant recipients, 2–38% in liver transplant recipients, 7–26% in heart transplant recipients and 32–57% in lung transplant recipients.[28–30] Immunosuppressants such as corticosteroids, CNIs and mTOR inhibitors have diabetogenic potential.[28] Corticosteroids have the strongest diabetogenic potential, which is dose dependent.

Infectious diseases

Infections are an important cause of morbidity and mortality in elderly patients taking immunosuppressants. Immunocompetence decreases with age, and older patients are more likely to die from bacterial infections than younger transplant recipients. The risk and severity of infection increases with the level of immunosuppression and is usually higher within the first six months after organ transplant.[31] SOT recipients aged >50 years have a 2-fold increase in the risk of developing bacteraemia with septic shock.[32]

The incidence of opportunistic infections – such as *Pneumocystis jirovecii* (PJP), herpes zoster and tuberculosis – has risen with the increased prescribing of biologics.[33] A prospective analysis examined the risk factors for opportunistic infections in patients with inflammatory bowel disease. An increased rate of opportunistic infections was seen in patients aged ≥50 years and with the use of steroids, thiopurines and combination immunosuppressant therapy.[34]

Immunosuppressive regimens prescribed may predispose to specific infections. For example, corticosteroids predispose to PJP, hepatitis B, bacterial and fungal infections, while T-lymphocyte depletion may activate latent Cytomegalovirus (CMV) reactivation.[35,36] Azathioprine has been associated with papillomavirus, and mycophenolate has been associated with late CMV.[35]

The GP will often be involved in the first-line management of infections in the elderly. The decision to withhold or alter the doses of immunosuppressive therapy should only be undertaken in close consultation with the transplant physician. Although most infectious complications related to immunosuppression are preventable, they can become life threatening in a matter of hours, as infection progresses rapidly in the immunocompromised host. Urgent referral for hospital management is sometimes necessary.

Treatment of infections can be problematic as it may destabilise immunosuppressant regimens as a result of medication interactions and toxicities (eg nephrotoxicity, leukopenias and hepatotoxicity). Table 3 provides a summary of some of the clinically significant medication interactions between immunosuppressants and other frequently prescribed medications in the elderly patient.

Vaccinations

GPs play a crucial part in ensuring that immunisation is up to date. Vaccinating immunocompromised patients can be challenging as they may have a reduced response to vaccines, as well as reduced protection from previous vaccinations. Immunocompromised patients may need extra doses of inactivated vaccines to optimise protection against specific diseases. Vaccination should ideally be undertaken prior to immunosuppressive therapy to improve the immune response.[37]

Administration of live vaccines – such as measles, mumps and rubella (MMR); varicella and zoster vaccines – to immunocompromised hosts is generally contraindicated. Mildly immunosuppressed patients, such as those taking conventional disease-modifying antirheumatic medications (eg low-dose methotrexate, azathioprine or corticosteroids), can receive live vaccines, but only under rheumatologist advice.[37] Otherwise, patients should ideally wait four weeks before starting immunosuppression after receiving a live vaccine.

Table 4 provides an overview of the recommended vaccines for an elderly patient receiving immunosuppressants, and Table 5 provides a list of vaccines that require case-by-case consideration. As recommendations are in a constant state of flux, practitioners are advised to refer to the *The Australian immunisation handbook* for complete and up-to-date information.

Malignancy

Immunosenescence may contribute to an increased risk of malignancy in the elderly because of decreased immunosurveillance.[5] Cancer incidence and mortality increase after the age of 65 years, levelling off at the age of approximately 85–90 years. The risk for malignancy in transplant recipients is approximately two or three times that seen in the non-transplant population, with the risk related to the intensity and duration of immunosuppression.[38]

Advanced age has shown to be an important predictor of malignancy in kidney transplant recipients.[39] One study reported a five-fold increase in the risk of cancers in kidney transplant recipients aged >60 years when compared with recipients aged <45 years.[40] Forty per cent of lung transplant recipients had at least one malignancy at 10 years post-transplantation. The most common cancers are skin related, followed by lymphoproliferative disorders. Recipients aged >65 years had higher rates of skin cancers than younger recipients.[24]

mTOR inhibitors may have a role in minimising the risk of malignancy

Table 3. Clinically significant interactions with immunosuppressants[42,49,51–56]

Drug class and interaction	Comments
Increase CNI and mTOR serum concentrations	
Macrolides: Erythromycin, clarithromycin	Avoid clarithromycin in *Helicobacter pylori* eradication therapies Erythromycin increases CNI level with added potential neurotoxicity Roxithromycin and azithromycin are safer alternatives
Azole antifungals: Voriconazole, posaconazole, fluconazole, itraconazole	Voriconazole and posaconazole are the most potent inhibitors Fluconazole <150 mg daily has minimal interaction Dose reduction of 50–67% required at initiation of therapy
Calcium channel blockers: Diltiazem, verapamil	Diltiazem has been used to boost CNI levels but is no longer common practice Nondihydropyridine (amlodipine, nidefipine) reverses the vasoconstriction of CNIs
Decrease CNI serum concentrations	
Anti-epileptics: Carbamazepine, phenytoin, phenobarbital	Levetiracetam is a safer alternative
Antibacterials: Rifampicin and rifabutin	Significant reductions in CNI and mTOR levels Reduction in mycophenolate and prednisolone exposure Rifabutin has lower potential but is still significant
Complementary medicines: St John's wort	Enhanced metabolism of CNIs, mTOR inhibitors and prednisolone
Additive nephrotoxicity without changing CNI/mTOR serum concentrations	
Non-steroidal anti-inflammatory drugs (including topical)	Methotrexate and CNIs
Antibiotics: Trimethoprim-sulfamethoxazole	Prophylaxis doses for *Pneumocystis jirovecii* unlikely to cause nephrotoxicity
Additive bone marrow suppression	
Antivirals: Valganciclovir	Valaciclovir is a safer alternative: Minimal bone marrow suppression
Antibacterials: Trimethoprim/sulfamethoxazole	Methotrexate: Life-threatening pancytopenias
Antiproliferatives: Myophenolate and azathioprine	Check TPMT levels prior to initiation of azathioprine
Allopurinol	Inhibits metabolism of azathioprine
Other	
Statins: Simvastatin amd atorvastatin	Cyclosporin increases statin exposure; increases risk of myopathy and rhabdomyolysis Rosuvastatin and pravastatin are safer alternatives
Colchicine	CNIs increase colchicine concentration; start low and monitor for myopathy and gastrointestinal disturbances
Direct-acting oral anticoagulants: Dabigitran	Most problematic; concomitant use with cyclosporine is contraindicated
Rivaroxaban	Levels increased by cyclosporin with increased risk of bleeding
Apixaban	Safest to use with CNIs
Antidepressants	SSRIs are weak CYP3A4 inhibitors, but sertraline and escitalopram are agents of choice

CNI, calcineurin inhibitor; CYP, cytochrome enzyme; mTOR, mammalian target of rapamycin; SSRI, selective serotonin reuptake inhibitor; TPMT, thiopurine methyltransferase

Table 4. Vaccination recommendations for elderly patients prescribed immunosuppressants[37]

Vaccine	Recommended	Comments
Influenza	All patients aged >65 years All patients who are immunocompromised	Annually Ideally at start of influenza season Higher immunogenic trivalent vaccine recommended
Streptococcus pneumoniae Pneumococcal conjugate vaccine (13vPCV) 23v pneumococcal polysaccharide vaccine (23vPPV)	All patients aged >65 years All patients who are immunocompromised	Refer to *The Australian immunisation handbook* Dosing schedule depends on: • Category A (highest risk of pneumococcal disease) • previous vaccination status • vaccine previously administered • pre-existing or newly diagnosed comorbidities
Hepatitis B	Patients with specific risk factors: • solid organ transplant • HSCT • HIV	Titres required prior to vaccination If seronegative and never been vaccinated, use standard schedule as accelerated schedule less immunogenic If have not responded to primary vaccination, give additional doses and remeasure titres Check immunity annually; if levels fall, give additional boosters
Hepatitis A	High-risk patients* Liver transplant recipients	
Human papilloma virus Quadrivalent vaccine	All immunocompromised, all ages	Cost may be prohibitive as elderly immunosuppressed patients not included in the National Immunisation Program
Diptheria, tetanus and pertussis dTpa	All patients	If no prior vaccination, give standard schedule Adults aged ≥65 years: Booster dose if last dose >10 years ago

**Chronic hepatitis B or C infection*
DMARD, disease-modifying anti-rheumatic drug; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplant

because of their dual antiproliferative and anti-cancer activity. mTOR inhibitors can be prescribed for renal cell and breast cancers.[41] Although early clinical trials have been promising, evidence to date has not been compelling.[38]

Conclusion

Age broadly affects the immune response as well as the pharmacokinetics of immunosuppressants. In general, elderly patients are more likely to experience over-immunosuppression, manifesting in infectious complications and malignancy. More studies with older patients are required, as clinical trials have generally excluded the elderly. Close surveillance and collaboration is necessary by all practitioners involved in their care.

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References

1. Jansen PA, Brouwers JR. Clinical pharmacology in old persons. Scientifica (Cairo) 2012;2012:723678. doi: 10.6064/2012/723678.
2. Heinbokel T, Elkhal A, Liu G, Edtinger K, Tullius SG. Immunosenescence and organ transplantation. Transplant Rev (Orlando) 2013;27(3):65–75. doi: 10.1016/j.trre.2013.03.001.
3. Exterkate L, Slegtenhorst BR, Kelm M, et al. Frailty and transplantation. Transplantation 2016;100(4):727–33. doi: 10.1097/TP.0000000000001003.
4. Wilson ME, Vakil AP, Kandel P, Undavalli C, Dunlay SM, Kennedy CC. Pretransplant frailty is associated with decreased survival after lung transplantation. J Heart Lung Transplant 2016;35(2):173–78. doi: 10.1016/j.healun.2015.10.014.
5. Krenzien F, El Hajj S, SG, Gabardi S. Immunosenescence and immunosuppressive drugs in the elderly. In: Fulop T, Franceschi C, Hirokawa K, Pawelec G. Handbook of immunosenescence: Basic understanding and clinical implications. Cham, Switzerland: Springer International Publishing, 2017; p. 2147–167.
6. Krenzien F, Elkhal A, Quante M, et al. A rationale for age-adapted Immunosuppression in organ transplantation. Transplantation 2015;99(11):2258–68. doi: 10.1097/TP.0000000000000842.
7. Peeters LEJ, Andrews LM, Hesselink DA, de Winter BCM, van Gelder T. Personalized immunosuppression in elderly renal transplant recipients. Pharmacol Res 2018;130:303–07. doi: 10.1016/j.phrs.2018.02.031.
8. Jacobson PA, Schladt D, Oetting WS, et al. Lower calcineurin inhibitor doses in older compared to younger kidney transplant recipients yield similar troughs. Am J Transplant 2012;12(12):3326–36.
9. Romano P, Agena F, Ebner P, et al. Pharmacokinetics of Mycophenolic Acid (MPA) in elderly compared to young recipients in the first year after renal transplantation. Data from the NEverOLd trial. Am J Transplant 2015;15 (suppl 3).

Table 5. Vaccines that require case-by-case consideration in immunosuppressed patients

Vaccine	Consideration	Comments
Zoster	Recommended for patients aged >60 years if not immunosuppressed Consider on a case-by-case basis: • patients aged >50 years who are mildly immunocompromised • patients with HIV: refer to *The Australian immunisation handbook* for recommendations • patients taking low-dose methotrexate, azathioprine or prednisolone Contraindicated in patients who are significantly immunosuppressed	Serological testing recommended in: • patients with HIV • patients who will be immunosuppressed in future
Varicella	Consider on a case-by-case basis: • patients aged >50 years who are mildly immunocompromised • patients taking <20 mg prednisolone equivalent daily. Contraindicated in patients who are significantly immunosuppressed	Test titres if unknown vaccination history
Measles, mumps and rubella (MMR)	Consider on a case-by-case basis for patients taking low-dose steroids Contraindicated in patients who are significantly immunosuppressed	Test titres if unknown vaccination history

HIV, human immunodeficiency virus

Available at https://atcmeetingabstracts.com/abstract/pharmacokinetics-of-mycophenolic-acid-mpa-in-elderly-compared-to-young-recipients-in-the-first-year-after-renal-transplantation-data-from-the-neverold-trial/ [Accessed 12 January 2020].

10. Tredger JM, Brown NW, Adams J, et al. Monitoring mycophenolate in liver transplant recipients: Toward a therapeutic range. Liver Transpl 2004;10(4):492–502. doi: 10.1002/lt.20124.
11. van Hest RM, Mathot RA, Pescovitz MD, Gordon R, Mamelok RD, van Gelder T. Explaining variability in mycophenolic acid exposure to optimize mycophenolate mofetil dosing: A population pharmacokinetic meta-analysis of mycophenolic acid in renal transplant recipients. J Am Soc Nephrol 2006;17(3):871–80. doi: 10.1681/ASN.2005101070.
12. Drosos A. Methotrexate intolerance in elderly patients with rheumatoid arthritis: What are the alternatives? Drugs Aging 20(10):723–36. doi: 10.2165/00002512-200320100-00002.
13. Bays AM, Gardner G. Pharmacologic therapies for rheumatologic and autoimmune conditions. Med Clin North Am 2016;100(4):719–31. doi: 10.1016/j.mcna.2016.03.001.
14. Gabardi S, Tullius SG, Krenzien F. Understanding alterations in drug handling with aging: A focus on the pharmacokinetics of maintenance immunosuppressants in the elderly. Curr Opin Organ Transplant 2015;20(4):424–30. doi: 10.1097/MOT.0000000000000220.
15. Cossart AR, Cottrell WN, Campbell SB, Isbel NM, Staatz CE. Characterizing the pharmacokinetics and pharmacodynamics of immunosuppressant medicines and patient outcomes in elderly renal transplant patients. Transl Androl Urol 2019;8(Suppl 2):S198–S213. doi: 10.21037/tau.2018.10.16.
16. Christians U, Klawitter J, Clavijo CF. Bioequivalence testing of immunosuppressants: Concepts and misconceptions. Kidney Int Suppl 2010;(115):S1–7. doi: 10.1038/ki.2009.504.
17. Uber PA, Ross HJ, Zuckermann AO, et al. Generic drug immunosuppression in thoracic transplantation: An ISHLT educational advisory. J Heart Lung Transplant 2009;28(7):655–60. doi: 10.1016/j.healun.2009.05.001.
18. Robertsen I, Åsberg A, Ingerø AO, et al. Use of generic tacrolimus in elderly renal transplant recipients: Precaution is needed. Transplantation 2015;99(3):528–32. doi: 10.1097/TP.0000000000000384.
19. Strand V, Gonçalves J, Hickling TP, Jones HE, Marshall L, Isaacs JD. Immunogenicity of biosimilars for rheumatic diseases, plaque psoriasis, and inflammatory bowel disease: A review from clinical trials and regulatory documents. BioDrugs 2020;34(1):27–37. doi: 10.1007/s40259-019-00394-x.
20. Edwards CJ, Hercogová J, Albrand H, Amiot A. Switching to biosimilars: Current perspectives in immune-mediated inflammatory diseases. Expert Opin Biol Ther 2019;19(10):1001–14. doi: 10.1080/14712598.2019.1610381.
21. Silverborn M, Jeppsson A, Mårtensson G, Nilsson F. New-onset cardiovascular risk factors in lung transplant recipients. J Heart Lung Transplant 2005;24(10):1536–43. doi: 10.1016/j.healun.2005.01.004.
22. Aymanns C, Keller F, Maus S, Hartmann B, Czock D. Review on pharmacokinetics and pharmacodynamics and the aging kidney. Clin J Am Soc Nephrol 2010;5(2):314–27. doi: 10.2215/CJN.03960609.
23. Biehl AJ, Katz JD. Pharmacotherapy pearls for the geriatrician: Focus on oral disease-modifying antirheumatic drugs including newer agents. Clin Geriatr Med 2017;33(1):1–15. doi: 10.1016/j.cger.2016.08.001.
24. Yusen RD, Christie JD, Edwards LB, et al. The registry of the International Society for Heart and Lung Transplantation: Thirtieth adult lung and heart-lung transplant report – 2013; Focus theme: Age. J Heart Lung Transplant 2013;32(10):965–78. doi: 10.1016/j.healun.2013.08.007.
25. Arora S, Gude E, Sigurdardottir V, et al. Improvement in renal function after everolimus introduction and calcineurin inhibitor reduction in maintenance thoracic transplant recipients: The significance of baseline glomerular filtration rate. J Heart Lung Transplant 2012;31(3):259–65. doi: 10.1016/j.healun.2011.12.010.
26. Gullestad L, Eiskjaer H, Gustafsson F, et al. Long-term outcomes of thoracic transplant recipients following conversion to everolimus with reduced calcineurin inhibitor in a multicenter, open-label, randomized trial. Transpl Int 2016;29(7):819–29. doi: 10.1111/tri.12783.
27. Peev VJ, Reiser J, Alachkar N. Diabetes mellitus in the transplanted kidney. Front Endocrinol (Lausanne) 2014;5:141. doi: 10.3389/fendo.2014.00141.
28. Räkel A, Karelis AD. New-onset diabetes after transplantation: Risk factors and clinical impact. Diabetes Metab 2011;37(1):1–14. doi: 10.1016/j.diabet.2010.09.003.

29. Hackman KL, Snell GI, Bach LA. Prevalence and predictors of diabetes after lung transplantation: A prospective, longitudinal study. Diabetes Care 2014;37(11):2919–25. doi: 10.2337/dc14-0663.
30. Fazekas-Lavu M, Reyes M, Malouf M, et al. High prevalence of diabetes before and after lung transplantation: Target for improving outcome? Int Med J 2018;48(8):916–24. doi: 10.1111/imj.13963.
31. Orlicka K, Barnes E, Culver EL. Prevention of infection caused by immunosuppressive drugs in gastroenterology. Ther Adv Chronic Dis 2013;4(4):167–85. doi: 10.1177/2040622313485275.
32. Candel FJ, Grima E, Matesanz M, et al. Bacteremia and septic shock after solid-organ transplantation. Transplant Proc 2005;37(9):4097–99. doi: 10.1016/j.transproceed.2005.09.181.
33. Bryant PA Baddley JW. Opportunistic infections in biological therapy, risk and prevention. Rheum Dis North Am 2017;43(1):27–41. doi: 10.1016/j.rdc.2016.09.005.
34. Naganuma M, Kunisaki R, Yoshimura N, Takeuchi Y, Watanabe M. A prospective analysis of the incidence of and risk factors for opportunistic infections in patients with inflammatory bowel disease. J Gastroenterol 2013;48(5):595–600. doi: 10.1007/s00535-012-0686-9.
35. Fishman JA. Opportunistic infections – Coming to the limits of immunosuppression? Cold Spring Harb Perspect Med 2013;3(10):a015669. doi: 10.1101/cshperspect.a015669.
36. Fishman JA. Infection in organ transplantation. Am J Transplant 2017;17(4):856–79. doi: 10.1111/ajt.14208.
37. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook. Canberra: Australian Government Department of Health, 2018.
38. Nair N, Gongora E, Mehra MR. Long-term immunosuppression and malignancy in thoracic transplantation: Where is the balance? J Heart Lung Transplant 2014;33(5):461–67. doi: 10.1016/j.healun.2014.03.002.
39. Vadnerkar A, Toyoda Y, Crespo M, et al. Age-specific complications among lung transplant recipients 60 years and older. J Heart Lung Transplant 2011;30(3):273–81. doi: 10.1016/j.healun.2010.08.032.
40. Danpanich E, Kasiske BL. Risk factors for cancer in renal transplant recipients. Transplantation 1999;68(12):1859–64. doi: 10.1097/00007890-199912270-00008.
41. Waldner M, Fantus D, Solari M, Thomson AW. New perspectives on mTOR inhibitors (rapamycin, rapalogs and TORKinibs) in transplantation. Br J Clin Pharmacol 2016;82(5):1158–170. doi: 10.1111/bcp.12893.
42. Australian Medicines Handbook. Adelaide: AMH, 2019.
43. Ranganath VK, Furst DE. Disease-modifying antirheumatic drug use in the elderly rheumatoid arthritis patient. Rheum Dis Clin North Am 2007;33(1):197–217. doi: 10.1016/j.rdc.2006.12.011.
44. Sammut L, Wallis D, Holroyd C. Progressive multifocal leukoencephalopathy associated with infliximab. J R Coll Physicians Edinb 2016;46(3):163–65. doi: 10.4997/JRCPE.2016.305.
45. Su YC, Lin PC, Yu HC, Wu CC. Hepatitis B virus reactivation in patients with resolved hepatitis B virus infection receiving chemotherapy or immunosuppressive therapy. Eur J Gastroenterol Hepatol 2018;30(8):925–29. doi: 10.1097/MEG.0000000000001130.
46. Weir MR, Salzberg DJ. Management of hypertension in the transplant patient. J Am Soc Hypertens 2011;5(5):425–32. doi: 10.1016/j.jash.2011.07.003.
47. Shrestha MP, Ruel J, Taleban S. Healthcare maintenance in elderly patients with inflammatory bowel disease. Ann Gastroenterol 2017;30(3):273–86. doi: 10.20524/aog.2017.0130.
48. De Cock D, Hyrich K. Malignancy and rheumatoid arthritis: Epidemiology, risk factors and management. Best Pract Res Clin Rheumatol 2018;32(6):869–86. doi: 10.1016/j.berh.2019.03.011.
49. Expert Group for Antibiotic. Antibiotic. In eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited, 2019.
50. Marra F, Lo E, Kalashnikov V, Richardson K. Risk of herpes zoster in individuals on biologics, disease-modifying antirheumatic drugs, and/or corticosteroids for autoimmune diseases: A systematic review and meta-analysis. Open Forum Infect Dis 2016;3(4):ofw205. doi: 10.1093/ofid/ofw205.
51. Vadnerkar A, Nguyen MH, Mitsani D, et al. Voriconazole exposure and geographic location are independent risk factors for squamous cell carcinoma of the skin among lung transplant recipients. J Heart Lung Transplant 2010;29(11):1240–44. doi: 10.1016/j.healun.2010.05.022.
52. Bartell A, Phatak A, Horn K, Postelnick M. Drug interactions involving antifungal drugs: Time course and clinical significance. Curr Fungal Infect Rep 2010;4(2):103–10. doi: 10.1007/s12281-010-0014-x.
53. Bellosta S, Corsini A. Statin drug interactions and related adverse reactions. Expert Opin Drug Saf 2012;11(6):933–46. doi: 10.1517/14740338.2012.712959.
54. Fitzgerald JL, Howes LG. Drug interactions of direct-acting oral anticoagulants. Drug Saf 2016;39(9):841–45. doi: 10.1007/s40264-016-0443-8.
55. Vanhove T, Spriet I, Annaert P, et al. Effect of the direct oral anticoagulants rivaroxaban and apixaban on the disposition of calcineurin inhibitors in transplant recipients. Ther Drug Monit 2017;39(1):77–82. doi: 10.1097/FTD.0000000000000356.
56. Shuster JE, LaRue SJ, Vader JM. Dabigatran may have more significant drug interactions with calcineurin inhibitors than oral anti-xa inhibitors. J Heart Lung Transplant 2016;35(4):S417.

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Table 1. Common immunosuppressants used in the elderly[13,23,42-45]

Class of medication	Generic name	Primary care monitoring	Main adverse effects
Calcineurin inhibitors	Cyclosporin Tacrolimus	Renal function: Creatinine Glucose Electrolytes (potassium, magnesium) Lipids Blood pressure Liver function tests TDM • Cyclosporin (C_0 and C_2) • Tacrolimus (C_0) • Levels dependent on indication	Nephrotoxicity Diabetes (tacrolimus > cyclosporin) Hypomagnesaemia, hyperkalaemia Hyperlipidaemia Hypertension Neurotoxicity (tacrolimus > cyclosporin) – tremor, headache, confusion, seizures, posterior reversible encephalopathy syndrome, hirsutism, gingival hypertrophy (cyclosporin > tacrolimus)
Mammalian target of rapamycin inhibitors	Everolimus Sirolimus	Renal function: Creatinine Lipids Full blood examination TDM • Everolimus (C_0) • Sirolimus (C_0)	Proteinuria Hyperlipidaemia Pancytopenia Pneumonitis Peripheral oedema Delayed wound healing (requires caution prior to major surgeries) Mouth ulcers
Nucleotide synthesis inhibitors	Azathioprine Mycophenolate Leflunomide*	Complete blood count Thiopurine methyltransferase: Azathioprine Liver function tests TDM Mycophenolate AUC0-12 may be considered but not universal practice	Dose-related myelosuppression Pancytopenia, neutropenia Liver dysfunction Nausea, diarrhoea Pneumonitis
Corticosteroids	Prednisolone	Glucose Lipids Blood pressure and weight Bone mineral density Ophthalmology Electrolytes	Hyperglycaemia Hyperlipidaemia Hypertension/heart failure Osteopenia Glaucoma and cataracts Adrenal suppression Sleep and mood disturbances Peptic ulcer disease
Antimetabolites	Methotrexate	Full blood examination Liver function tests Pulmonary function tests Gastrointestinal Renal function	Bone marrow suppression Hepatic fibrosis Acute interstitial pneumonitis Nausea, vomiting, stomatitis
Tumor necrosis factor alpha antagonists	Adalimumab Certolizumab Etanercept Golimumab Infliximab	Full blood examination Tuberculosis and hepatitis B screening Renal function – creatinine Liver function tests	Neutropenia Reactivation of hepatitis B Worsening heart failure Progressive multifocal leukoencephalopathy

Table 1. Common immunosuppressants used in the elderly[13,23,42–45]

Class of medication	Generic name	Primary care monitoring	Main adverse effects
Cytokine modulators	Abatacept Anakinra Baricitinib Rituximab Secukinumab Tocilizumab Tofacitinib Ustekinumab	Full blood examination Tuberculosis and hepatitis B screening Renal function: Creatinine Liver function tests Lipids	Neutropenia, lymphopenia Reactivation of hepatitis B Progressive multifocal leukoencephalopathy
Alkylating agents	Cyclophosphamide	Full blood examination Midstream urine Urinalysis	Anaemia, neutropenia Haemorrhagic cystitis Heart failure in patients aged >50 years Pulmonary fibrosis

**Safety profile unchanged in the elderly – monitor for hypertension and unintended weight loss*
AUC_{0-12}, area under the curve concentration; C_0, trough concentration (or lowest concentration) reached before the next dose administered; C_2, concentration taken two hours after receiving dose; TDM, therapeutic drug monitoring

Table 2. Management of complications caused by immunosuppressants[38,39,42,46–51]

System	Monitoring	Comments
Haematological	Myelosuppression • Haemoglobin and platelets • Full blood count	• 1–3 monthly • 1–3 monthly, suspend likely causative agent if neutrophils <1.5 × 10^9 cells/L and contact specialist
	Lymphoid malignancy • No screening guidelines • Monitor for signs: fever, weight loss, night sweats, fatigue, swollen lymph nodes	• Post-transplant lymphoproliferative disorder associated with Epstein–Barr virus mismatch • Associated with thioprine use in inflammatory bowel disease • Associated with DMARDs for rheumatoid arthritis • Routine testing of oncogenic viruses required (Cytomegalovirus, Epstein–Barr virus, Herpes simplex virus)
Cardiovascular*	Fasting lipids	6–12 monthly
	Diabetes management plan	Glycated haemoglobin 3–6 monthly
	Blood pressure goals	
	Smoking cessation	
	Assessment of weight	
Hepatic and renal	Liver function tests	1–3 monthly
	Electrolytes, urea, creatinine	1–3 monthly
Respiratory	Community-acquired pneumonia	Prophylaxis not required Intravenous therapy may be required
	Pneumocystis jiroveci prophylaxis	Recommended for: • solid organ transplants, active autoimmune disease • all patients on equivalent prednisolone 20 mg or higher for two weeks or longer Treatment of choice: Trimethoprim/sulfamethoxazole • duration depends on immunosuppressive regimen • continue for six weeks after ceasing prednisolone
	Cytomegalovirus pneumonitis	Treatment recommended for transplants with specialist advice Associated with rejection in kidney, lung and heart transplant Treatment with oral valganciclovir or intravenous ganciclovir Also covers Cytomegalovirus, Herpes simplex virus, Herpes zoster virus
Gastrointestinal	Colonoscopy	Refer to National Bowel Cancer Screening Program Dependent on risk factors
	Cytomegalovirus colitis	Refer to Respiratory recommendations
Ophthalmology	Glaucoma	Annually
	Cataracts	Annually
	Cytomegalovirus retinitis	Refer to Respiratory recommendations
Musculoskeletal	Bone mineral density	Preventive strategies • Yearly vitamin D level review • Minimise corticosteroid use • Antiresorptive therapy as indicated (bisphosphonates or denosumab)
	Dental examination for oral hygiene and cancer screening	3–6 monthly

Table 2. Management of complications caused by immunosuppressants[38,39,42,46–51]

System	Monitoring	Comments
Dermatology	Dermatological examination	Annually Avoid voriconazole use in patients at risk of skin cancers Associated with thiopurine use in inflammatory bowel disease
Genitourinary	Urinary tract infections	Prophylaxis not required Caution with trimethoprim because it elevates serum creatinine Avoid nitrofurantoin eGFR <60 mL/minute
	Gynaecological examinations	Refer to National Cervical Screening Program Dependent on risk factors (2–5 yearly)
	Breast screening	Refer to Breast Screen Australia recommendations (two-yearly)
	Prostate screening	Evidence does not support routine testing Refer to Prostate Cancer Foundation of Australia Clinical Practice Guidelines

**No current evidence-based guidelines for cardiovascular disease in patients who are taking immunosuppressive medication*
DMARD, disease-modifying antirheumatic drug; eGFR, estimated glomerular filtration rate